BEFORE THE CONTROLLER OF PATENTS,
THE PATENT OFFICE, KOLKATA

THE PATENTS ACT, 1970
AND
THE PATENTS RULES, 2003

IN THE MATTER OF PRE-GRANT
OPPOSITION UNDER SECTION 25(1) THE
PATENTS ACT, 1970 AND RULE 55 OF THE
PATENT RULES, 2003

And

IN THE MATTER OF PATENT APPLICATION
NO. 201737004817 DATED 10.02.2017
TITLED: HETEROBICYCLIC COMPOUNDS
AND THEIR USE FOR THE TREATMENT OF
TUBERCULOSIS
Filed by OTSUKA PHARMACEUTICAL CO.
LTD.

And

IN THE MATTER OF REPRESENTATION BY
WAY OF NOTICE OF OPPOSITION UNDER
SECTION 25(1) OF PATENTS ACT, 1970 FILED
BY GANESH ACHARYA

......OPPONENT
REPRESENTATION BY WAY OF OPPOSITION U/S 25(1), PATENTS ACT, 1970

1. A pre-grant opposition under Section 25(1) of the Patents Act, 1970, is hereby submitted by Ganesh Acharya (hereinafter the ‘Opponent’) against Indian Patent Application number 201737004817 (hereinafter the ‘Present Application’) filed by Otsuka Pharmaceutical Co. Ltd. (hereinafter the ‘Applicant’). The Present Application claims agents for treatment of multi-drug resistant tuberculosis.

LOCUS STANDI

2. The Opponent, is a resident of India and is a person living with HIV who has twice survived Tuberculosis (TB) ailment. Having survived the TB ailment and being aware of the issues faced by TB patients, the Opponent started working on access to treatment and medicines for persons living with TB. Towards this end, he works with civil society organisations across India on advocacy to ensure access to medicines relating to TB and in particular by overcoming intellectual property barriers to access to medicines. He also engages with several persons living with TB, including drug-resistant TB (DR-TB) who face challenges in accessing new DR-TB drugs and government mandated nutritional support. The Opponent has also worked with national and international organisations on issues of TB in India.

3. Section 25(1) of the Patents Act provides that any person may make a representation by way of an opposition against grant of patent to an application. Hence, the Opponent has the locus standi to make the present representation by way of an opposition against the grant of patent to the Present Application.

4. Further, it is submitted that on 10.02.2017 the Present Application was filed at the Patent Office, Kolkata and published on 12.05.2017. On 27.09.2019 a First Examination Report (FER) was issued for the Present Application and on 28.01.2020 the Applicant filed a response to the FER. No patent has been granted to the Present Application and therefore, the present representation by way of an opposition against the Present Application is maintainable before the Patent Office, Kolkata.
BACKGROUND ON TUBERCULOSIS AND MULTI-DRUG RESISTANT TUBERCULOSIS

5. The TB epidemic poses one of the greatest challenges to global public health today. India had over 21.5 Lakh cases of TB were notified in 2018 (both from the public and private sector) (India TB Report, 2019). In the same year 2019, India had 27% of the global TB cases.

6. TB is the leading killer of People Living with HIV (PLHIV) with one-third of HIV related deaths occurring due to TB co-infection in 2015. The risk of developing TB is estimated to be between 26 and 31 times greater in PLHIV than among those not affected by HIV. The rapid progression of TB and re-activation of latent TB risk is about 12 and 20 times greater in PLHIV.

7. Drug-Resistant TB (DR-TB) is a form of active tuberculosis caused by Mycobacterium Tuberculosis bacilli resistant to one or more anti-TB drugs. Types of DR-TB include Mono-resistant TB, Poly-Drug Resistant TB, Multi-drug resistant TB (MDR-TB), Rifampicin-Resistant TB (RR-TB), Pre-Extensively Drug Resistant TB and Extensively-Drug Resistant TB(XDR-TB). MDR-TB occurs when the TB affected person is resistant to Isoniazid and rifampicin with or without resistance to other anti-TB drugs. XDR-TB is where a person with MDR-TB is resistant to any fluoroquinolone as well as one or more of the three second-line injectable drugs.

8. Although there is a gradual decrease in TB cases worldwide, nearly half a million people acquire DR-TB each year. WHO’s Global Tuberculosis Report, 2019 has reported that in 2018, 50% of the global MDR/RR-TB population was in India with a MDR/RR-TB incidence in India at 1,30,000. In 2019, 66,359 MDR/ RR-TB cases were notified in India.

ACCESS TO MEDICINES AND STRICT INTERPRETATION OF INDIAN PATENTABILITY STANDARDS

9. One of the ways of ensuring low and affordable costs for essential medicines is to promote competition. However, for effective generic competition, it is imperative that patents not be
granted in India for uninventive, incremental improvements or to inventions that do not meet the strict patentability standards set in the Indian patent law.

10. This becomes particularly important in times where it has been reported by a study that in a cohort of 2,293 pharmaceutical patents granted between 2009 and 2016 about 72 per cent of patents granted for pharmaceuticals are secondary patents, granted for marginal improvements over previously known drugs for which primary patents exist. That is, the strict standards of patentability laid down in the Patents Act, 1970 under Section 3 were not followed adequately. (See Dr. Feroz Ali et al, Pharmaceutical Patents Granted in India: How our safeguards against ever-greening have failed, and why the system must be Reformed, Accessibsa, 2018)

11. It is submitted that the Hon’ble Patent Controller, while considering the present pre-grant opposition, must bear in mind the intent of Parliament in enacting the Patents (Amendment) Act that introduced stricter standards of patentability while ensuring India’s compliance with its obligations under the Agreement on Trade Related Aspects of Intellectual Property Rights. These amendments including Section 3(d) of the Patents Act ensuring that patent protection does not come in the way of India’s fundamental duty to provide good health care to its citizens.

12. Drug resistance in patients of TB, which results from inadequate, incomplete or poor treatment quality, is emerging as a significant public health crisis. The 2018 Report of the First National Anti-Tuberculosis Drug Resistance Survey, released by the Ministry of Health and Family Welfare indicated there is almost 22% resistance to floroquinolones in India. That is, there is a high number of persons living with TB who progress to MDR-TB thereby reducing their possible drugs that could be used to treat them.

13. Therefore, there is an urgent and pressing need to ensure better availability of existing and new drugs for treatment of MDR-TB. However, patents, if erroneously granted to an alleged invention, not meeting the standards of patentability under the Indian patent law, would result in market monopoly of drugs critical to safeguard the health of many. Hence, the need to ensure that patent application for treatment of MDR-TB including those, like the Present Application, be scrutinized strictly. The grant of patent to the Present
Application would have an impact on the availability of access to lifesaving treatment for MDR-TB not only in India but across the world.

PRESENT APPLICATION

14. The Present Application relates to compounds allegedly having bactericidal activity against TB bacteria, multidrug-resistant tuberculosis bacteria and non-tuberculous mycobacteria.

15. The Present Application was filed in India on 10.02.2017 with 17 claims. The PCT phase application for the Present Application was filed on 28.08.2015 and was assigned application no. PCT/JP2015/004371. The Present Application claims a priority date of 28.08.2014 from the Japanese patent application no. 2014-174528. The First Examination Report (FER) for the Present Application was issued on 27.09.2019. The Applicant filed a response to the FER on 28.01.2020 and in order to overcome the objections therein amended the claims, increasing the total number of claims to 22.

16. These 22 claims are not being reproduced here for the sake of brevity. It is submitted that the Opponent herein is filing the present opposition against grant of patent to claims 1-10, 17, 18, 21 and 22.

SUMMARY OF GROUNDS OF OPPOSITION

17. The Opponent bring this representation by way of opposition under the following grounds, each of which is without prejudice to the other:

i) Claims 1-10, 17, 18, 21 and 22 of the Present Application are not novel as the compounds claimed therein have been published before the priority date of the Present Application. Therefore, the Opponent brings this Opposition under Section 25(1)(b)(ii) - that the invention as claimed in the complete specification has been published before the priority date of the claim in India or elsewhere in any other document;

ii) Claims 1-10, 17, 18, 21 and 22 of the Present Application lack inventive step, and therefore fail under Sections 2(1)(j) and 2(1)(ja) of the Patents Act. Therefore, the Opponent brings this opposition under Section 25(1)(e) - that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step,
having regard to the matter published before the priority date in India or elsewhere in any document;

iii) Claims 1-10, 17, 18 do not satisfy the test of Section 3(d) of the Patents Act as the subject matter does not exhibit enhancement of the known efficacy of known substance. Therefore, the Opponent brings this opposition under Section 25(1)(f) - that the subject of any claim of the complete specification is not an invention within the meaning of the Patents Act and is not patentable under the Patents Act;

iv) Claims 21-22 do not satisfy the test of Section 3(e) of the Patents Act as the subject matter does not exhibit any synergistic effect. Therefore, the Opponent brings this opposition under Section 25(1)(f) - that the subject of any claim of the complete specification is not an invention within the meaning of the Patents Act and is not patentable under the Patents Act;

v) The Opponent also brings this Opposition under Section 25(1)(g) - that the complete specification does not sufficiently and clearly describe the invention.

DETAILED GROUNDS

I. CLAIMS 1-10, 17, 18, 21, 22 ARE NOT NOVEL, AND THEREFORE HAVE TO BE REJECTED UNDER SECTION 25(1)(b) OF THE PATENTS ACT

18. Section 2(1)(j) of the Patents Act defines an ‘invention’ as a ‘new product or process involving an inventive step and capable of industrial application.’ (emphasis supplied) Section 25(1) (b) (ii) of the Patents Act allows opposition to a patent application if the alleged invention, as claimed in any claim of the complete specification has been published before the priority date of the claim, in India or elsewhere, in any other document other than a specification filed in pursuance of an application for a patent made in India. Therefore, claims of a patent application are to be rejected if a publication dated before the priority date of the application in question discloses the alleged invention. Disclosure of the alleged invention by such a publication may be determined by comparing the claims of the patent application in question to the disclosures in the prior art, read in light of the general knowledge available to a person skilled in the art.
19. The Opponent submits that a document published before the priority date of Present Application discloses the alleged invention claimed in the Present Application, hence the claims should be rejected for lack of novelty.

20. Further, it is submitted that while determining the question of novelty, the Hon’ble Patent Office has upheld lack of novelty when a markush claimed in an impugned application was a narrower markush structure of one that has already been disclosed on date prior to the priority date of the impugned application. (See order of the Deputy Controller of Patents and Designs dated 16.08.2019 in post-grant opposition against patent no. 276026, annexed herewith as Exhibit-A). It is submitted that this is precisely the case in the Present Application.

WO2010004347 (Published 14.01.2010)

21. The Opponent relies on PCT publication number WO2010004347 (hereinafter “WO’347” and annexed herewith as Exhibit-B). WO ’347 is a PCT phase application titled “Heterocyclic GPCR Agonists” and was published on 14.02.2010. Given that WO’347 was published earlier than the priority date of the Present Application, WO’347 can be relied on for the purposes of Section 25(1)(b).

22. WO ’347 discloses compounds of following general formula or pharmaceutically acceptable salts thereof (see Exhibit-B at abstract at internal page 2 ) –

23. WO ’347 discloses each of these substitutions for the disclosed formula as below:

“wherein Z is phenyl or a 6-membered N containing heteroaryl group which phenyl or heteroaryl group is substituted by -(CH₂)₂-C(O)NR₁R₁₁, -E₁CO₂H₂, -CH(CH₃)-C(O)NR₁R₁₁, a 5- or 6-membered N containing heterocyclyl ring, which ring is substituted with oxo and optionally substituted by methyl, or a 5- or 6-membered N containing heteroaryl ring optionally containing up to 3 additional heteroatoms selected from N, O and S, which ring...
is substituted by C\textsubscript{1,3} alkyl or -NH\textsubscript{2}; or Z is lH-quinazoline-4-one, 2,3-dihydroisoindol-1-one, 1,3-dihydroindol-2-one, 3,4-dihydro-lH-quinolin-2-one, or 3,4-dihydro-2H-isoquinolin-l-one, which is attached to W through an aromatic carbon atom; and wherein Z is further optionally substituted by one or more C\textsubscript{1-2}alkyl, C\textsubscript{1-2} alkoxy, CH\textsubscript{2}NH\textsubscript{2}, or fluoro groups;

\( j \) is 0, 1 or 2;

\( E^1 \) is -CH\textsubscript{2}-, -CH\textsubscript{2}CH\textsubscript{2}-, or -CH(CH\textsubscript{3})-;

W and Y are independently a bond, an unbranched or a branched C\textsubscript{1-4} alkyene optionally substituted by hydroxy or C1-3 alkoxy, or an unbranched or a branched C\textsubscript{2-4} alkenylene;

X is selected from CH\textsubscript{2}, O, S, CH(OH), CH(halogen), CF\textsubscript{2}, C(O), C(O)O, C(O)S, SC(O), C(O)CH\textsubscript{2}S, C(O)CH\textsubscript{2}C(OH), C(OH)CH\textsubscript{2}C(O), C(O)CH\textsubscript{2}C(O), OC(O), NR\textsubscript{5}, CH(NR\textsubscript{5}R\textsubscript{55}), C(O)NR\textsubscript{2}, NR\textsubscript{2} C(O), S(O) and S(O)\textsubscript{2};

R\textsuperscript{5} is hydrogen or hydroxy;

G is CHR\textsubscript{3}, N-C(O)OR\textsubscript{4}, N-C(O)NR\textsubscript{4}R\textsubscript{5}, N-C\textsubscript{1-4} alkyene-C(O)OR\textsubscript{4}, N-C(O)C(O)OR\textsubscript{4}, N-S(O)\textsubscript{2}R\textsubscript{4}, N-C(O)R\textsubscript{4} or N-P(O)(O-Ph)\textsubscript{2}; or N-heterocyclyl or N-heteroaryl, either of which may optionally be substituted by one or two groups selected from C\textsubscript{1-4} alkyl, C\textsubscript{1-4} alkoxy or halogen; provided that G is not optionally substituted N-pyridazinyl;

R\textsubscript{4} and R\textsubscript{11} together with the N atom to which they are attached form a 4- to 6-membered ring substituted by -N(R\textsubscript{2})\textsubscript{2} or -CH\textsubscript{2}NH\textsubscript{2} and optionally further substituted with methyl; or R\textsubscript{4} is hydrogen and R\textsubscript{11} is C\textsubscript{5-6} alkyl substituted by amino or -(CH\textsubscript{2})\textsubscript{k}-L; in addition, when Z is -CH(CH\textsubscript{3})-C(O)NR\textsubscript{4}R\textsubscript{11}, R\textsuperscript{4} may be hydrogen and R\textsubscript{11} may be hydrogen, C\textsubscript{1-3}alkyl, or C\textsubscript{2-3}alkyl substituted by one or two hydroxy groups;

L is a γ- or δ-lactam optionally substituted with methyl;

k is 0, 1 or 2;

R\textsubscript{2} are independently hydrogen or C\textsubscript{1-4} alkyl;
$R^2$ is $C_{3,6}$ alkyl;

$R^4$ is $C_{1,8}$ alkyl, $C_{2,8}$ alkenyl or $C_{2,8}$ alkynyl, any of which may be optionally substituted by one or more substituents selected from halo, $NR^5R^{55}$, $OR^5$, $C(O)OR^5$, $OC(O)R^5$ and CN, and may contain a $CH_2$ group that is replaced by $O$ or $S$; or a $C_{3,7}$ cycloalkyl, aryl, heterocyclyl, heteroaryl, $C_{4,4}$ alkyne, $C_{3,7}$ cycloalkyl, $C_{1,4}$ alkyleneary, $C_{1,4}$ alkyleneheterocyclyl or $C_{1,4}$ alkyleneheteroaryl, any of which may be substituted with one or more substituents selected from halo, $C_{1,4}$ alkyl, $C_{1,4}$ fluoroalkyl, $OR^5$, $CN$, $NR^5R^{55}$, $SO_2Me$, $NO_2$ and $C(O)OR^5$;

$R^5$ and $R^{55}$ are independently hydrogen or $C_{1,4}$ alkyl or taken together $R^5$ and $R^{55}$ may form a 5- or 6-membered heterocyclic ring; or a group $NR^5$ may represent $NS(O)_2$-(2-$NO_2$-$C_6H_4$);

d is 0, 1, 2 or 3; and

e is 1, 2, 3, 4 or 5, provided that $d + e$ is 2, 3, 4 or 5.”

(See Exhibit-B at internal page 2 at para 5 onwards, and internal page 3, lines 1-28)

24. WO’347 further explains the terms used for the substitution, indicating,

“…”alkyl” as well as other groups having the prefix “alk” such as, for example, alkenyl, alkynyl, and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. “Alkenyl”, “alkynyl” and other like terms include carbon chains having at least one unsaturated carbon-carbon bond.

The term “fluoroalkyl” includes alkyl groups substituted by one or more fluorine atoms, e.g. $CH_2F$, $CHF_2$ and $CF_3$.

The term “cycloalkyl” means carbocycles containing no heteroatoms, and includes monocyclic and bicyclic saturated and partially saturated carbocycles. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Examples of partially saturated cycloalkyl groups include cyclohexene and indane.
Cycloalkyl groups will typically contain 3 to 10 ring carbon atoms in total (e.g. 3 to 6, or 8 to 10).

The term “halo” includes fluorine, chlorine, bromine, and iodine atoms (in particular fluorine or chlorine).

The term “aryl” includes phenyl and naphthyl, in particular phenyl.

Unless otherwise indicated the term “heterocyclyl” and “heterocyclic ring” includes 4-to 10-membered monocyclic and bicyclic saturated rings, e.g. 4- to 7-membered monocyclic saturated rings, containing up to three heteroatoms selected from N, O and S. Examples of heterocyclic rings include oxetane, tetrahydrofuran, tetrahydropyran, oxepane, oxocene, thietane, tetrahydrothiophene, tetrahydrothiopyran, thiepane, thiocane, azetidine, pyrrolidine, piperidine, azepane, azocane, [1,3]dioxane, oxazolidine, piperazine, and the like. Other examples of heterocyclic rings include the oxidised forms of the sulfur-containing rings. Thus, tetrahydrothiophene 1-oxide, tetrahydrothiophene 1,1-dioxide, tetrahydrothiopyran 1-oxide, and tetrahydrothiopyran 1,1-dioxide are also considered to be heterocyclic rings.

Unless otherwise stated, the term “heteroaryl” includes mono- and bicyclic 5- to 10-membered, e.g. monocyclic 5- or 6-membered, heteroaryl rings containing up to 4 heteroatoms selected from N, O and S. Examples of such heteroaryl rings are furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl. Bicyclic heteroaryl groups include bicyclic heteroaromatic groups where a 5- or 6-membered heteroaryl ring is fused to a phenyl or another heteroaromatic group. Examples of such bicyclic heteroaromatic rings are benzofuran, benzothiophene, indole, benzoxazole, benzothiazole, indazole, benzimidazole, benzotriazole, quinoline, isoquinoline, quinazoline, quinoxaline and purine. Preferred heteroaryl groups are monocyclic 5- or 6-membered, heteroaryl rings containing up to 4 heteroatoms selected from N, O and S.” (See Exhibit-B at internal page 6, line 23 onwards, and internal page 7, lines 1-14)
25. In fact, preferred form of substitution can be seen in claim 1 of WO ’347 which reads:

“1. The present invention is directed to a compound of formula (I), or a pharmaceutically
acceptable salt

\[
\begin{array}{c}
\text{Z} \quad \text{W} \quad \text{X} \quad \text{Y} \\
\end{array}
\]

(I)

wherein Z is phenyl or a 6-membered N containing heteroaryl group which phenyl or heteroaryl group is substituted by -(CH\(_2\))\(_j\)-C(O)NR\(_1\)R\(_2\), -E\(_1\)CO\(_2\)H, -CH(CH\(_3\))-C(O)NR\(_1\)R\(_2\), a 5- or 6-membered N containing heterocyclyl ring, which ring is substituted with oxo and optionally substituted by methyl, or a 5- or 6-membered N containing heteroaryl ring optionally containing up to 3 additional heteroatoms selected from N, O and S, which ring is substituted by C\(_1\) alkyl or -NH\(_2\);

or Z is 1H-quinazoline-4-one, 2,3-dihydroisoindol-l-one, 1,3-dihydroindol-2-one, 3,4-
dihydro-1H-quinolin-2-one, or 3,4-dihydro-2H-isoquinolin-l-one, which is attached to W through an aromatic carbon atom;

and wherein Z is further optionally substituted by one or more C\(_1\) alkyl, C\(_1\) alkoxy, CH\(_2\)NH\(_2\), or fluoro groups;

j is 0, 1 or 2;

W and Y are independently a bond, an unbranched or a branched C\(_{1-4}\) alkylene optionally substituted by hydroxy or C\(_{1-3}\) alkoxy, or an unbranched or a branched C\(_{2-4}\) alkenylene;

X is selected from CH\(_2\), O, S, CH(OH), CH(halogen), CF\(_2\), C(O), C(O)O, C(O)S, SC(O), C(O)CH\(_2\)S, C(O)CH\(_2\)C(OH), C(OH)CH\(_2\)C(O), C(O)CH\(_2\)C(O), OC(O), NR\(_2\), CH(NR\(_2\)R\(_3\)), C(O)NR\(_2\), NR\(_2\)C(O), S(O) and S(O)\(_2\);

R\(_2\) is hydrogen or hydroxy;

G is CHR\(_3\), N-C(O)OR\(_4\), N-C(O)NR\(_2\)R\(_3\), N-Cl\(_{4\text{alkylene}}\)-C(O)OR\(_4\), N-C(O)C(O)OR\(_4\), N-S(O)R\(_4\), N-C(O)R\(_4\) or N-P(O)(O-Ph)\(_2\); or N-heterocyclyl or N-heteroaryl, either of which
may optionally be substituted by one or two groups selected from $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy or halogen; provided that $G$ is not optionally substituted $N$-pyridazinyl;

$R^1$ and $R^{11}$ together with the $N$ atom to which they are attached from a 4- to 5- membered ring substituted by $-N(R^2)_2$ or $-CH_2NH_2$ and optionally further substituted with methyl; or $R^1$ is hydrogen and $R^{11}$ is $C_{5-6}$ alkyl substituted by amino or $-(CH_2)_k$-$L$;

in addition, when $Z$ is $-CH(CH_3)-C(0)NR^1R^{11}$, $R^1$ may be hydrogen and $R^{11}$ may be hydrogen, $C_{i-3}$alkyl, or $C_{2-3}$alkyl substituted by one or two hydroxy groups;

$L$ is a $\gamma$- or $\delta$-lactam optionally substituted with methyl; $k$ is 0, 1 or 2;

$R^2$ are independently hydrogen or $C_{1-4}$ alkyl;

$R^3$ is $C_{3-6}$ alkyl;

$R^4$ is $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl or $C_{2-8}$ alkynyl, any of which may be optionally substituted by one or more substituents selected from halo, $NR^5R^{55}$, $OR^5$, $C(O)OR^5$, $OC(O)R^5$ and $CN$, and may contain a $CH_2$ group that is replaced by $O$ or $S$; or a $C_{3-7}$ cycloalkyl, aryl, heterocyclyl, heteroaryyl, $C_{1-4}$ alkylene$C_{3-7}$ cycloalkyl, $Q_4$ alklynearyl, $C_{1-4}$ alkyleneheterocyclyl or $C_{1-4}$ alkyleneheteroaryyl, any of which may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-8}$fluoroalkyl, $OR^5$, $CN$, $NR^5R^{55}$, $SO_2Me$, $NO_2$ and $C(O)OR^5$;

$d$ is 0, 1, 2 or 3;

and $e$ is 1, 2, 3, 4 or 5, provided that $d + e$ is 2, 3, 4 or 5.” (emphasis supplied) (see internal pages 55, 56 of Exhibit-B)

26. WO’347 also discloses material and methods for preparation of invention of the publication (see Exhibit-B, at internal pages 18 “Examples”- internal page 51)

27. On perusing the substitutions for the compound of WO’347, it can be seen that the compound of claim 1 was disclosed much before the priority date of the Present Application. The substitution on the compound of WO’347 and the compound of claim 1 of the Present Application are compared below in a tabular manner. Each of the branches of the compound of claim 1 of the Present Application corresponding to the substitution to the compound of WO’347 has been highlighted/encircled.
<table>
<thead>
<tr>
<th>WO2010004347</th>
<th>Present Application</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Claim 1</strong></td>
</tr>
</tbody>
</table>

**Compound of Formula**

(See Exhibit-B internal page 3 and internal page 55, claim 1)

N=2, e=2

or a pharmaceutically acceptable salt

A salt thereof
See Exhibit-B internal page 55, claim 1

Z is 3,4-dihydro-1H-quinolin-2-one which is attached to W through an aromatic carbon atom

(See Exhibit-B internal page 3 and internal page 55 at line 10, claim 1)

\[
\begin{align*}
\text{wherein } R^1 & \text{ is (1) } \text{hydrogen.} \\
R^2 & \text{ is (1) } \text{halogen... (3) } C_{1-6} \text{-alkyl. (4) } C_{1-6} \text{-alkoxy} \\
m \text{ is an integer of 0 to 3:} \\
\text{provided that when } m \text{ is 2 or 3, } R^2 \text{ may be different from each other;}
\end{align*}
\]
**W** is a bond (See **Exhibit-B** at internal page 55, claim 1, line 17)

![Chemical Structure](image1.png)

**X** is from \( \text{CH}_2, \text{O}, \text{S}, \text{NR}^5, \text{S(O)} \text{ and } \text{S(O)}_2 \),

Wherein \( R^5 \) includes hydrogen or hydroxy [See WO’347, internal page 55, claim 1, lines 19-21]

![Chemical Structure](image2.png)

“a partial structure \((Y)\) of formula (a) is represented by the following partial structure:

![Chemical Structure](image3.png)

Wherein *1 is a binding point to a partial structure \((X)\) of formula (1) and *2 is a binding point to Ring A, and the partial structure \((X)\) of formula (a)
Wherein * is a binding point to structure X,

The partial structure (Y) is any one of the structures selected from the group consisting of the following formulae (Y1) to (Y8):

![Chemical structures](image_url)
“a partial structure (Y) of formula (a) is represented by the following partial structure:

Wherein *1 is a binding point to a partial structure (X) of formula (1) and *2 is a binding point to Ring A, and the partial structure (X) of formula (a) is represented by the following partial structure:

Wherein * is a binding point to structure X⁴.

The partial structure (Y) is any one of the structures selected from the group
Y is branched or unbranched C$_{1-4}$ alkyene consisting of the following formulae (Y1) to (Y8):

- $R^{G11}$ or $R^{G12}$ are each independently hydrogen or C$_{1-6}$ alkyl.
$R^x$ is hydrogen or hydroxy

...The partial structure (Y) is any one of the structures selected from the group consisting of the following formulae (Y1) to (Y8):

$R^7$ is

(1) hydrogen, (2) amino, (3) C$_{1-7}$ alkanoyl or (4) C$_{1-6}$ alkyl;

wherein $R^{3a}$ is (1) hydrogen, (2) carboxy, (3) halogen, (4) C$_{1-6}$ alkyl, which may have one or more hydroxy, or (5) cyano;
<table>
<thead>
<tr>
<th><strong>G</strong> is N-heterocycl or N-heteroaryl, either of which may optionally be substituted by one or two groups selected from C(<em>{1-4}) alkyl, C(</em>{1-4}) alkoxy or halogen (See Exhibit-B at internal page 55, lines 23-26, claim 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R(^{ab}) and R(^{ac}) are each independently</strong> (1) hydrogen, (2) C(_{1-6}) alkyl, or (3) C(=O)-R(_6);</td>
</tr>
<tr>
<td><strong>R(^6)</strong> is (1) C(<em>{1-6}) alkoxy or (2) C(</em>{1-6}) alkyl wherein the C(<em>{1-6}) alkyl may have amino which may have one or two of the same or different C(</em>{1-6}) alkyl;</td>
</tr>
<tr>
<td><strong>N or CH</strong></td>
</tr>
<tr>
<td><strong>aryl which may have one or more substituents, or heterocyclyl which may have one or more substituents.</strong></td>
</tr>
<tr>
<td><strong>X(^2)</strong> is N or CH;</td>
</tr>
<tr>
<td><strong>Ring A</strong> is</td>
</tr>
<tr>
<td>(1) aryl which may have one or more substituents, or</td>
</tr>
</tbody>
</table>
| (2) heterocyclyl which may have one or more substituents.
28. That is, the compound of claim 1 of the Present Application has been disclosed in WO’347 as seen above. Each of the substitutions in WO’347 disclose identical substitution to that in the compound of claim 1 of the Present Application as seen below:

29. In other words:
Z in WO’374 is 3,4- dihydro-1H-quinolin-2-one optionally substituted by 1 or more C_{1-2} alkyl, C_{1-2}alkoxy or fluoro groups;

W of WO’347 represents a bond thus Z (quinolinonemoiety) is directly attached to X which would correspond to X^1 of the markush structure of the WO’347 which is represented by various substituents including -O-;
G¹ of WO’347 corresponds to Y of the Present Application and is represented by an unbranched or a branched C₁⁴-alkylene;

d in WO’347 is 2 and e is 2; and

the ring attached to Y in WO’347 becomes piperidine when G corresponds to N-hetero aryl or N-heterocyclyl;

Here G of WO ‘347 would correspond to X²-A of the markush structure of the Present Application and is represented by CHR³, N-heterocyclyl or N-heteroaryl.

30. As explained above, the markush formula of claim 1 of the Present Application has been unambiguously disclosed in WO’347. WO’347 also invariably discloses the partial structures “X” and “Y” and Ring “A” of the Present Application with substitutions that are identified in claims 2-10, 17 and 18 of the Present application. Hence, claim 1 and the dependent claims 2-10, 17, 18 are anticipated by way of disclosure in WO’374 and must be rejected.

II. CLAIMS 1-10 AND CLAIMS 17-18, 21-22 OF THE PRESENT APPLICATION ARE CHALLENGED UNDER SECTION 25(1)(e) OF THE PATENTS ACT, ON GROUND OF LACK OF INVENTIVE STEP AS DEFINED UNDER SECTIONS 2(1)(ja) OF THE PATENTS ACT

31. Section 2(1)(j), requires that an invention be either a new product or process involving an inventive step and capable of industrial application. ‘Inventive step’ is further defined in Section 2(1)(ja) as ‘a feature of an invention that involves technical advance as compared to the existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art’. Without prejudice to other grounds raised herein, the
Opponent submits that claims 1-10, 17, 18, 21-22 of the Present Application lack an inventive step and therefore should be rejected.

32. It may be submitted at the outset that the Hon’ble Patent Office while determining inventive step, has held that mere “replacement of alkyl and/or other group” to a known structure cannot be considered as technical advancement under Section 2(1)(ja) (See order dated 21.02.2020 of the Assistant Controller of Patents and Designs in the matter of patent application no.478/MUMNP/2015 and annexed herewith as Exhibit-C). Further, the Hon’ble Patent office has also held that when prior art document discloses that certain substitutions have been used in a particular manner for their certain characteristics, one could expect a Person Skilled in the Art (POSITA) to use that substitution to induce the stated characteristic/behavior, if that step is not technically impossible (see internal page 40, lines 17-25 of order dated 04.03.2020 of the Joint Controller of Patents and Designs in post grant opposition against patent no.262968 annexed herewith as Exhibit-D). Further, in absence of any teaching away, i.e. teaching, and when examples with similar substitutions are disclosed in the prior art, a POSITA could be said to be motivated to look at structurally and functionally similar groups. (see internal page 41 of Exhibit-D)

33. It is submitted that on the priority date of the claims of the Present Application, the following was well known in the art:

- Heterocyclic compounds have shown anti-tuberculosis activity.

**Heterocyclic compounds have shown anti-tuberculosis activity**

**WO2006134378** (Published: 21.12.2006)

34. The Opponent relies on patent publication no. WO2006134378 (hereinafter, “WO’378” and annexed herewith as Exhibit-E) published on 21.12.2006,
titled, “Compounds for the treatment of multi-drug resistant bacterial infections”. WO’378 was published before the priority date of the Present Application viz. 28.08.2014 and therefore can be relied on as prior art document.

35. WO’378 discloses compounds that demonstrate antibacterial activity, processes for their preparation, pharmaceutical compositions containing them as the active ingredient stated to be for treatment of multi-drug resistant bacterial infections (See Exhibit-E, abstract). This document discloses compounds represented by formula II (emphasis supplied, See Exhibit-E at internal page 4):

\[
\begin{align*}
\text{or a pharmaceutically acceptable salt thereof, wherein} \\
\text{R}_2a, \text{R}_2b, \text{R}_2c, \text{and R}_2d \text{ are each independently H, fluoro, chloro, cyano, (C}_1-C_6)\text{alkyl, halo(C}_1-C_6)\text{alkyl, halo(C}_1-C_6)\text{alkoxy, (C}_1-C_6)\text{alkoxy;} \\
"---- " \text{ is a bond or is absent;} \\
\text{Z is CH or N when "---- "is a bond, or Z is O or NH when "---- " is absent;} \\
\text{U}_1 \text{ is CR}_a\text{R}_b-\text{CR}_c\text{R}_d \text{ or CR}_a\text{R}_b-\text{CR}_c\text{R}_d-\text{CR}_e\text{R}_f, \text{ wherein R}_a, \text{R}_b, \text{R}_c, \text{R}_d, \text{R}_e \text{ and R}_f \text{ are each independently hydrogen} \text{ or (C1-C6)alkyl;} \\
\end{align*}
\]
M is a group of formula M1a or M2-M5:

Ry and Ry’ are each independently H, hydroxy………;
when M is a group of formula M2, M3, or M5, U₂ is W; and
when W is CH₂, CO or SO₂, R is aryl, heteroaryl, heterocycl or ortho-fused bicyclic heteroaryl,……….. wherein any R may be optionally substituted on carbon; ……. 

36. That is one of the compounds identified in WO’378 with the substitutions disclosed (and emphasised by the Opponent) would include the following compound:

37. Hence a POSITA working on developing an anti-bacterial agent for treatment of Tuberculosis, on reading WO’378, would be motivated to make structural changes to the known anti-bacterial compounds including the one as discussed
above. Therefore, a POSITA on reading the above discussed prior art document would be motivated to look at the use of above disclosed fused heterocyclic ring as an anti-bacterial agent.

38. Therefore, a POSITA on reading the above discussed prior art document would be motivated to look at the use of above disclosed fused heterocyclic ring as an anti-bacterial agent.

**WO2010/045987** (Published 29.04.2010)

39. The Opponent relies on patent publication number WO2010045987 (hereinafter ‘WO’987’ and annexed herewith Exhibit-F), titled, ‘Substituted (Aza)-1-methyl-1H-Quinolin-2-ones as Antibacterials’ and published on 29.04.2010. WO’987 was published before the priority date of the Present Application viz. 28.08.2014 and therefore can be relied on as prior art document.

40. WO’987 relates to bicyclic nitrogen containing compounds used as antibacterial medicaments (See Exhibit-F at abstract. It discloses the use of the compounds disclosed therein for the treatment of bacterial infections including treatment of tuberculosis caused by Mycobacterium tuberculosis (See Exhibit-F at internal page 25, lines 7-10).

41. WO’987 discloses (highlighted parts represent relevant substitutions) a compound of formula (I) or a pharmaceutically acceptable salt or N-oxide thereof: (See Exhibit-F internal page 1 to 3, lines 17-18, emphasis supplied)
wherein:

Z\(^1\) and Z\(^2\) are independently selected from N and CH; AB is OCH\(_2\), CH\(_2\)O, NR\(^1\)CH\(_2\) or CH\(_2\)NR\(^1\);

R\(^{1a}\) is selected from hydrogen; halogen; cyano; (C\(_{1-6}\))alkyl; (C\(_{1-6}\))alkythio; trifluoromethyl; trifluoromethoxy; carboxy; hydroxy optionally substituted with (C\(_{1-6}\))alkyl or (C\(_{1-6}\))alkoxy-substituted(C\(_{1-6}\))alkyl; (C\(_{1-6}\))alkoxy-substituted(C\(_{1-6}\))alkyl; hydroxy (C\(_{1-6}\))alkyl; an amino group optionally N-substituted by one or two (C\(_{1-6}\))alkyl, formyl, (C\(_{1-6}\))alkylcarbonyl or (C\(_{1-6}\))alkylsulphonyl groups; or aminocarbonyl wherein the amino group is optionally substituted by (C\(_{1-4}\))alkyl; R\(^{1b}\) is H or F;

R\(^3\) is hydrogen;

R\(^y\) and R\(^w\) are hydrogen, R\(^y\) is absent and R\(^w\) is in the 1-position and R\(^w\) is hydrogen or R\(^y\) and R\(^w\) together are a bond;

R\(^3\) is hydrogen; or when R\(^v\) and R\(^w\) are a bond, R3 is in the 2-, 3- or 4-position and when R\(^w\) is hydrogen, R3 is in the 1-, 2-, 3- or 4-position and R\(^3\) is: hydroxy optionally substituted by (C\(_{1-6}\))alkyl; amino optionally mono- or disubstituted independently by (C\(_{1-6}\))alkyl or (C\(_{1-6}\))alkylcarbonyl; fluoro; carboxy; cyano; (C\(_{1-6}\))alkoxycarbonyl; aminocarbonyl wherein the amino group is optionally substituted by (C\(_{1-6}\))alkyl or (C\(_{1-6}\))alkylcarbonyl, or (C\(_{1-4}\))alkyl
optionally substituted with any of the groups listed above for \( R^3 \); provided that when \( R^3 \) is in the 4- position it is not optionally substituted hydroxyl or amino; provided that when \( R^3 \) is in the 1 -position and AB is CH\(_2\)NRI 1 or \( R^3 \) is in the 4- position, it is not optionally substituted hydroxyl or amino; and provided that when \( R^3 \) is in the 1 -position and AB is CH\(_2\)O, it is not optionally substituted amino;

\[ R^4 \text{ is } UR^5; \]

\( U \) is selected from CO and CH\(_2\) and

\[ R^5 \text{ is an optionally substituted bicyclic carbocyclic or heterocyclic ring system (B):} \]

![Diagram](A)

containing up to four heteroatoms in each ring in which at least one of rings (a) and (b) is aromatic; \( X^1 \) is C or N when part of an aromatic ring, or \( CR^{14} \) when part of a non-aromatic ring; \( X^2 \) is N, NR\(^{13}\), O, S(O)X, CO or \( CR^{14} \) when part of an aromatic or non-aromatic ring or may in addition be \( CR^{14}R^{15} \) when part of a non-aromatic ring;

\( X^3 \) and \( X^5 \) are independently N or C;

\( Y^1 \) is a 0 to 4 atom linker group each atom of which is independently selected from N, NR\(^{13}\), O, S(O)X, CO and \( CR^{14} \) when part of an aromatic or non-aromatic ring or may additionally be \( CR^{14}R^{15} \) when part of a non-aromatic ring;
Y² is a 2 to 6 atom linker group, each atom of Y2 being independently selected from N, NR₁, O, S(O)X, CO, CR¹⁴ when part of an aromatic or non-aromatic ring or may additionally be CR¹⁴R¹⁵ when part of a non-aromatic ring; each of R¹⁴ and R¹⁵ is independently selected from: H; (C₁₋₂)alkythio; halo; carboxy(C₁₋₂)alkyl; (C₁₋₂)alkyl; (C₁₋₂)alkoxycarbonyl; (C₁₋₂)alkylcarbonyl; (C₁₋₂)alkoxy(C₁₋₂)alkyl; hydroxy; hydroxy(C₁₋₂)alkyl; (C₁₋₂)alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally mono- or di-substituted by (C₁₋₂)alkyl.

42. WO’987 discloses examples with fused heterocyclic compounds with optional substitution of halogen with preference of Fluorine. For instance, example 19 (See Exhibit-F at internal page 46)

![Chemical Structure](image1)

Example 21 (See Exhibit-F at internal page 49)
In fact, WO’987 also discloses the process for producing these compounds.

44. Other exemplified compounds such as examples 1 (at internal page 27), example 2 (at internal page 34), example 3, 4 (at internal page 34), example 5 (at internal page 35), example 6,7 (at internal page 36), example 8,9 (at internal page 37), example 11 (at internal page 39), example 12 (at internal page 40), example 14 (at internal page 41), example 18A (at internal page 43) also show preferred halogen substitution on the fused heterocyclic rings.

45. Further, a closer look at the exemplified compounds would motivate a POSITA to look at the common features of the shown compounds. One of them would be the nature of the fused heterocyclic rings used. Several of the exemplified compounds comprise the following fused heterocyclic ring:

46. Hence, a POSITA working on developing an agent with anti-bacterial properties for treatment of tuberculosis, on reading WO’987 with the available substitutions on the above identified fused heterocyclic ring as a part of the scaffold would expect similar properties of compounds with very close structural similarities. Further, as WO’987 discloses compounds of the claimed compounds to show anti-bacterial properties, a POSITA would be motivated to pick up compound of this nature as the lead compound. A POSITA would be
motivated to modify this known compound to obtain new compounds. That is
given the disclosures in WO’378 and further developments seen in WO’987, a
POSITA would be motivated to develop on a formula disclosed in these prior
art documents, such as

![Chemical Structure]

**WO2013029548** (Published 07.03.2013)

47. The Opponent relies on patent publication number WO2013029548 (hereinafter
“WO’548” and annexed herewith as **Exhibit-G**) titled, “Quinolone Compound”
and filed by the Applicant of the Present Application. WO’548 was published
before the priority date of the Present Application viz. 28.08.2014 and therefore
can be relied on as prior art document.

48. WO ’548 discloses quinolone compounds useful as anti-bacterial agents (See
**Exhibit-G** at internal page 1, line 35).

49. The quinolone compound disclosed in WO’548 is disclosed below (See
**Exhibit-G** at internal page 2):
Wherein $R^3$ is a fused heterocyclic group of the general formula

![Diagram of fused heterocyclic group]

50. WP ‘548 discloses several examples of fused heterocyclic groups used for the claimed anti-bacterial compound. These examples include (see Exhibit-G at internal page 42):

![Multiple examples of fused heterocyclic groups]
Wherein the said fused heterocyclic group is optionally substituted by one or two substituents selected from the group consisting of a halogen atom, cyano, nitro, hydroxy and alkyl (See Exhibit-G at internal page 42, lines 2-5)

51. Further, WO’548 also discloses the method of producing these compounds with fused heterocyclic groups. See for instance Reaction Scheme I (See Exhibit-G internal page 71), Reaction Scheme II (See Exhibit-G at internal page 74) and Reaction Scheme III (See Exhibit- at internal page 78).

52. Further, Table I at internal page 93 also discloses compounds of the invention where the fused heterocyclic groups are optionally substituted with halogen including the following examples:

(compound 1-7 at internal page 93; compound 1-9, internal page 94; compound 1-35, internal page 97, Exhibit-G)

(compound 1-8 and compound 1-10 at internal page 94; compound 1-37, internal page 98 Exhibit-G)

(compound 1-17, internal page 95, Exhibit-G)
53. Hence, a person skilled in the art (POSITA), on reading WO’548 would be taught that fused heterocyclic compounds with different substitutions including halo substitutions would show anti-microbial activity.

54. Hence, a POSITA on reading WO’987, WO ’378 and WO’548 would be further motivated to work on fused heterocyclic rings with halo substitutions to develop agents with anti-microbial properties. This is akin to the fused heterocyclic rings with halogen substitution on one of the rings in the claimed invention.

**WO2005042542** (Published 12.05.2005)

55. The Opponent relies on patent publication no. WO2005042542 (hereinafter ‘WO’542’ and annexed as **Exhibit-H**) titled, ‘2-3-Dihydro-6-Nitroimidazo (2,1-B) Oxazole for the treatment of Tuberculosis’ and was filed by the Applicant of the Present Application. WO’542 was published before the priority date of the Present Application viz. 28.08.2014 and therefore can be relied on as prior art document.

56. WO’542 relates to compounds with heterocyclic structure possessing bactericidal action against Mycobacterium tuberculosis, multi-drug resistant Mycobacterium tuberculosis and atypical acid fast bacteria. The document discloses the markush general formula (See **Exhibit-H** internal page 8 ,lines 1-26 and page 17, line 4. Emphasis supplied)

\[
R^1 \text{ represents a hydrogen atom or a } C_{1-6} \text{ alkyl group, } n \text{ represents an integer between 0 and 6,}
\]
$R^2$ represents a group described in any one of the following (a) to (y) : a 1, 2, 3, 4-tetrahydroquinolyloxy group (wherein, on the 1, 2, 3, 4-tetrahydroquinoline ring, at least one selected from the group consisting of an oxo group, a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C$_1$-C$_6$ alkyl group, and a halogen substituted or unsubstituted C$_1$-C$_6$ alkoxy group, may be substituted] , and a phenyl C$_1$-C$_6$ alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C$_1$-C$_6$ alkyl group, and a halogen substituted or unsubstituted C$_1$-C$_6$ alkoxy group, may be substituted] , may be substituted)

57. WO’542 discloses a list of groups or moieties to be substituted to the above disclosed formula. Of these disclosed substitutions, several examples disclose quinolone moiety as the terminal substituent. For instance, examples 284, 287 (See Exhibit-H at internal page 673):

![Chemical structure 284](image)

![Chemical structure 287](image)

58. Further, example nos. 609, 611, 617 and 621 which include a quinoline moiety at the terminal(See Exhibit-H at internal pages 698, 699)
59. WO ’542 also claims the disclosed compound and its pharmaceutically acceptable salts (see claim 1 at internal page 860) and a pharmaceutical composition comprising the disclosed compound I (See Exhibit-H, internal page 83, lines 1-6). Therefore, WO’542 discloses quinolone based terminal to compounds that have been found to have excellent antibacterial activity against Mycobacterium tuberculosis, multi-drug resistant tuberculosis and atypical acid fast-bacteria.

60. The teachings from the WO’542 when combined with WO’347 and WO’548, would enable a POSITA to work on anti-microbial agents to treat tuberculosis that could be developed from structural modification and associated substitutions to the quinolone core.

WO2006038172 (Published: 13.06.2006)

61. Further, piperidine derivatives have been shown to have anti-bacterial characteristics. In this regard, the Opponent relies on PCT patent publication no. WO2006038172 (hereinafter “WO ’172” and annexed herewith as Exhibit-
I) titled, “New piperidine antibiotics” and published on 13.06.2006. WO’172 was published before the priority date of the Present Application viz. 28.08.2014 and therefore can be relied on as prior art document.

62. WO’172 describes novel bicyclic derivatives are useful antimicrobial agents and effective against a variety of multi-drug resistant bacteria. It discloses piperidine derivatives of the general formula (See Exhibit-I at internal page 2, emphasis supplied)

![Chemical Structure]

wherein
U represents CH and \textbf{V represents N};

M represents CH$_2$CH$_2$, CH(OH)CH(OH), CH(OH)CH$_2$ or OCH$_2$;

R$^1$ represents alkoxy;

R$^2$ represents hydrogen or \textbf{halogen};

R$^3$ represents carboxy, \textbf{hydroxy} or aminocarbonyloxy;

R$^4$ represents \textbf{arylalkyl}, aryl-\textbf{S(O)}$_m$-alkyl, heteroarylalkyl, heteroarylaminocarbonylalkyl, heteroaryl-\textbf{S(O)}$_m$-alkyl or CH$_2$-CH=CH-aryl;

\textbf{n is an integer between 0 and 3}; and

m is 0.

63. WO’712 also discloses the process for producing the compounds of the general formula disclosed (See Exhibit-I at internal page 22). Particularly, the
preferred piperidin comprising compounds have been claimed in claims 8 and 9 of WO’712 (See Exhibit-I at internal page 77 and 78)

64. Based on these teachings along with the disclosure that the compounds discussed in these references are effective in the treatment of bacterial infections including tuberculosis, a person skilled in the art would have reasonable motivation to start at WO’378 and modify the structure disclosed therein based on teachings in WO’987, WO’548 and WO’542. Using teachings of WO’172, a POSITA would be able to develop appropriate attachment of the piperidine group on the bicyclic ring and closely related substituents.

**WO 2012141338** (Published: 18.10.2012)

65. In the later developed anti-bacterial agents as well, piperidine substitutions were seen.

66. In this regards, the Opponent relies on patent publication no. WO2012141338 (hereinafter “WO’338” and annexed herewith as Exhibit-J) titled, “6,7 - Dihydroimidazo [2, 1 - b] [1, 3] Oxazine Bactericides” was published on 18.10.2020. WO’338 was published before the priority date of the Present Application viz. 28.08.2014 and therefore can be relied on as prior art document.

67. WO’338 relates to, “a novel 6,7-dihydroimidazo[2,1-b][1,3]oxazine compound that has excellent bactericidal action against tubercle bacilli, multidrug-resistant tubercle bacilli, and atypical acid-fast bacilli.” (See Exhibit-J, at abstract)

68. This document discloses a compound represented by Formula (1) (See Exhibit-J at internal page 5)
or a salt thereof,

wherein \( R^2 \) represents \textit{hydrogen} or lower alkyl.

wherein \( R^1 \) is a group represented by Formula (2):

\[
-A_1-L_1-B_1-L_2-C_1-D_1 \quad \text{(2)}
\]

wherein \( \text{A} \) represents a divalent group selected from (A1) to (A12):

\[
(A2) \quad \text{tetrahydroquinolinediyl},
\]

these groups (A1) to (A12) being optionally substituted on the ring(s) with at least one group selected from the group consisting of \textit{halogen} and lower alkyl;

\( \text{L}_1 \) represents a single bond, lower alkylene, \(-\text{N}(\text{lower alkyl})-\), \(-\text{O}-\), \(-\text{O}-\text{lower alkylene}\), \(-\text{O}-\text{lower alkylene}-\text{O}-\), lower alkylene-\text{O}-, lower alkylene-O-lower alkylene, or lower alkenylene;

\( \text{B} \) represents a divalent group selected from (B1) to (B11):

\[
(B9) \quad \text{piperidinediyl},
\]

these groups (B1) to (B11) being optionally substituted on the ring(s) with at least one group selected from the group consisting of lower alkyl, halo-lower alkyl, alkenyl, lower alkoxy, halo-lower alkoxy, lower alkoxy carbonyl, lower alkenyloxycarbonyl, \textit{hydroxy}, lower alkylsulfonyl, and halo-lower alkylsulfonyl;
L2 represents a **single bond**...;

C represents a divalent group or a single bond selected from (C1) to (C28):

(C27) phenylene, ...

these groups (C1) to (C27) being optionally substituted on the ring(s) with at least one group selected from the group consisting of alkoxy, halo-lower alkoxy, alkyl, haloalkyl, **halogen**...;

D represents a group or an atom selected from (D1) to (D35):

(D35) hydrogen. (emphasis supplied)

69. A POSITA on reading WO’338 would be motivated to try all the substitutions disclosed therein, including those supplied emphasis above. A representation of the above-mentioned substitution can also be thus:

![Chemical Diagram]

70. Given such close structural similarity in the above identified substitution and the other substitutions on the lead compound that could be made, a POSITA working on developing an anti-bacterial agent for treatment of Tuberculosis, on

**WO2010004347** (Published 14.01.2010)

71. The Opponent relies on WO’347 (annexed herewith as **Exhibit-B**). WO ’347 is a PCT phase application titled “Heterocyclic GPCR Agonists” and was published on 14.02.2010. WO’347 was published before the priority date of the Present Application viz. 28.08.2014 and therefore can be relied on as prior art document.

72. WO ’347 discloses compounds of following general formula or pharmaceutically acceptable salts thereof (see **Exhibit-B** at abstract at internal page 2 ) –

![Chemical Structure](image)

73. In fact, preferred form of substitution in claim 1 of WO ’347 reads:

“I. The present invention is directed to a compound of formula (I), or a pharmaceutically acceptable salt

![Chemical Structure](image)

wherein, wherein Z is phenyl or a 6-membered N containing heteroaryl group which phenyl or heteroaryl group is substituted by -(CH₂)₁-C(O)NR₁R₁¹.
E^{1}CO_{2}H, -CH(CH_{2})-C(O)NR^{1}R^{11}, a 5-or 6-membered N containing heterocyclyl ring, which ring is substituted with oxo and optionally substituted by methyl, or a 5- or 6-membered N containing heteroaryl ring optionally containing up to 3 additional heteroatoms selected from N, O and S, which ring is substituted by C_{1-3} alkyl or -NH_{2};

or Z is 1H-quinazoline-4-one, 2,3-dihydroisoindol-1-one, 1,3-dihydroindol-2-one, 3,4-dihydro-1H-quinolin-2-one, or 3,4-dihydro-2H-isoquinolin-1-one, which is attached to W through an aromatic carbon atom;

and wherein Z is further optionally substituted by one or more C_{1-2} alkyl, C_{1-2} alkoxy, CH_{2}NH_{2}, or fluoro groups;

j is 0, 1 or 2;

W and Y are independently a bond, an unbranched or a branched C_{1-4} alkyene optionally substituted by hydroxy or C_{1-3} alkoxy, or an unbranched or a branched C_{2-4} alkenylene;

X is selected from CH_{2}, O, S, CH(OH), CH(halogen), CF_{2}, C(O), C(O)O, C(O)S, SC(O), C(O)CH_{2}S, C(O)CH_{2}C(OH), C(OH)CH_{2}C(O), C(O)CH_{2}C(O), OC(O), NR^{5}, CH(NR^{5}R^{55}), C(O)NR^{2}, NR^{2} C(O), S(O) and S(O)_{2};

R^{8} is hydrogen or hydroxy;

G is CHR^{3}, N-C(O)OR^{4}, N-C(O)NR^{4}R^{5}, N-C_{i4}alkylene-C(O)OR^{4}, N-C(O)C(O)OR^{4}, N- S(O)_{2}R^{4}, N-C(O)R^{4} or N-P(O)(O-Ph)_{2}; or N-heterocyclyl or N-heteroaryl, either of which may optionally be substituted by one or two groups selected from C_{1-4} alkyl, C_{1-4} alkoxy or halogen; provided that G is not optionally substituted N-pyridazinyl;

R^{1} and R^{11} together with the N atom to which they are attached from a 4- to 5-membered ring substituted by –N(R^{2})_{2} or –CH_{2}NH_{2} and optionally further
substituted with methyl; or $R^1$ is hydrogen and $R^{11}$ is $C_{5-6}$ alkyl substituted by amino or $-(CH_2)_k$-$L$;

in addition, when $Z$ is $-CH(CH_3)$-$C(0)NR^1R^{11}$, $R^1$ may be hydrogen and $R^{11}$ may be hydrogen, $Ci_{3-alkyl}$, or $C_{2-3}$alkyl substituted by one or two hydroxy groups; $L$ is a $\gamma$- or $\delta$-lactam optionally substituted with methyl; $k$ is 0, 1 or 2;

$R^2$ are independently hydrogen or $C_{1-4}$ alkyl;

$R^3$ is $C_{3-6}$ alkyl;

$R^4$ is $C_{1-8}$ alkyl, $C_{2-8}$ alkenyl or $C_{2-8}$ alkynyl, any of which may be optionally substituted by one or more substituents selected from halo, $NR^5R^{55}$, $OR^5$, $C(O)OR^5$, $OC(O)R^5$ and CN, and may contain a CH$_2$ group that is replaced by O or S; or a $C_{3-7}$ cycloalkyl, aryl, heterocylecyl, heteroaryl, $C_{1-4}$ alkylenec$C_{3-7}$ cycloalkyl, $Q_{4}$ alkylenearyl, $C_{1-4}$ alkyleneheterocyclycyl or $C_{1-4}$ alkyleneheteroaryl, any of which may be substituted with one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ fluoroalkyl, $OR^5$, $CN$, $NR^5R^{55}$, $SO_2Me$, $NO_2$ and $C(O)OR^5$;

d is 0, 1, 2 or 3;

and e is 1, 2, 3, 4 or 5, provided that $d + e$ is 2, 3, 4 or 5.” (emphasis supplied)

(see internal pages 55, 56 of Exhibit-B)

74. On analyzing the emphasized substitution, one would find that one of the preferred disclosures include a structure as below:
75. That is, one would find N-heterocyclyl or N-heteroaryl (optionally substituted by one or two groups from C\textsubscript{1-4} alkyl, C\textsubscript{1-4} alkoxy or halogen, attached to a ring which is an extended substitution to a fused heterocyclic ring. That is, there is a continued teaching that piperidin like substitutions to extended substitutions may be effective in use as anti-bacterial agents.

76. Hence a POSITA would have reasonable motivation to start at WO’378 and modify the structure disclosed therein based on teachings in WO’987, WO’548 and WO’542. Using teachings of WO’172 and WO’378, a POSITA would be able to develop appropriate attachment of the piperidine group on the bicyclic ring and closely related substituents.

77. Therefore, a POSITA starting with the disclosure in WO’378 would have reasonable motivation to attempt modifications taught in other prior art document including WO’987, WO’548 and WO’542, WO’172 and WO’378, and WO’338. In absence of any teaching away from these documents, a POSITA would be able to develop appropriate attachment of the piperidine group on the bicyclic ring and closely related substituents.

78. Hence, it would be obvious for a POSITA to arrive at compound of Formula 1 as described in claim 1 of the Present Application. Further, given the independent claim is obvious, the related substitutions and identified in dependent claims of the Present Application would also be obvious to a POSITA. That is the compounds of claims 2-10, including 5-\{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy\}-8-fluoro-3,4-dihydroquinolin-2(1H)-one which corresponds to the structure:
and its salt as claimed in claims 17-18 of the Present Application are obvious, lacking an inventive step and should be rejected for failure to meet the test of Section 2(1)(ja) of the Patents Act. Further, given the independent claim is obvious, its dependent claims 21, 22 for claiming of composition of claim 1 and the compound of claim 1 with pharmaceutically acceptable carrier are rendered obvious.

80. As regards claims 21-22 of the Present Application, they claim a composition of the compounds of earlier claims with a pharmaceutical carrier. There is no specific carrier that is mentioned. There is no discussion on why a plain admixture results in any inventive step. As noted earlier, Otsuka’s own (applicant of the Present Application) WO’542 gives examples of composition of compound with similar activity with a pharmaceutical carrier. Hence, to that extent claims 21-22 are rendered obvious and ‘not-patentable’ over WO’542 since they do not show any inventive merit of such composition over the WO’542.
III. THAT CLAIMS OF THE PRESENT APPLICATION DO NOT SATISFY THE TEST OF SECTION 3(d) AND SECTION 3(e) AND THEREFORE ARE OBJECTED TO UNDER SECTION 25(1)(f)

79. Section 25(1)(f) of the Patents Act allows opposition to grant of patent on the ground of the claimed invention not being an invention within the meaning of the Patents Act, 1970. Section 25(1)(f) reads as follows:

“(1) Where an application for a patent has been published but a patent has not been granted, any person may, in writing, represent by way of opposition to the Controller against the grant of patent on the ground

.. (f) that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act.”

Claims of Present Application not an invention under Section 3(d)

80. Without prejudice to other grounds raised herein, the Opponent raises objection under Section 25(1)(f) as the claims of the Present Application fail under Section 3(d).

81. Section 3(d) of the Patents Act does not consider certain modifications of known substances as an invention, hence rendering them as subject matter that cannot be patented. It is an established position of law that S. 3(d) has to be satisfied independent of Section 2(1)(j) and S. 2(1)(ja) [see Novartis AG versus Union of India and Others (2013) 6 SCC 1]. The burden of showing enhanced (therapeutic) efficacy of modified known substance, under S. 3(d) is on the Applicant. Further, such data has to be provided by the Applicant as laid down by the Hon’ble IPAB in Novartis AG versus Union of India, MIPR 2009 (2) 0345, para 9(xvii)).
82. The Applicant of the Present Application has failed to show how the compound claimed shows an enhanced efficacy over the known and disclosed compound in WO’347 and hence fails to meet the standard laid down under Section 3(d). Hence, the claims of the present application are liable to be rejected under Section 3(d).

83. It is submitted that the Present Application does not provide any data on comparative or enhanced efficacy between the compounds disclosed in the prior art and the compound claimed in claim 1 of the present application or compound of Claim 9 bearing the formula: 5-{{[3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one

(see complete specification of the Present Application at internal page 504, lines 24-25)

Or with compound claimed in Claim 10 of the Present application bearing formula:

5-{{[3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;

(see complete specification of the Present Application at internal page 507 at lines 10-11)

Or with compound claimed in claim 17 of the Present Application that claims 5-{{[3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one, or a salt thereof;

Or with compound claimed in claim 18 of the Present Application that claims:
5-{{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy}-8-fluoro-3,4-dihydroquinolin-2(1H)-one;

(see complete specification of the Present Application at internal page 509 at claims 17 and 18)

Or with the composition claimed in claims 20 and 21 of the Present Application.

84. Further, it is submitted that the Applicant has not even compared the efficacy of the compounds of the Present Application, with the known compounds of the Applicant that have been previously claimed and disclosed to have similar properties in WO ’347.

85. Hence, compound of claims 1-10, 17-18 and 20-21 have not been shown to have any enhanced therapeutic efficacy as required under Section 3(d) and should be rejected for as they do not qualify as an invention under the Patents Act.

Claims of Present Application not an invention under Section 3(e)

86. Without prejudice to other grounds raised herein, the Opponent raises objection under Section 25(1)(f) as the claims 21 and 22 of the Present Application fail under Section 3(e).

87. An applicant claiming a combination of compounds is required to show and enhanced additive effect or synergism in the complete specification itself. It is a settled principle that, “The question of efficacy and or synergism are matters of scientific facts which are required to be embodied in the specification so that the said characteristics are apparent from the specification.” (See order of the Asst. Controller of Patents & Designs in patent application no. 314/MUM/2008, at lines 3-5 at internal page 7 annexed herewith as Exhibit-K).
88. It is submitted that claims 21 and 22 of the Present Application are mere admixtures resulting in mere aggregation of properties. The Present Application nowhere produces any data or explanation on how the combinations claimed in claims 21 and 22 show any synergistic effect. The Present Application does not even provide the weight of each of the components of the composition claimed in the said claims.

89. The Present Application also does not provide preferred combination of compound of any of the claims from 1-20, or any preferred excipients or carriers – in claims 21 and 22.

90. Given the Present Application does not indicate any data how the compounds of claims show any synergistic effect, or even explain the nature of the compound claimed therein, claims 21 and 22 fail the test of Section 3(e) and should be rejected for not being an invention.

IV. THAT CLAIMS OF THE PRESENT APPLICATION MUST BE REJECTED AS THE COMPLETE SPECIFICATION DOES NOT SUFFICIENTLY AND CLEARLY DESCRIBE THE INVENTION

91. Without prejudice to the grounds raised in this representation, the Opponent invokes Section 25(1) (g). It is submitted that the Present Application does not sufficiently and clearly describe the invention claimed.

92. The disclosed compound in the form of a markush claim in claim 1 (Markush) potentially covers millions of compounds, with very limited number of them exemplified in the complete specification of the Present Application.

93. While only a limited number of the compounds have been exemplified in the complete specification of the Present Application, claim 1 covers a broad range
of compounds that have not been exemplified or identified, leading to vague and broad reach of claim 1.

94. The complete specification of the Present Application also does not disclose any specific clinical data for the entire spectrum of compounds of claim 1-10 and 17-18. Particularly, there is no data disclosed regarding the therapeutic efficacy of the compound 5-\{[(3R,4R)-1-(4-chloro-2,6-difluorophenyl)-3,4-dihydroxypiperidin-4-yl]methoxy\}-8-fluoro-3,4-dihydroquinolin-2(1H)-one, there is no clinical data or IC$_{50}$.

95. Similarly, the complete specification does not discuss the advantages of using the compounds of claims 1-20 in a combination, the advantages of doing so or the synergistic effect of using the compounds of claims 1-20 with other excipients.

96. In absence of identifying why certain compounds have been claimed over others, and in absence of any data indicating their efficacy or their synergistic effect when in combination, the complete specification fails to fully and particularly describe the invention as required under Section 10 of the Patents Act. The claims 1-10, 17-18, 21-22 must therefore be rejected.

**PRAYER**

In view of the above said references Opponent prays as follows:

a) To be granted hearing and be allowed to lead evidence (documentary and oral) before any order is passed;

b) To reject the claims 1-10, 17, 18, 21 and 22 of Application No. 201737004817;
c) To allow the Opponent to file further documents as evidence if necessary to support the averments;

d) To allow amendment of the Opposition as and when the need may arise;

e) To allow the Opponent to make further submissions in case the Applicant amends the claims;

f) For costs in this matter;


g) For any further and other relief in the facts and circumstances that may be granted in favour of the Opponent in the interest of justice.

Dated this the 3rd day of July 2020

PRIYAM LIZMARY CHERIAN
[COUNSEL FOR THE OPPONENT]

To
The Controller,
The Patent Office Branch
KOLKATA
THE PATENTS ACT, 1970
(AMENDED BY THE PATENTS ACT 2005)
AND
THE PATENTS RULES, 2003
(AMENDED BY THE PATENTS RULES 2006)

In the matter of Patent
No. 276026 (Application
No. 3951/DELNP/2009)

AND

In the matter of a notice of opposition
under Section 25(2) of the Patents Act
1970 as amended by the Patents
(Amendment) Act 2005

NOVARTIS AG ................................................................. PATENTE

VS.

Natco Pharma Ltd. ......................................................... OPPONENT

Hearing held on 9TH April 2019

Present:

Applicant
1) Mr. Sanjeev Kumar Tiwari
2) Mr. Amrish Tiwari
3) Dr. Jyoti C. Ramani
4) Mr. Peter Rode
5) Mr. Atul Bede
Opponent
1) Ms Rajeshwari H
2) Ms Sweety Sharma
3) Deepika Dhar
4) Shyam Gupta

Examiners
1) Ms Vishakha Gupta
2) Mr Kartikey Yadav
3) Mr Manoj Kumar

ORDER

1) A Patent numbered 276026 was granted to Novartis AG on their Application No. 3951/DELNP/2009. Natco Pharma Limited filed notice of opposition on Form-7 to oppose the said patent on September 26, 2017 along with written statement and evidences under Rule 57 of the Patents Rules 2003. Thereafter, the copy of notice of opposition along with statement and evidences was sent to the Patentee by the Opponent under Rule 57. The Patentee filed reply statement and evidence under Rule 58(1).

2) On completion of the presentation of evidence and on receiving the recommendation of the opposition board under Section 25(4) of the Act, a hearing under Rule 62(1) was fixed on April 9, 2019. Opponent’s agent has submitted written submissions pursuant to hearing on April 25, 2019. Applicant’s agent also submitted written arguments on May 24, 2019.

3) The Agent for the Opponent submitted additional submissions on 7th May 2019. Thereafter, Patentee filed a document on 9th July 2019. The Patentee and the Opponent are regularly filing further evidences after the completion of hearing and written submissions. Since Opponent and Patentee were instructed not to file further evidences after filing written submissions, therefore, further evidences submitted by Opponent and Patentee are not taken into record.

4) In Notice of opposition filed via Form 7 u/s 25(2) of the Patents Act, 1970 and u/r 55A and 57 of the Patents Rules, 2003 (as amended in 2016) on 26/09/2017, following grounds of opposition were raised:
   i. Section 25(2)(b)/(c): Lack of novelty and prior claiming;
   ii. Section 25(2)(e): Lack of inventive step;
   iii. Section 25(2)(f): Subject of claims 1 to 7 are not an invention within the meaning of this Act or is not patentable under this Act;
   iv. Section 25(2)g: The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed;
   v. Section 25(2)h:
   vi. The Applicant has failed to disclose to the Controller the information required under Section 8.
5) In the following paragraphs, I wish to analyze the relevant grounds which the Opponent has raised:

i) Lack Of Novelty

**IN 232653 (2241/CHENP/2005)**

If the compounds claimed in IN276026 (3951/DELNP/2009) and IN 232653 (2241/CHENP/2005) are compared then both Patents disclose substituted pyrimidine compounds.

![Chemical Structures](image)

The structure I is a structure claimed in claim-1 of impugned Patent IN276026 (3951/DELNP/2009). This structure I is the representative of the compounds claimed in IN276026 (3951/DELNP/2009). The structure II is the representative of the compounds claimed in IN232653 (2241/CHENP/2005). The structure I and II are structurally same only the presentation on paper is different. The tri substituted phenyl moiety attached to -NH is horizontally placed in structure II whereas it is vertically placed in structure I.

In Structure I R^4 is Hydrogen and n is 0 or 1 which means R^4 is hydrogen when n=0 While in structure II R^0 R^1 and R^2 are also hydrogen.

In Structure I R^3 is (CR_2)_{n-1}SO_2R^{12} means it includes only SO_2 R^{12} when (CR_2) is 0 while R^{12} is C1-C6 alkyl. Whereas in structure II R^3 also discloses C1-C8 alkyl (includes C1-C6 alkyl), sulphonyl which is equivalent to SO_2 R^{12}

In Structure I linking nitrogen (N) between the rings is attached with hydrogen (H) while in Structure II nitrogen is attached to R^4 wherein R^4 is disclosed as hydrogen.

In Structure I R^1 & R^2 is equivalent to R^5 and R^6 of structure II.
In Structure I $R^1$ is halo or $C_{1-6}$ alkyl; $R^2$ is H; in Structure II each of $R^5$ and $R^6$ is independently hydrogen, $C_{1-8}$ alkyl (which includes $C_{1-6}$ alkyl) or halogen.

In Structure I, tri substituted phenyl moiety is substituted by $R^6$, $R^9$ and $R^8$ which is equivalent to $R^{10}$, $R^7$ and $R^8$ respectively of structure II.
In Structure I $R^9$ is isopropoxy or methoxy; in Structure II $R^{10}$ is $C_{1-8}$alkoxy (which includes isopropoxy or methoxy).

In Structure I $R^9$ is $C_{1-6}$ alkyl, cyano, CONR($R^{12}$) ; $R^{12}$ is H or $C_{1-6}$ alkyl. In Structure II $R^7$ is $C_{1-8}$alkyl or cyano. For e.g. $R^7$ in Structure I and $R^7$ in Structure II are methyl group.

In Structure I $R^8$ is $(CR_2)_qY$ wherein $q=0$ which means $R^8$ is Y and is directly attached to C atom of the ring; Y is pyrrolidinyl, piperidinyl or azetidinyl, each of which is attached to the phenyl ring via a carbon atom.

In Structure II $R^8$ is unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1,2, or 3 hetero atoms selected from N, O and S( which includes pyrrolidinyl, piperidinyl or azetidinyl ). Thus, these heterocycles are also attached to ring through C atom.

In Structure II if $R^9$ is hydrogen and A is equal to carbon then Structure II is equivalent to structure I with respect to the position 3 in phenyl ring (in between $R^6$ and $R^8$ of structure I).

Therefore, Structure I is narrower Markush structure of Structure II

**IN240560 (553/CHENP/2006)**

---

<table>
<thead>
<tr>
<th>IN 276026</th>
<th>IN240560 (Prior art)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claim 1 of US'026</td>
<td>Claim 1 markush structure discloses ceritinib.</td>
</tr>
<tr>
<td><img src="image1.png" alt="" /></td>
<td><img src="image2.png" alt="" /></td>
</tr>
<tr>
<td>5-cloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-[2-(propane-2-sulfonyl)phenyl]pyrimidine-2,4-diamine</td>
<td>R1'= phenyl substituted by 3 radicals; Methyl, isopropyloxy, and piperidiny; R2'= halo R3'=-S(O)<em>{2-5}R6, and R'6 is selected $C</em>{1-6}$alkyl</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>Ceritinib</td>
</tr>
</tbody>
</table>
The substituents R1'R2'R3'R6 as defined in IN240560 when substituted in Markush structure given in claim 1 of IN240560 results in the structure given in claim 4 of IN276026 (impugned Patent) as shown below:-

Therefore, conclusively it can be said that impugned Patent IN276026 (3951/DELNP/2009) lacks novelty with respect to IN232653 (2241/CHENP/2005) and IN240560 (553/CHENP/2006).

Since IN232653 (2241/CHENP/2005) and IN240560 (553/CHENP/2006) was published by WIPO on 23/09/2004 and 24/02/2005 respectively. The priority date of the impugned Patent IN276026 (3951/DELNP/2009) was 08/12/2006; therefore, it lacked novelty on the date of filing of first convention application filed in USA i.e. 08 Dec 2006.

ii) Lack of Inventive Step

The novelty aspect of the impugned Patent IN276026 (3951/DELNP/2009) with respect to IN232653 (2241/CHENP/2005) and IN240560 (553/CHENP/2006) has been discussed in detail earlier, therefore, for the sake of brevity I am of the opinion that the impugned Patent IN276026 lacks inventive step also. Similarly impugned Patent IN276026 (3951/DELNP/2009) lacks inventive step with respect to WO2001/64654 also.

Considering above reasons subject matter of granted claims does not constitute an invention under section 2(1)(j) of the Patents Act 1970, therefore, I allow ground raised by the opponent under Section 25(2)(b) of the Patents Act 1970.
iii) Section 25(2)(f): Subject of claims are not an invention within the meaning of this Act or is not patentable under this Act

Section 3(d) in The Patents Act, 1970 states that

(d) the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant. Explanation. -For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy;

Since the compounds lack novelty and inventiveness, therefore, the subject matter of claims is not patentable under Section 3(d) of The Patent Act, 1970. The Patentee has not provided any in vivo efficacy data in comparison to compounds disclosed in IN232653 (2241/CHENP/2005) and IN240560 (553/CHENP/2006). Interestingly, it has been noted that the applicant of the impugned Patent and both the prior art documents is same i.e. Novartis AG.

Considering above reasons, I allow ground under Section 25(2)(f) of the Patents Act 1970 raised by the opponent.

6. During Hearing the Opponent has submitted an important document (seeking extension of Patent term in USA by Patentee) which has brought into light the relationship of the impugned Patent 276026 (corresponding US patent no. 8377921) with cited documents IN 232653 (corresponding US patent no. 7964592); IN240560 (corresponding US patent no. 7893074) and WO2001/64654 (corresponding US patent no. 7153964). Since, this document was very important and relevant in deciding the case before me, therefore, document was taken into record and a copy was given to Patentee to rebut the objection raised by opposition. The Patentee was given additional time (written submission filed on 24.05.2019) to file the rebuttal regarding this disclosure of Orange Book where the details of extension was filed, but Patentee failed to give any reasonable and convincing argument.

7. As decided in the preceding grounds of opposition, granted claims are already in public domain before priority date of the granted claims. Therefore these claims are not new and have no inventive step.

Considering above reasons subject matter of granted claims does not constitute an invention under section 2(1) (j) of the Patents Act 1970.

The Opponent has succeeded in the grounds under sections 25(2) (b), 25(2) (e) and 25(2) (f) of the Patents Act, 1970. I do not agree with the recommendations of the opposition Board. Having considered all the relevant documents and pleadings of both
the parties, and in view of my findings above, as per Section 25(4) of the Patents Act 1970. I hereby revoke the Patent numbered 276026 granted on the Patent Application No. 3951/DELNP/2009. There is no order as to the costs.

Dated:  16.08.2019

Dr. Kavita Taunk

(Deputy Controller of Patents and Designs)

Copy to:-
1. RAJESHWARI & ASSOCIATES Trademark & patent attorneys, AMSOFT Business Centre Unitech Trade Centre, Sector 43, Gurgaon- 122 002, Haryana, India; (rajeshwari@ralegal.co.in) (Opponent)
2. Sanjeev K. Tiwari & Amrish Tiwari [K & S Partners], 109, Sector 44, Gurgaon - 122 003, National Capital Region, India (sanjeev.tiwari@knspartners.com; amrish@knspartners.com) (Patentee)
HETEROCYCLIC GPCR AGONISTS

(57) Abstract. Compounds of formula (I) or pharmaceutically acceptable salts thereof, are GPCR (GPR119) agonists and are useful as for the treatment of diabetes and obesity.

WO 2010/004347 A1

[Continued on next page]
HETEROCYCLIC GPCR AGONISTS

BACKGROUND OF THE INVENTION

The present invention is directed to G-protein coupled receptor (GPCR) agonists. In particular, the present invention is directed to agonists of GPR119 that are useful for the treatment of obesity, e.g. as regulators of satiety, metabolic syndrome and for the treatment of diabetes.

Obesity is characterized by an excessive adipose tissue mass relative to body size. Clinically, body fat mass is estimated by the body mass index (BMI; weight/(kg)/height(m)²), or waist circumference. Individuals are considered obese when the BMI is greater than 30 and there are established medical consequences of being overweight. It has been an accepted medical view for some time that an increased body weight, especially as a result of abdominal body fat, is associated with an increased risk for diabetes, hypertension, heart disease, and numerous other health complications, such as arthritis, stroke, gallbladder disease, muscular and respiratory problems, back pain and even certain cancers.

Pharmacological approaches to the treatment of obesity have been mainly concerned with reducing fat mass by altering the balance between energy intake and expenditure. Many studies have clearly established the link between adiposity and the brain circuitry involved in the regulation of energy homeostasis. Direct and indirect evidence suggest that serotonergic, dopaminergic, adrenergic, cholinergic, endocannabinoid, opioid, and histaminergic pathways in addition to many neuropeptide pathways (e.g. neuropeptide Y and melanocortins) are implicated in the central control of energy intake and expenditure. Hypothalamic centres are also able to sense peripheral hormones involved in the maintenance of body weight and degree of adiposity, such as insulin and leptin, and fat tissue derived peptides.

Drugs aimed at the pathophysiology associated with insulin dependent Type I diabetes and non-insulin dependent Type II diabetes have many potential side effects and do not adequately address the dyslipidaemia and hyperglycaemia in a high proportion of patients. Treatment is often focused at individual patient needs using diet, exercise, hypoglycaemic agents and insulin, but there is a continuing need for novel antidiabetic agents, particularly ones that may be better tolerated with fewer adverse effects.

Similarly, metabolic syndrome (syndrome X) places people at high risk of coronary artery disease, and is characterized by a cluster of risk factors including central obesity (excessive fat tissue in the abdominal region), glucose intolerance, high triglycerides and low HDL cholesterol, and high blood pressure. Myocardial ischemia and microvascular disease is an established morbidity associated with untreated or poorly controlled metabolic syndrome.

There is a continuing need for novel antiobesity and antidiabetic agents, particularly ones that are well tolerated with few adverse effects.

GPR119 (previously referred to as GPR116) is a GPCR identified as SNORF25 in WO00/50562 which discloses both the human and rat receptors. US 6,468,756 also discloses the mouse receptor (accession numbers: AAN95194 (human), AAN95195 (rat) and AN95196 (mouse)).

In humans, GPR119 is expressed in the pancreas, small intestine, colon and adipose tissue. The expression profile of the human GPR119 receptor indicates its potential utility as a target for the treatment of obesity and diabetes.

The present invention relates to agonists of GPR119 which are useful for the treatment of diabetes and as peripheral regulators of satiety, e.g. for the treatment of obesity and metabolic syndrome.

SUMMARY OF THE INVENTION

Compounds of formula (I):

\[
\begin{array}{c}
Z-W-X-Y-CR^x \\
| \\
| \\
(\text{CH}_2)_n \\
| \\
(\text{CH}_2)_m \\
\end{array}
\]

(II)

or pharmaceutically acceptable salts thereof, are agonists of GPR119 and are useful for the prophylactic or therapeutic treatment of diabetes and obesity.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof:

\[
\begin{array}{c}
Z-W-X-Y-CR^x \\
| \\
| \\
(\text{CH}_2)_n \\
| \\
(\text{CH}_2)_m \\
\end{array}
\]

(II)

wherein Z is phenyl or a 6-membered N containing heteroaryl group which phenyl or heteroaryl group is substituted by -(CH\(_2\))\(_n\)-C(O)NR\(^{1+}\), -(CH\(_2\))\(_n\)-CO\(_2\)H, -(CH\(_2\))\(_n\)-CH(CH\(_3\))C(O)NR\(^{1+}\), a 5- or 6-membered N containing heterocyclyl ring, which ring is substituted with oxo and optionally substituted by methyl, or a 5- or 6-membered N containing heteroaryl ring optionally containing up to 3 additional heteroatoms selected from N, O and S, which ring is substituted by C\(_{1-3}\) alkyl or -NH\(_2\);

or Z is 1H-quinazoline-4-one, 2,3-dihydroisoindol-1-one, 1,3-dihydroindol-2-one, 3,4-dihydro-1H-quinolin-2-one, or 3,4-dihydro-2H-isoquinolin-1-one, which is attached to W through an aromatic carbon atom;

and wherein Z is further optionally substituted by one or more C\(_{1-2}\) alkyl, C\(_{1-2}\) alkoxy, CH\(_3\)NH\(_2\), or fluoro groups;

j is 0, 1 or 2;

E\(^1\) is -CH\(_2\)-, -CH\(_2\)CH\(_2\)-, or -CH(CH\(_3\))-

W and Y are independently a bond, an unbranched or a branched C\(_{1-4}\) alkylene optionally substituted by hydroxy or C\(_{1-3}\) alkoxy, or an unbranched or a branched C\(_{2-4}\) alkenylene;
X is selected from CH$_2$, O, S, CH(OH), CH(halogen), CF$_2$, C(O), C(O)O, C(O)S, SC(O), C(O)CH$_2$, C(O)CH$_2$(OH), C(OH)CH$_2$(C), C(O)CH$_2$C(O), OC(O), NC(O), NC(O)R$^2$, C(O)NR$^2$, NR$^2$ C(O), S(O) and S(O)$_2$; 

R$^2$ is hydrogen or hydroxy; 

G is CH$_3$, N-C(O)OR$^2$, N-C(O)NR$^2$R$^5$, N-C$_{14}$alkylene-C(O)OR$^2$, N-C$_{14}$alkylene-C(O)NR$^2$R$^5$, N-C$_{14}$alkylene-C(O)OR$^2$, C$_{14}$alkylene-C(O)NR$^2$R$^5$, or N-$\text{heteroaryl}$ or N-$\text{heteroaryl}$, either of which may optionally be substituted by one or two groups selected from C$_{14}$alkyl, C$_{14}$alkoxy or halogen; provided that G is not optionally substituted N-pyridazinyl; 

R$^4$ and R$^{11}$ together with the N atom to which they are attached form a 4- to 6-membered ring substituted by -N(R$^3$)$_2$ or -CH$_2$NH$_2$ and optionally further substituted with methyl; or R$^4$ is hydrogen and R$^{11}$ is C$_{5-6}$ alkyl substituted by amino or -(CH$_2$)$_k$-L; 

in addition, when Z is -CH(CH$_3$)C(O)NR$^2$R$^{11}$, R$^1$ may be hydrogen and R$^{11}$ may be hydrogen, C$_{1-3}$alkyl, or C$_{2-3}$alkyl substituted by one or two hydroxy groups; 

L is a $\neq$ or $\delta$ lactam optionally substituted with methyl; 

k is 0, 1 or 2; 

R$^2$ are independently hydrogen or C$_{1-4}$alkyl; 

R$^3$ is C$_{2-6}$alkyl; 

R$^4$ is C$_{1-4}$alkyl, C$_{2-6}$alkenyl or C$_{2-8}$alkynyl, any of which may be optionally substituted by one or more substituents selected from halo, NR$^2$R$^{15}$, OR$^2$, C(O)OR$^2$, OC(O)R$^2$ and CN, and may contain a CH$_2$ group that is replaced by O or S; or a C$_{5-7}$cycloalkyl, ary1, heteroaryl, C$_{1-4}$alkyleneC$_{3-7}$cycloalkyl, C$_{1-4}$alkylenearyl, C$_{1-4}$alkyleneheteroaryl, C$_{1-4}$alkyleneheteroaryl, any of which may be substituted with one or more substituents selected from halo, C$_{1-4}$alkyl, C$_{1-4}$fluoroalkyl, OR$^2$, CN, NR$^2$R$^{15}$, SO$_2$Me, NO$_2$ and C(O)OR$^2$; 

R$^5$ and R$^{15}$ are independently hydrogen or C$_{1-4}$alkyl; or taken together R$^5$ and R$^{15}$ may form a 5- or 6-membered heterocyclic ring; or a group NR$^2$ may represent NS(O)$_2$-(2-NO$_2$-C$_4$H$_4$); 

d is 0, 1, 2 or 3; and 

e is 1, 2, 3, 4 or 5, provided that d + e is 2, 3, 4 or 5. 

The molecular weight of the compounds of formula (I) is preferably less than 800, more preferably less than 600, even more preferably less than 500. 

Preferably Z is phenyl or a 6-membered heteroaryl group containing up to two N heteroatoms e.g. pyridyl such as 2-pyridyl. Even more preferably Z is phenyl. 

Examples of heteroaryl rings that Z may be substituted by include tetrazolyl, e.g. tetrazol-1-yl, oxadiazolyl, e.g. [1,2,4]oxadiazol-5-yl or [1,3,4]oxadiazol-2-yl, thiazolyl, e.g. thiazol-2-yl and pyridyl, e.g. pyrid-2-yl, which rings are substituted by C$_{1-4}$alkyl or -NH$_2$. 

Preferred substituents for Z are -(CH$_2$)$_k$-C(O)NR$^2$R$^{11}$ and -E$^1$-CO$_2$H. 

Suitably, j is 0 or 1. In one embodiment of the invention j represents 0. In a second embodiment of the invention j represents 1. Preferably, j is 0. 

E$^1$ is preferably $\text{-CH}_2\text{-}$. 

Suitably W and Y are independently a bond, an unbranched or a branched C$_{1-4}$alkylene optionally substituted by hydroxy, or an unbranched or a branched C$_{1-4}$alkylene. 

In one embodiment of the invention W and Y are independently a bond, an unbranched or a branched C$_{1-4}$alkylene, or an unbranched or a branched C$_{2-4}$alkylene. 

Preferably W and Y do not both represent a bond.
Preferably W is a bond.
Preferably Y is an unbranched or a branched C₃₋₄ alkyne optionally substituted by hydroxy or C₁₋₃ alkoxy, e.g. an unsubstituted unbranched or a branched C₃₋₄ alkyne.

In certain embodiments of the invention -W-X-Y- preferably represents a chain of 2 to 6 atoms in length. -W-X-Y- preferably represents a 4 to 5 atom chain.

When W is C₂₋₃ alkenylene, the stereochemistry at the double bond is preferably (E).
Suitably, X is selected from CH₂, O, S, CH(OH), CH(halogen), CF₂, C(O), C(O)O, C(O)S, SC(O), C(O)CH₂S, C(O)CH₂(C(OH), C(O)CH₂C(O), OC(O), NR², CH(R³NR²)², C(O)NR², S(O) and S(O)₂. More suitably X is selected from CH₂, O, S, CH(OH), CH(halogen), C(O), C(O)O, C(O)S, SC(O), C(O)CH₂S, C(O)CH₂C(OH), C(O)CH₂C(O), OC(O), NR², CH(R³NR²)², C(O)NR², S(O) and S(O)₂.

X is preferably CH₂, CF₂, O or NR² e.g. NH, in particular CH₂, O or NR², especially O.

A preferred group represented by -W-X-Y- is -O-CH₂-CH₂-CR³₂-, where R³ is hydrogen or methyl.

R² is preferably hydrogen.

G is preferably N-C(O)OR², N-C(O)NR²R³, N-C₁₋₃alkylene-C(O)OR², N-C(O)C(O)OR², N-heterocyclyl, N-heteroaryl, N-S(O)₂R³, N-C(O)R³ or N-P(O)(O-Ph)₂; especially N-C(O)OR², N-C(O)NR²R³, N-C₁₋₃alkylene-C(O)OR², N-heterocyclyl, N-S(O)₂R³ or N-C(O)R³; in particular N-C(O)OR², N-C(O)NR²R³, N-heteroaryl, N-S(O)₂R³ or N-C(O)R³. More preferably, G is N-C(O)OR² or N-heteroaryl. G is most preferably N-heteroaryl. When G is N-heteroaryl the heteroaryl ring is preferably a 5- or 6-membered heteroaryl ring containing up to three heteroatoms selected from O, N and S, for example pyridin-2-yl, oxadiazolyl, or pyrimidinyl, especially oxadiazolyl or pyrimidin-2-yl. Particularly preferred heteroaryl rings which G may represent are 3-C₅₋₄ alkyl-[1,2,4]oxadiazol-5-yl, especially 3-isopropyl-[1,2,4]oxadiazol-5-yl and 5-chloropyrimidin-2-yl. Alternatively, G is CHR³.

Suitably R² is hydrogen, methyl or tert-butyl, preferably hydrogen or methyl, more preferably hydrogen.

Exemplary R² groups include n-pentyl.

Exemplary R⁴ groups include methyl, ethyl, propyl, iso-propyl, sec-butyl, tert-butyl, butynyl, cyclobutyl, pentyl, 2,2-dimethylpropyl, cyclopentyl, hexyl, cyclohexyl, trifluoroethyl, trichloroethyl, phenyl, methoxyphenyl, tolyl, fluoro phenyl, chlorophenyl, trifluoromethyl phenyl, nitrophenyl, naphthalenyl, chlorobenzyl, methylsulfanylethyl- and tetrahydrofuran methyl-. Preferably R⁴ represents C₁₋₅ alkyl, C₂₋₅ alkenyl or C₂₋₈ alkynyl optionally substituted by one or more halo atoms or cyan, and may contain a CH₂ group that is replaced by O or S; or a C₃₋₇ cycloalkyl, aryl or C₁₋₅ alkyl[C₃₋₇ cycloalkyl, any of which may be substituted with one or more substituents selected from halo, C₁₋₅ alkyl, C₁₋₄ fluoroalkyl, OR², CN, NR²R³, NO₂ and C(O)OC₁₋₅ alkyl. More preferably R⁴ represents C₁₋₅ alkyl, C₂₋₅ alkenyl or C₂₋₅ alkynyl optionally substituted by one or more halo atoms or CN, and may contain a CH₂ group that is replaced by O or S; or a C₃₋₇ cycloalkyl or aryl, either of which may be substituted with one or more substituents selected from halo, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, OR², CN, NR²R³, NO₂ and C(O)OC₁₋₅ alkyl. Most preferred R⁴ groups are C₂₋₅ alkyl, e.g. C₃₋₅ alkyl and especially isopropyl or tert-butyl, optionally substituted by one or more halo or CN groups, and which may contain a CH₂ group that is replaced by O or S, or C₃₋₅ cycloalkyl optionally substituted by C₁₋₄ alkyl.
In one embodiment of the invention d + e is 2, 3, or 4. Suitably, d is 1 or 2 and e is 1 or 2. In a preferred embodiment of the invention d and e each represent 1. In a more preferred embodiment of the invention d and e each represent 2.

Suitably R's and R's are independently hydrogen or Calkyl; or taken together R's and R's may form a 5- or 6-membered heterocyclic ring; in particular R's represents hydrogen or methyl, especially methyl.

A preferred group of compounds of are those of formula (Ia) and pharmaceutically acceptable salts thereof:

![Chemical Structure](image)

(Ia)

wherein:
Z is as described previously for compounds of formula (I);
R is hydrogen or methyl;
R is -C(O)OR or a 5- or 6-membered heteroaryl group optionally substituted by one or two groups selected from Calkyl, Calkoxy or halogen; and
R is Calkyl.

In one embodiment of the compounds of formula (Ia) R is hydrogen and in another R is methyl. When R is methyl, the stereocentre created preferably has the (R)-configuration.

A group of compounds which may be mentioned are those of formula (Ib) and pharmaceutically acceptable salts thereof:

![Chemical Structure](image)

(Ib)

wherein Z is phenyl or a 6-membered N containing heteroaryl group which is substituted by -(CH)C(O)NR or a 5- or 6-membered N containing heteroaryl ring optionally containing up to 3 additional heteroatoms selected from N, O and S, which ring is substituted by Calkyl or -NH; and wherein Z is further optionally substituted by one or more Calkyl, Calkoxy or fluoro groups;

j is 0, 1 or 2;
W and Y are independently a bond, an unbranched or a branched Calkylene optionally substituted by hydroxy or Calkoxy, or an unbranched or a branched Calkylene;
X is selected from CH, O, S, CH(OH), CH(halogen), CF, C(O), C(O)O, C(O)S, SC(O), C(O)CH, C(O)CH(OH), C(O)CH=C(O), C(O)CH=C(O), C(O)CH=C(O), OC(O), NR, CH(NR)R, C(O)NR, NR C(O), S(O) and S(O)2;
R is hydrogen or hydroxy;
G is CHR, N=C(O)OR, N=C(O)NR R, N=Calkylene-C(O)OR, N=C(C)O(OH)2, N=Calkyl or N-heteroaryl, either of which may optionally be substituted by one or two groups selected from Calkyl, Calkoxy or halogen; provided that G is not optionally substituted N-pyridazinyl;
R¹ and R¹¹ together with the N atom to which they are attached form a 4- to 6-membered ring substituted by -NH₂ or -CH₂NH₂;
R² are independently hydrogen or C₁₄ alkyl;
R³ is C₂₄ alkyl;
R⁴ is C₁₄ alkyl, C₂₄ alkenyl or C₂₈ alkylnyl, any of which may be optionally substituted by one or more substituents selected from halo, NR⁵R⁵⁺, OR⁵, COOR⁵, OC(O)R⁵ and CN, and may contain a CH₂ group that is replaced by O or S; or a C₅ cycloalkyl, ary1, heterocyc1, heteroaryl, C₄ alkylene-C₅ cycloalkyl, C₄ alkynylaryl, C₄ alkynyle heterocyc1 or C₄ alkynylheteroaryl, any of which may be substituted with one or more substituents selected from halo, C₄ alkyl, C₁₄ fluoroalkyl, OR⁵, CN, NR⁵R⁵⁺, SO₂Me, NO₂ and C(O)OR⁴;
R⁵ and R⁵⁺ are independently hydrogen or C₁₄ alkyl; or taken together R⁵ and R⁵⁺ may form a 5- or 6-membered heterocyclic ring; or a group NR² may represent NS(O)₂-(2-N O₂-C₃H₄);

d is 0, 1, 2 or 3; and
c is 1, 2, 3, 4 or 5, provided that d + c is 2, 3, 4 or 5.

While the preferred groups for each variable have generally been listed above separately for each variable, preferred compounds of this invention include those in which several or each variable in formula (I), (Ia) or (Ib) is selected from the preferred, more preferred or particularly listed groups for each variable. Therefore, this invention is intended to include all combinations of preferred, more preferred and particularly listed groups.

Specific compounds of the invention which may be mentioned are those included in the Examples and pharmaceutically acceptable salts thereof.

As used herein, unless stated otherwise, “alkyl” as well as other groups having the prefix “alk” such as, for example, alkenyl, alkynyl and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. “Alkenyl”, “alkynyl” and other like terms include carbon chains having at least one unsaturated carbon-carbon bond.

The term “fluoroalkyl” includes alkyl groups substituted by one or more fluorine atoms, e.g. CH₃F, CHF₂ and CF₃.

The term “cycloalkyl” means carbocycles containing no heteroatoms, and includes monocyclic and bicyclic saturated and partially saturated carbocycles. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Examples of partially saturated cycloalkyl groups include cyclohexene and indane. Cycloalkyl groups will typically contain 3 to 10 ring carbon atoms in total (e.g. 3 to 6, or 8 to 10).

The term “halo” includes fluorine, chlorine, bromine, and iodine atoms (in particular fluorine or chlorine).

The term “aryl” includes phenyl and naphthyl, in particular phenyl.

Unless otherwise indicated the term “heterocyc1” and “heterocyclic ring” includes 4- to 10-membered monocyclic and bicyclic saturated rings, e.g. 4- to 7-membered monocyclic saturated rings, containing up to three heteroatoms selected from N, O and S. Examples of heterocyclic rings include oxetane, tetrahydrofuran, tetrahydropyran, oxepane, oxocene, thietane, tetrahydrothiophene, tetrahydrothiopyran, thiepane, thiocane, azetidine, pyrrolidine, piperidine, azepane, azocane, [1,3]dioxane, oxazolidine, piperazine, and the like. Other
examples of heterocyclic rings include the oxidised forms of the sulfur-containing rings. Thus, tetrahydrothiophene 1-oxide, tetrahydrothiophene 1,1-dioxide, tetrahydrothiopyran 1-oxide, and tetrahydrothiopyran 1,1-dioxide are also considered to be heterocyclic rings.

Unless otherwise stated, the term “heteroaryl” includes mono- and bicyclic 5- to 10-membered, e.g. monocyclic 5- or 6-membered, heteroaryl rings containing up to 4 heteroatoms selected from N, O and S. Examples of such heteroaryl rings are furyl, thienyl, pyrrol, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyridinyl and triazinyl. Bicyclic heteroaryl groups include bicyclic heteroaromatic groups where a 5- or 6-membered heteroaryl ring is fused to a phenyl or another heteroaromatic group. Examples of such bicyclic heteroaromatic rings are benzofuran, benzothiophene, indole, benoxazole, benzothiazole, indazole, benzimidazol, benzotriazol, quinoline, isoquinoline, quinazoline, quinoxaline and purine. Preferred heteroaryl groups are monocyclic 5- or 6-membered, heteroaryl rings containing up to 4 heteroatoms selected from N, O and S.

Compounds described herein may contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above formula (I) is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of formula (I) and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

When a tautom is the compound of formula (I) exists, the present invention includes any possible tautomers and pharmaceutically acceptable salts thereof, and mixtures thereof, except where specifically drawn or stated otherwise.

When the compound of formula (I) and pharmaceutically acceptable salts thereof exist in the form of solvates or polymorphic forms, the present invention includes any possible solvates and polymorphic forms. A type of a solvent that forms the solvate is not particularly limited so long as the solvent is pharmacologically acceptable. For example, water, ethanol, propanol, acetone or the like can be used.

The term “pharmaceutically acceptable salts” refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ii and iii), ferric, ferrous, lithium, magnesium, potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include arginine, betaine, caffeine, choline, N”,N”-dibenzylethlenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol.
ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, malic, malonic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluensulfonic acid and the like.

Since the compounds of formula (I) are intended for pharmaceutical use they are preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure, especially at least 98% pure (% are on a weight for weight basis).

The compounds of formula (I) can be prepared as described below, in which Z, d, e, W, X, Y, E and G are as defined above, Ak is C_{1-3} alky1 and T is C_{1-2} alky1, C_{1-2} alkoxy or F. The Schemes are illustrated using compounds wherein R^1 is hydrogen, compounds wherein R^1 is hydroxy may be prepared using analogous methods.

Compounds of formula (I) in which X is CO_2, COS, or CONR^2 can be prepared by condensing the appropriate acid (II) with an alcohol, thiol, or amine (III), as shown in Scheme 1 where E is O, S, or NR^2, using a typical reagent for such a condensation reaction, e.g., EDCI (Pottorf, R. S.; Szeto, P. In *Handbook of Reagents for Organic Synthesis: Activating Agents and Protecting Groups*; Pearson, A. J., Roush, W. R., Eds.; Wiley: Chichester, 1999; pp 186–188). The acids (II) and alcohols, thiols, and amines (III) are either commercially available or are prepared easily using known techniques.

![Scheme 1](image)

Compounds of formula (I) in which X is SCO or OCO can be prepared by condensing the appropriate thiol or alcohol (IV) with the appropriate acid (V), as shown in Scheme 2 where E is S or O, employing a reagent typically used for effecting such reactions, e.g., EDCI (Pottorf, R. S.; Szeto, P. In *Handbook of Reagents for Organic Synthesis: Activating Agents and Protecting Groups*; Pearson, A. J., Roush, W. R., Eds.; Wiley: Chichester, 1999; pp 186–188). The alcohols and thiols (IV), as well as acids (V), are either commercially available or are prepared straightforwardly using known techniques.

![Scheme 2](image)
Compounds of formula (I) in which X is S or O can be prepared by alkylation of the appropriate thiol or alcohol (IV) with the appropriate alkyl halide or sulfonate ester (VI), as shown in Scheme 3 where E is S or O and LG is chloro, bromo, iodo, alkanesulfonate, or aranesulfonate. The reaction is typically carried out using a base, e.g., potassium tert-butoxide (Hall, S. E., et al. J. Med. Chem. 1989, 32, 974–984). The alcohols and thiols (IV), as well as the alkyl halides or sulfonates (VI), are either commercially available or are made easily using known techniques. The compounds of formula (I) where X is SO or SO₂ can easily be obtained from the compounds of formula (I) where X is S by oxidation with, for example, mCPBA (Fyfe, M. C. T. et al. International Patent Publication WO 04/72031).

![Scheme 3]

Compounds of formula (I) in which W is C₂₋₃ alkenylene can be prepared by a Wittig reaction between the appropriate phosphonium salt (VII) and the appropriate aldehyde (VIII), as indicated in Scheme 4 where m is 1 or 2 and n is 0 or 1 with the proviso that \( m + n < 3 \). As an alternative, to the approach described in Scheme 4, the compounds of formula (I) in which W is C₂₋₃ alkenylene can be prepared by a Wittig reaction between the appropriate aldehyde (IX) and the appropriate phosphonium salt (X), as indicated in Scheme 5 where q is 0 or 1 and r is 1 or 2 with the proviso that \( q + r < 3 \). The reactions are carried out in the presence of a suitable base, e.g., NaOMe or LiHMDS (March, J. Advanced Organic Chemistry. 4th edn.; Wiley: New York, 1992; pp 956–963). The phosphonium salts (VII) and (X), as well as the aldehydes (VIII) and (IX), are either commercially available or are made easily using known techniques. The compounds of formula (I) where W is C₂₋₃ alkenylene can easily be synthesized from the compounds of formula (I) where W is C₂₋₃ alkenylene by a hydrogenation reaction using, for example, palladium on charcoal as a catalyst.

![Scheme 4]

![Scheme 5]

Compounds of the formula (I) where W is a bond, X is S or O, and the group Z is unsubstituted or substituted by CN can be prepared by condensation of the appropriate heteroaryl halide (XI), where with the appropriate alcohol or thiol (III), as depicted in Scheme 6.
where \( \text{Hal} \) represents a halogen and \( E \) is \( S \) or \( O \). The reaction is carried out in the presence of a suitable basic system, e.g., potassium hydroxide and potassium carbonate in the presence of tris(3,6-dioxahexyl)amine (Ballesteros, P.; Claramunt, R. M.; Elguero, J. *Tetrahedron* 1987, 43, 2557–2564). The heteroaryl halides (XI) and alcohols/thiols (III) are either commercially available or are made easily using known techniques.

![Scheme 6](image)

Compounds of the formula (I) where \( G \) is \( N\text{C(O)OR}^1 \), \( N\text{C(O)NR}^2 R^2 \), \( N\text{C(O)R} \), or \( N\text{C(O)O}R^1 \) can be prepared by the route shown in Scheme 7, where an amine of formula (XII) is condensed with an acyl chloride of formula (XIII) where \( A \) is \( O \), \( NR^2 \), a bond, or \( \text{CO} \). The reaction is carried out in the presence of a suitable base, such as triethylamine (Picard, P., et al. *J. Med. Chem.* 2002, 45, 3406–3417). Compounds of the formula (I) where \( G \) is \( N\text{CONR}^2 R^2 \) and \( R^3 \) is hydrogen may also be prepared by reacting the amine (XII) with a suitable isocyanate \( \text{R} = C = \text{N} - R^2 \) (Boswell, R. E., Jr., et al. *J. Med. Chem.* 1974, 17, 1000–1008). Compounds of the formula (I) where \( G \) is \( N\text{C} = \text{Calkylene} - \text{C(O)OR} \) may be prepared by acylating the amine (XII) with the appropriate \( \alpha \)-haloester (Rooney, C. S., et al. *J. Med Chem.* 1983, 26, 700–714). The amine (XII) is generally derived from its \( N\text{-tert-butoxycarbonyl} \) precursor (prepared by one of the routes outlined in Schemes 1–6) by deprotection with an acid, e.g., trifluoroacetic acid (Fyfe, M. C. T., et al. *International Patent Publication* WO 04/72031).

![Scheme 7](image)


![Scheme 8](image)

Compounds of the formula (I) where where the group \( Z \) is substituted by \( \text{CN} \) can be prepared from the corresponding unsubstituted \( Z \) group by the Reissert reaction (Fyfe, W. K. J. *Org. Chem.* 1983, 48, 1375–1377). Similar reactions can be used to prepare the compounds.
where Z is substituted by halogen (Walters, M. A.; Shay, J. J. Tetrahedron Lett. 1995, 36, 7575-7578). The compounds where Z is substituted by halogen can be transformed into the corresponding compounds where Z is substituted by C\textsubscript{1-4} alkyl by transition metal-catalysed cross-coupling reactions (Fürstner, A., et al. J. Am. Chem. Soc. 2002, 124, 13856-13863).

Compounds of formula (I) where Z is phenyl substituted by a 1,2,4-oxadiazole or 1,3,4-oxadiazole which is optionally substituted by C\textsubscript{1-3} alkyl, and W is a bond and X is O, can be prepared as outlined in Scheme 9. Compounds of formula (XVII) can be prepared by reaction of compounds of formula (XV) with compounds of formula (XVI) under standard conditions, for example Mitsunobu conditions. Compounds of formula (I) where Z is phenyl substituted by a 1,2,4-oxadiazole which is optionally substituted by C\textsubscript{1-3} alkyl can be prepared from compounds of formula (XVII) by reaction with amidoximes of formula (XVIII) (which are either commercially available, or readily prepared from the corresponding carboxylic acids using well known techniques) under standard conditions. Compounds of formula (I) where Z is phenyl substituted by a 1,3,4-oxadiazole, which is optionally substituted by C\textsubscript{1-3} alkyl, can be prepared from compounds of formula (XVII) by initial reaction with hydrazine to form the corresponding hydrazide, under standard conditions, followed by reaction with an anhydride of formula (XIX), under standard conditions.

![Scheme 9](image)

Compounds of formula (I) where Z is phenyl substituted by -(CH\textsubscript{2})\textsubscript{j}C(O)NR\textsubscript{1}R\textsubscript{11}, as described above and where j is 0, and W is a bond and X is O, can be prepared as outlined in Scheme 10. Saponification of compounds of formula (XVII) under standard conditions, followed by formation of an amide bond under standard conditions well known by those with skill in the art, yields compounds of formula (I) as described above. Amino-containing amides of formula (I) may be prepared by forming the amide bond with a diamino compound where one of the amine moieties is protected by an appropriate protecting group. The free amine group is liberated by removal of the protecting group following the amide-bond forming step.

![Scheme 10](image)
Compounds of formula (I) where Z is phenyl substituted by -E\(^1\)-CO\(_2\)H, as described above and where W is a bond and X is O, can be prepared as outlined in Scheme 11. Mitsunobu condensation (Org. React. 1992, 42, 335-656) of a phenol of formula (XVIII) with an alcohol of formula (XVI) affords the ester of formula (XIX). Saponification of this ester furnishes the compounds of formula (I) where Z is a phenyl substituted by -E\(^1\)-CO\(_2\)H.

Other compounds of formula (I) may be prepared by methods analogous to those described above or by methods known per se.

Further details for the preparation of the compounds of formula (I) are found in the examples.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000, compounds and more preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial “split and mix” approach or by multiple parallel synthesis using either solution or solid phase chemistry, using procedures known to those skilled in the art.

During the synthesis of the compounds of formula (I), labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. The protecting groups may be removed at any stage in the synthesis of the compounds of formula (I) or may be present on the final compound of formula (I). A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in, for example, Protective Groups in Organic Chemistry, T.W. Greene and P.G.M. Wuts, (1991) Wiley-Interscience, New York, 2nd edition.

Any novel intermediates, such as those defined above, may be of use in the synthesis of compounds of formula (I) and are therefore also included within the scope of the invention, for example compounds of formula (XII):
or a salt or protected derivative thereof, wherein the groups Z, W, X, Y, R', d and e are as defined above for compounds of formula (I).

The processes for the production of compounds of formula (I) described above also represent further aspects of the invention.

As indicated above the compounds of formula (I) are useful as GPR119 agonists, e.g. for the treatment and/or prophylaxis of obesity and diabetes. For such use the compounds of formula (I) will generally be administered in the form of a pharmaceutical composition.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), in combination with a pharmaceutically acceptable carrier.

Preferably the composition is comprised of a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Moreover, the invention also provides a pharmaceutical composition for the treatment of disease by modulating GPR119, resulting in the prophylactic or therapeutic treatment of obesity, e.g. by regulating satiety, or for the treatment of diabetes, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula (I), or a pharmaceutically acceptable salt thereof.

The pharmaceutical compositions may optionally comprise other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practice, the compounds of formula (I), or pharmaceutically acceptable salts thereof, can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g. oral or parenteral (including intravenous).

Thus, the pharmaceutical compositions can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound of formula (I), or a pharmaceutically acceptable salt thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more
necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

The compounds of formula (I), or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, tate, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably containing from about 0.05mg to about 5g of the active ingredient.

For example, a formulation intended for the oral administration to humans may contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 2g of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg, or 1000mg.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action...
of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, using a compound of formula (I), or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of formula (I), or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

Generally, dosage levels on the order of 0.01mg/kg to about 150mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5mg to about 7g per patient per day. For example, obesity may be effectively treated by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of formula (I) may be used in the treatment of diseases or conditions in which GPR119 plays a role.

Thus the invention also provides a method for the treatment of a disease or condition in which GPR119 plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof. Diseases or conditions in which GPR119 plays a role include obesity and diabetes. In the context of the present application the treatment of obesity is intended to encompass the treatment of diseases or conditions such as obesity and other eating disorders associated with excessive food intake e.g. by reduction of appetite and body weight, maintenance of weight reduction and prevention of rebound and diabetes (including Type 1 and Type 2 diabetes, impaired glucose tolerance, insulin resistance and diabetic complications such as neuropathy, nephropathy, retinopathy, cataracts, cardiovascular complications and dyslipidaemia). And the treatment of patients who have an abnormal sensitivity to ingested fats leading to functional
dyspepsia. The compounds of the invention may also be used for treating metabolic diseases such as metabolic syndrome (syndrome X), impaired glucose tolerance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels and hypertension.

The compounds of the invention may offer advantages over compounds acting via different mechanisms for the treatment of the above mentioned disorders in that they may offer beta-cell protection, increased cAMP and insulin secretion and also slow gastric emptying.

The compounds of the invention may also be used for treating conditions characterised by low bone mass such as osteopenia, osteoporosis, rheumatoid arthritis, osteoarthritis, periodontal disease, alveolar bone loss, osteotomy bone loss, childhood idiopathic bone loss, Paget's disease, bone loss due to metastatic cancer, osteolytic lesions, curvature of the spine and loss of height.

The invention also provides a method for the regulation of satiety comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the treatment of obesity comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the treatment of diabetes, including Type 1 and Type 2 diabetes, particularly type 2 diabetes, comprising a step of administering to a patient in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the treatment of metabolic syndrome (syndrome X), impaired glucose tolerance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels or hypertension comprising a step of administering to a patient in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition as defined above.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a condition as defined above.

In the methods of the invention the term “treatment” includes both therapeutic and prophylactic treatment.

The compounds of formula (I) may exhibit advantageous properties compared to known GPR119 agonists, for example, the compounds may exhibit improved potency or stability, or improved solubility thus improving absorption properties and bioavailability, or other advantageous properties, such as longer half-life, exposure or pharmacokinetic properties, for compounds to be used as pharmaceuticals.

The compounds of formula (I), or pharmaceutically acceptable salts thereof, may be administered alone or in combination with one or more other therapeutically active compounds. The other therapeutically active compounds may be for the treatment of the same disease or condition as the compounds of formula (I) or a different disease or condition. The therapeutically active compounds may be administered simultaneously, sequentially or separately.
The compounds of formula (I) may be administered with other active compounds for the treatment of obesity and/or diabetes, for example insulin and insulin analogs, gastric lipase inhibitors, pancreatic lipase inhibitors, sulfonyl ureas and analogs, biguanides, α2 agonists, glitazones, PPAR-γ agonists, mixed PPAR-α/γ agonists, RXR agonists, fatty acid oxidation inhibitors, α-glucosidase inhibitors, dipeptidyl peptidase IV inhibitors, GLP-1 agonists e.g. GLP-1 analogues and mimetics, β-agonists, phosphodiesterase inhibitors, lipid lowering agents, glycogen phosphorylase inhibitors, antiobesity agents e.g. pancreatic lipase inhibitors, MCH-1 antagonists and CB-1 antagonists (or inverse agonists), amylin antagonists, lipoxygenase inhibitors, somostatin analogs, glucokinase activators, glucagon antagonists, insulin signalling agonists, PTP1B inhibitors, gluconeogenesis inhibitors, antilypolitic agents, GSK inhibitors, galanin receptor agonists, anoecotic agents, CCK receptor agonists, leptin, serotonergic/dopaminergic antiobesity drugs, reuptake inhibitors e.g. sibutramine, CRF antagonists, CRF binding proteins, thyromimetic compounds, aldose reductase inhibitors, glucocorticoid receptor antagonists, NHE-1 inhibitors or sorbitol dehydrogenase inhibitors.

Combination therapy comprising the administration of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and at least one other antiobesity agent represents a further aspect of the invention.

The present invention also provides a method for the treatment of obesity in a mammal, such as a human, which method comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and another antiobesity agent, to a mammal in need thereof.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and another antiobesity agent for the treatment of obesity.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in combination with another antiobesity agent, for the treatment of obesity.

The compound of formula (I), or a pharmaceutically acceptable salt thereof, and the other antiobesity agent(s) may be co-administered or administered sequentially or separately.

Co-administration includes administration of a formulation which includes both the compound of formula (I), or a pharmaceutically acceptable salt thereof, and the other antiobesity agent(s), or the simultaneous or separate administration of different formulations of each agent. Where the pharmacological profiles of the compound of formula (I), or a pharmaceutically acceptable salt thereof, and the other antiobesity agent(s) allow it, coadministration of the two agents may be preferred.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and another antiobesity agent in the manufacture of a medicament for the treatment of obesity.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and another antiobesity agent, and a pharmaceutically acceptable carrier. The invention also encompasses the use of such compositions in the methods described above.

GPR119 agonists are of particular use in combination with centrally acting antiobesity agents.

Other diseases or conditions in which GPR119 has been suggested to play a role include those described in WO 00/50562 and US 6,468,756, for example cardiovascular disorders, hypertension, respiratory disorders, gestational abnormalities, gastrointestinal disorders, immune disorders, musculoskeletal disorders, depression, phobias, anxiety, mood disorders and Alzheimer's disease.

All publications, including, but not limited to, patents and patent application cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as fully set forth.

The invention will now be described by reference to the following examples which are for illustrative purposes and are not to be construed as a limitation of the scope of the present invention.

EXAMPLES

Materials and methods

Column chromatography was carried out on SiO2 (40–63 mesh) unless specified otherwise. LCMS data were obtained as follows: Method A: Atlantis 3μ C18 column (3.0 × 20.0 mm, flow rate = 0.85 mL/min) eluting with a H2O-CH3CN solution containing 0.1% HCO2H over 6 min with UV detection at 220 nm. Gradient information: 0.0–0.3 min 100% H2O; 0.3–4.25 min: Ramp up to 10% H2O-90% CH3CN; 4.25–4.4 min: Ramp up to 100% CH3CN; 4.4–4.9 min: Hold at 100% CH3CN; 4.9–6.0 min: Return to 100% H2O. The mass spectra were obtained using an electrospray ionisation source in either the positive (ES⁺) or negative (ES⁻) ion modes; Method B: Waters Xterra MS C18, 5μm (4.6 × 50mm, flow rate 1.5mL/min) eluting with a H2O-MeCN gradient containing 0.1% v/v ammonia over 12 min with UV detection at 215 and 254 nm. Gradient information: 0.0-8.0 min: Ramp from 95% H2O-5% MeCN to 5% H2O-95% MeCN; 8.0-9.9 min: Hold at 5% H2O-95% MeCN; 9.9-10.0 min: Return to 95% H2O-5% MeCN; 10.0-12.0 min: Hold at 95% H2O-5% MeCN. Mass spectra were obtained using an electrospray ionization source in either the positive (ES⁺) or negative (ES⁻) mode.

Abbreviations and acronyms: Ac: Acetyl; ADDP: azodicarboxylidipiperidide; Boc: tert-butoxycarbonyl; t-Bu: tert-Butyl; DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene; DCM: Dichloromethane; DEAD: Diethyl azodicarboxylate; DIAD: Diisopropyl azodicarboxylate; DIPEA: N,N-Diisopropylethylamine; DMF: Dimethylformamide; DMSO: Dimethyl sulfoxide;
EDCI: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; Et: Ethyl; h: hour(s); min: minute(s); HOBt: 1-Hydroxybenzotriazole; IH: Isohexane; i-Pr: iso-propyl; LDA: Lithium diisopropylamide; Me: Methyl; Ph: Phenyl; RP-HPLC: Reverse phase-high performance liquid chromatography; RT: Retention time; SCX column: strong cation exchange column (silica bound toxic acid column); TFA: Trifluoroacetic acid; TBAD: di-tert-butyl azodicarboxylate; THF: Tetrahydrofuran.


**Preparation 1:** 4-(3-Hydroxypropyl)piperidine-1-carboxylic acid isopropyl ester

![Image of chemical structure]

i-ProCOCl (1M in PhMe, 28.1 mL, 28.1 mmol) was added to a solution of 3-piperidin-4-ylpropyl acetate (10.0 g, 54.0 mmol) and NEt3 (8.1 g, 80.2 mmol) in anhydrous DCM (100 mL) over 5 min. The reaction was stirred for 3 h, then the mixture was washed with 1M HCl (2×), saturated aqueous Na2CO3, and brine and dried (MgSO4). The solution was filtered and concentrated, before being taken up in MeOH (50 mL). 2M NaOH was added and the reaction stirred for 4 h. The MeOH was removed under reduced pressure and the remainder extracted with EtOAc. The organic extracts were dried (MgSO4), filtered and concentrated to give an oil that was purified by flash chromatography (EtOAc-DCM, 1:1) to afford the title compound: δH (CDCl3) 1.05–1.15 (m, 2H), 1.23 (d, 6H), 1.25–1.35 (m, 2H), 1.40–1.50 (m, 1H), 1.55–1.60 (m, 2H), 1.65–1.70 (m, 2H), 2.65–2.75 (m, 2H), 3.60–3.67 (m, 2H), 4.05–4.15 (br s, 2H), 4.90 (sept, 1H).

**Preparation 2:** 4-(3-Hydroxypropyl)piperidine-1-carbonitrile

![Image of chemical structure]

A slurry of NaHCO3 (35.2 g, 0.42 mol) in H2O (70 mL) was added to a stirred solution of 3-piperidin-4-ylpropan-1-ol (20.0 g, 0.14 mol) in DCM at 0°C. A solution of BrCN (17.8 g, 0.17 mol) in DCM (19 mL) was added to the reaction over 1 min, then stirring was continued at 0°C for 0.5 h. The reaction was then stirred at 20°C for 2 h, before being washed with saturated aqueous NaHCO3 and brine. The DCM solution was dried (MgSO4), filtered and concentrated in vacuo to furnish an oil that was dissolved in a small amount of DCM, before being filtered through a SiO2 pad, eluting with EtOAc. The filtrate was concentrated under reduced pressure to afford the title compound: m/z (ES) = 169.1 [M + H]+ (Method A).
Preparation 3: 3-[1-(3-Isopropyl[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propan-1-ol

ZnCl₂ (1M in Et₂O, 145 mL, 145 mmol) was added over 20 min to a stirred solution of 4-(3-hydroxypropyl)piperidine-1-carbonitrile (Preparation 2, 20.3 g, 121 mmol) and N-hydroxyisobutryramidine (14.8 g, 145 mmol) in EtOAc (290 mL) and THF (270 mL). After 2 h, the white precipitate that had formed was collected and washed with THF-EtOAc (1:1, 50 mL). This precipitate was dissolved in EtOH (550 mL) and 12 M HCl (70 mL), then the solution was stirred with heating to 70°C for 16 h. The EtOH was removed in vacuo, then the remainder was diluted with H₂O and adjusted to pH 7 with solid NaHCO₃. The mixture was extracted with EtOAc (3×), then the combined extracts were washed with brine, before being dried (MgSO₄). Filtration and solvent removal furnished the title compound: m/z (ES⁺) = 254.1 [M + H]⁺ (Method A).

Preparation 4: Methanesulfonic acid 3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]-propyl ester

Methanesulfonyl chloride (1.64 mL, 21.2 mmol) in DCM (5 mL) was added dropwise to a solution of 3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propan-1-ol (Preparation 3, 4.46 g, 17.6 mmol) and NEt₃ (4.9 mL, 35.3 mmol) in DCM (35 mL) at 0°C. The reaction mixture was stirred at ambient temperature for 0.5 h, then partitioned between EtOAc (250 mL) and 0.5M HCl (150 mL). The organic layer was separated, washed with H₂O, saturated aqueous NaHCO₃ solution and brine, before being dried (MgSO₄), filtered, and concentrated in vacuo to afford the title compound: RT = 3.32 min; m/z (ES⁺) = 332.08 [M + H]⁺ (Method A).

Preparation 5: 3-Fluoro-4-(5-methyltetrazol-1-yl)phenol

1,1,1-Triethoxethane (3.70 mL, 19.69 mmol) was added to a solution of 4-amino-3-fluorophenol (2.50 g, 19.69 mmol) in AcOH (27.5 mL) at 75°C and the resulting solution was heated at 75°C for 5 h. The reaction was removed from the heat, sodium azide (4.09 g, 62.99 mmol) was added portionwise and the resulting reaction mixture was heated at 75°C for 72 h. The reaction mixture was cooled to ambient temperature, poured into ice-water and extracted with EtOAc (10×). The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (EtOAc-III, 3:2) afforded the title compound: RT = 2.50 min; m/z (ES⁺) = 195.00 [M + H]⁺ (Method A).
Preparation 6: 4-[3-(3-Fluoro-4-methoxycarbonylphenoxy)propyl]piperidine-1-carboxylic acid isopropyl ester

The title compound was synthesised from methyl 2-fluoro-4-hydroxybenzoate and 4-(3-hydroxypropyl)piperidine-1-carboxylic acid isopropyl ester (Preparation 1), employing a procedure similar to that outlined in Example 1: RT = 4.12 min; m/z (ES') = 382.10 [M + H]⁺ (Method A).

Preparation 7: 4-[3-(3-Fluoro-4-hydrazinocarbonylphenoxy)propyl]piperidine-1-carboxylic acid isopropyl ester

Hydrazine hydrate (80% aqueous solution, 172 μL, 2.70 mmol) was added to a solution of 4-[3-(3-fluoro-4-methoxycarbonylphenoxy)propyl]piperidine-1-carboxylic acid isopropyl ester (Preparation 6, 700 mg, 1.80 mmol) in MeOH (5 mL) and the resulting solution was heated under reflux conditions for 32 h. Further hydrazine hydrate (80% aqueous solution, 344 μL, 5.40 mmol) was added and heating under reflux conditions was continued for 72 h. The MeOH was removed in vacuo and H₂O was added to the resulting solid. The solid was collected by filtration, washed with saturated aqueous NaHCO₃ solution and then recrystallised from EtOH to afford the title compound: RT = 3.24 min; m/z (ES') = 382.15 [M + H]⁺ (Method A).

Preparation 8: 2-Fluoro-4-{3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}-benzoic acid

DIAD (20.2 mL, 102.8 mmol) was added to a stirred solution of methyl 2-fluoro-4-hydroxybenzoate (13.43 g, 79.1 mmol), 3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]-propan-1-ol (Preparation 3, 20.00 g, 79.1 mmol), and PPh₃ (24.85 g, 95.0 mmol) in anhydrous THF. After 30 min, the solvent was removed in vacuo, then the remainder was triturated with IH–Et₂O. The solid produced was filtered and washed with Et₂O. The combined washings and filtrate were concentrated under reduced pressure, then the residue was purified by column chromatography (EtOAc–IH, 1:4) to generate methyl 2-fluoro-4-{3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}benzoate. This compound was stirred with LiOH·H₂O (33.2 g, 791 mmol) in MeOH (400 mL) and H₂O (100 mL) for 16 h. The MeOH was
evaporated off under reduced pressure, then the remainder was partitioned between 2M NaOH and Et₂O. The aqueous phase was acidified to pH 2, before being extracted with EtOAc. The organic extracts were dried (MgSO₄), filtered, concentrated, and recrystallised from EtOAc to furnish the title compound: δₓ(CDCl₃) 1.26–1.40 (m, 8H), 1.46–1.62 (m, 3H), 1.81–1.93 (m, 4H), 2.95 (sept, 1H), 3.02–3.12 (m, 2H), 4.03 (t, 2H), 4.16–4.22 (m, 2H), 6.67 (dd, 1H), 6.78 (dd, 1H), 8.01 (t, 1H); m/z (ES⁺) = 392.0 [M + H]⁺ (Method A).

**Preparation 9:** 4-{{[1-(3-Isopropyl-1,2,4]oxadiazol-5-yl)piperidin-4-yl}propoxy}-2-methylbenzoic acid

![Structure](image)

The title compound was synthesised by Mitsunobu condensation of 4-hydroxy-2-methylbenzoic acid methyl ester with 3-[1-(3-isopropyl-1,2,4]oxadiazol-5-yl)piperidin-4-yl]-propan-1-ol (Preparation 3), followed by saponification, employing procedures similar to those outlined in **Preparation 8:** δₓ(CDCl₃) 1.26–1.40 (m, 7H), 1.46–1.62 (m, 4H), 1.81–1.92 (m, 4H), 2.64 (s, 3H), 2.94 (sept, 1H), 3.02–3.13 (m, 2H), 4.04 (t, 2H), 4.15–4.21 (m, 2H), 6.78–6.81 (m, 2H), 8.07 (d, 1H).

**Preparation 10:** tert-Butyl 4-((E)-2-carboxy-1-methylvinyl)piperidine-1-carboxylate

![Structure](image)

A solution of tert-butyl 4-((E)-2-ethoxycarbonyl-1-methylvinyl)piperidine-1-carboxylate (18.7 g, 62.9 mmol) in MeOH (90 mL) and H₂O (25 mL) was treated with 2M NaOH (94.5 mL, 189 mmol). The reaction was stirred for 16 h, the MeOH was removed under reduced pressure, then the remainder was partitioned between EtOAc and H₂O. The aqueous layer was separated and acidified to pH 2 with 12M HCl, before being extracted with EtOAc (2×). The organic extracts were washed with brine, dried (MgSO₄), filtered, and concentrated in vacuo, then the remainder was recrystallised from EtOAc–H₂O to provide the title compound: m/z (ES⁺) = 268.3 [M − H]⁻ (Method A).

**Preparation 11:** tert-Butyl 4-((R)-2-carboxy-1-methylethyl)piperidine-1-carboxylate

![Structure](image)

tert-Butyl 4-((E)-2-carboxy-1-methylvinyl)piperidine-1-carboxylate (Preparation 10, 130.0 g, 0.483 mol) was placed in a hydrogenation flask under an Ar atmosphere, then degassed MeOH (400 mL) was added. [Rh(norbornadiene)₂]BF₄ (1.80 g, 4.81 mmol) and (S)-1-[(R)-2-(diter-butylphosphino)ferrocenyl]ethylbis(2-methylphenyl)phosphine (2.90 g, 5.08 mmol) were
placed in a separate Schlenk flask under Ar, before being treated with degassed MeOH (200 mL). This catalyst mixture was stirred for 15 min at ambient temperature, before being transferred via cannula into the hydrogenation flask. The Schlenk flask was rinsed with more degassed MeOH (100 mL). These washings were transferred to the hydrogenation flask, then more degassed MeOH (300 mL) was added. The hydrogenation flask was sealed, the Ar replaced by H₂, and the pressure set to 1.05 bar. The reaction mixture was heated to 35°C, and stirring/shaking was started. After 48 h, the reaction was stopped and a representative sample of the reaction mixture was analysed by HPLC and ¹H NMR. The conversion was 100% and the enantiomeric purity of the crude (R)-acid was 98.2%, as ascertained by the following HPLC method: Column: CHIRALPAK AD-H (previously used with CF₃CO₂H-containing solvents) 4.6 × 250 mm; Solvent: C₅H₁₂-iPrOH (97:3 isocratic); Temperature: 20°C; Flow rate: 1 mL/min; UV-detection (210, 230 nm); Sample: 100 µL reaction solution dissolved with 1 mL MeOH. Retention times: (S)-acid: 19.3 min, (R)-acid: 20.6 min, starting enolic acid: 22.1 min. Isolation procedure: The MeOH was evaporated, then the crude hydrogenation product was dissolved in t-BuOMe and extracted with aqueous NaOH. The aqueous phase was added to a mixture of 1M HCl and EtOAc. The aqueous phase was extracted further with EtOAc, then the combined organic extracts were washed with brine and dried (MgSO₄). The title compound was isolated following filtration and complete removal of the solvent.

**Preparation 12**: tert-Butyl 4-((R)-3-hydroxy-1-methylpropyl)piperidine-1-carboxylate

![Chemical structure](image)

BH₃-THF (1M, 15.7 mL, 15.7 mmol) was added dropwise over 5 min to a stirred solution of tert-butyl 4-((R)-2-carboxy-1-methyl ethyl)piperidine-1-carboxylate (Preparation 11, 1.70 g, 6.30 mmol) in anhydrous THF at 0°C. After 1 h, the reaction was treated with Et₂O, then with 2M HCl. The organic layer was washed with brine, before being dried (Na₂SO₄). Filtration, solvent evaporation, and column chromatography (EtOAc:DCM, 1:3) provided the title compound: RT = 3.17 min; m/z (ES⁺) = 258.1 [M + H]⁺ (Method A).

**Preparation 13**: 4-((R)-3-Hydroxy-1-methylpropyl)piperidine-1-carbonitrile

![Chemical structure](image)

A mixture of tert-butyl 4-((R)-3-hydroxy-1-methylpropyl)piperidine-1-carboxylate (Preparation 12, 6.20 g, 14.9 mmol) and 4M HCl in dioxane (10 mL) were stirred at ambient temperature. After 3 h, the solvents were removed under reduced pressure to furnish the hydrochloride salt of (R)-3-piperidin-4-ylbutan-1-ol: δ (CDCl₃,SO) 0.83 (d, 3H), 1.19–1.28 (m, 1H), 1.38–1.59 (m, 5H), 1.64–1.76 (m, 2H), 2.75–2.87 (m, 2H), 3.20–3.30 (m, 2H), 3.35–3.60 (m, 4H). A stirred mixture of this compound (930 mg, 4.80 mmol) and NaHCO₃ (1.61 g, 19.2 mmol) in DCM–H₂O (4:1, 15 mL) at 0°C was treated with a solution of BrCN (610 mg, 5.80 mmol) in DCM (2 mL). The reaction was stirred at 20°C for 2 h, before being partitioned between H₂O and DCM. The organic phase was separated and dried (MgSO₄). Filtration, solvent
evaporation, and column chromatography (EtOAc) provided the title compound: RT = 2.45 min; m/z (ES⁺) = 183.1 [M + H]⁺ (Method A).

Preparation 14: (R)-3-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]butan-1-ol

Condensation of 4-((R)-3-hydroxy-1-methylpropyl)piperidine-1-carbonitrile (Preparation 13, 530 mg, 2.90 mmol) with N-hydroxyisobutramidine (360 mg, 3.50 mmol), employing a procedure similar to that outlined in Preparation 3, afforded the title compound: RT = 2.92 min; m/z (ES⁺) = 268.1 [M + H]⁺ (Method A).

Preparation 15: 4-[3-(4-Bromo-3,5-dimethylphenoxy)propyl]piperidine-1-carboxylic acid tert-butyl ester

4-Bromo-3,5-dimethylphenol (13.75 g, 68.4 mmol) and K₂CO₃ (18.90g, 136.8 mmol) were added to a solution of 4-(3-methanesulfonyloxypropyl)piperidine-1-carboxylic acid tert-butyl ester (21.98 g, 68.4 mmol) in sulfolane (260 mL) and the resulting solution was heated at 85°C for 4 h. The reaction mixture was diluted with Et₂O (500 mL) and H₂O (500 mL) and the organic layer was washed with H₂O (4×), 2M NaOH (2×) and brine, before being dried (MgSO₄). Filtration, solvent removal and purification by column chromatography (DCM) furnished the title compound: RT = 4.94 min; m/z (ES⁺) = 426.20 [M + H]⁺ (Method A).

Preparation 16: 4-[3-(4-Carboxy-3,5-dimethylphenoxy)propyl]piperidine-1-carboxylic acid tert-butyl ester

To a solution of 2.5 M n-butyllithium in hexane (20.64 mL, 51.6 mmol) in anhydrous THF (23 mL) at -78°C under argon, was added a solution of 4-[3-(4-bromo-3,5-dimethylphenoxy)propyl]piperidine-1-carboxylic acid tert-butyl ester (Preparation 15, 11.00 g, 25.8 mmol) in anhydrous THF (34 mL). The reaction mixture was stirred at -78°C for 50 min, then CO₂ gas was bubbled through the reaction mixture as it warmed to ambient temperature (~0.5 h). The reaction mixture was quenched with H₂O and diluted with EtOAc. The organic layer was extracted with 2M NaOH (2×) and the combined basic extracts were combined with the aqueous layer. The aqueous was acidified to pH 1 with 2M HCl and extracted with EtOAc (3×), then the combined organic extracts were washed with brine and dried (MgSO₄). Filtration,
solvent removal and purification by column chromatography ([EtOAc–IH, 3:7]) furnished the title compound; RT = 3.93 min; \textit{m/z} (ES\textsuperscript{+}) = 392.23 \ [M + H]\textsuperscript{+} (Method A).

**Preparation 17:** 2,6-Dimethyl-4-(3-piperidin-4-ylpropoxy)benzoic acid hydrochloride

![Chemical Structure]

4M HCl in dioxane (21.95 mL) was added to a stirred solution of 4-[3-(4-carboxy-3,5-dimethylphenoxo)propyl]piperidine-1-carboxylic acid tert-butyl ester (Preparation 16, 4.91 g, 12.5 mmol) in dioxane (20 mL) at ambient temperature. After 2.5 h, the solid product that had formed was collected by filtration and washed with Et\textsubscript{2}O to afford the title compound: RT = 2.50 min; \textit{m/z} (ES\textsuperscript{+}) = 291.40 \ [M + H]\textsuperscript{+} (Method A).

**Preparation 18:** 4-{3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]propoxy}-2,6-dimethylbenzoic acid

![Chemical Structure]

To 2,6-dimethyl-4-(3-piperidin-4-ylpropoxy)benzoic acid hydrochloride (Preparation 17, 600 mg, 1.83 mmol) in DMSO (850 \mu L) was added 2,5-dichloropyrimidine (327 mg, 2.20 mmol), DBU (960 \mu L, 6.41 mmol) and H\textsubscript{2}O (6 drops). The resulting suspension was heated in a sealed tube in the microwave at 130\degree C for 3 h. The reaction mixture was diluted with H\textsubscript{2}O, acidified to pH 5 with 2M HCl and extracted with EtOAc (3\times). Then the combined organic extracts were washed with brine, before being dried (MgSO\textsubscript{4}). Filtration, removal of solvent under reduced pressure and purification by column chromatography (EtOAc–IH, 2:3 to 3:2) afforded the title compound: RT = 4.20 min; \textit{m/z} (ES\textsuperscript{+}) = 404.16 \ [M + H]\textsuperscript{+} (Method A).

**Preparation 19:** 4-[3-(4-Methoxycarbonyl-3-methylphenoxy)propyl]piperidine-1-carboxylic acid tert-butyl ester

![Chemical Structure]

DIAD (8.00 mL, 40.9 mmol) was added to a stirred solution of 4-hydroxy-2-methylbenzoic acid methyl ester (6.00 g, 37.4 mmol), tert-butyl 4-(3-hydroxypropyl)piperidine-1-carboxylate (8.25 g, 34.0 mmol) and PPh\textsubscript{3} (10.71 g, 40.9 mmol) in anhydrous THF (60 mL) at ambient temperature. After stirring for 7.5 h, the solvent was removed in vacuo, and the remainder was dissolved in EtOAc and washed with 2M NaOH (2\times) and brine. The organic layer was dried (MgSO\textsubscript{4}), concentrated under reduced pressure and the remainder was triturated...
with IH–Et₂O. The solid produced was filtered and washed with Et₂O. The combined washings and filtrate were concentrated under reduced pressure and purified by column chromatography (EtOAc–IH, 1:9) to afford the title compound: RT = 4.48 min; m/z (ES⁺) = 392.3 [M + H]⁺ (Method A).

**Preparation 20:** 4-[3-(4-Carboxy-3-methylphenoxy)propyl]piperidine-1-carboxylic acid tert-butyl ester

![Chemical Structure Image]

To a solution of 4-[3-(4-methoxycarbonyl-3-methylphenoxy)propyl]piperidine-1-carboxylic acid tert-butyl ester (**Preparation 19**, 6.00 g, 15.3 mmol) in MeOH (200 mL) and H₂O (20 mL) was added LiOH·H₂O (6.43 g, 153.3 mmol) and the resulting mixture was stirred at 40°C for 16 h. The MeOH was evaporated off under reduced pressure, then the remainder was dissolved in H₂O (200 mL), washed with EtOAc and acidified to pH 4 with 2M HCl, before being extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (MgSO₄), filtered, and concentrated in vacuo to yield the title compound RT = 4.06 min; m/z (ES⁺) = 378.22 [M + H]⁺ (Method A).

**Preparation 21:** 2-Methyl-4-(3-piperidin-4-ylpropoxy)benzoic acid hydrochloride

![Chemical Structure Image]

A mixture of 4-[3-(4-carboxy-3-methylphenoxy)propyl]piperidine-1-carboxylic acid tert-butyl ester (**Preparation 20**), 11.82 g, 37.7 mmol) and 4M HCl in dioxane (150 mL) was stirred at ambient temperature for 1 h. The solvent was removed in vacuo, azeotroping with toluene (2×), to afford the title compound: RT = 2.37 min; m/z (ES⁺) = 278.17 [M + H]⁺ (Method A).

**Preparation 22:** 4-[3-(5'-Chloro-3,4,5,6-tetrahydro-2H-[1,2]bipyridinyl-4-yl)propoxy]-2-methylbenzoic acid

![Chemical Structure Image]

To 2-methyl-4-(3-piperidin-4-ylpropoxy)benzoic acid hydrochloride (**Preparation 21**, 574 mg, 1.83 mmol) in DMSO (850 µL) was added 5-chloro-2-fluoropyridine (288 mg, 2.20 mmol), DBU (960 µL, 6.41 mmol) and H₂O (6 drops). The resulting suspension was heated in a sealed tube in the microwave at 130°C for 3 h. The reaction mixture was diluted with H₂O,
acidified to pH 5 with 2M HCl and extracted with EtOAc (3×), then the combined organic
extracts were washed with brine, before being dried (MgSO4). Filtration, removal of solvent
under reduced pressure and purification by column chromatography (EtOAc–IH, 2:3 to 3:2)
afforded the title compound: RT = 3.87 min; m/z (ES+) = 403.11 [M + H]+ (Method A).

**Preparation 23:** 3-[1-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propan-1-ol

The title compound was prepared using a procedure similar to that outlined in

**Preparation 3:** m/z (ES+) = 268.2 [M + H]+.

**Preparation 24:** 4-{3-[1-(3-tert-Butyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy]-2-
methylbenzoic acid

The title compound was synthesised by Mitsunobu condensation of 4-hydroxy-2-
methylbenzoic acid methyl ester with 3-[1-(3-tert-butyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]-
propan-1-ol (Preparation 23), followed by saponification, employing procedures similar to
those outlined in Preparation 8: m/z (ES+) = 401.5 [M − H]+.

**Preparation 25:** (R)-Methanesulfonic acid-3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-
yl]butyl ester

Methanesulfonyl chloride (610 µL, 7.90 mmol) and NEt3 (2.01 mL, 15.0 mmol) were
added to a solution of (R)-3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]butan-1-ol
(Preparation 14, 2.00 g, 7.50 mmol) in DCM (30 mL) at 0°C. After stirring for 10 min, the
reaction was diluted with DCM (100 mL) and poured into saturated aqueous NaHCO3 solution
(100 mL). The organic layer was separated, washed with 0.1M HCl (100 mL), dried (MgSO4),
filtered and concentrated in vacuo. Purification by column chromatography (EtOAc–IH, 1:1)
afforded the title compound: RT = 3.42 min; m/z (ES+) = 346.1 [M + H]+ (Method A).

**Preparation 26:** (5-Hydroxy-2-(2-oxo-pyrrolidin-1-yl)benzyl)carboxylic acid tert-butyl ester
A stirred solution of 1-bromo-2-bromomethyl-4-methoxybenzene (4.00 g, 14.3 mmol) in DMF (100 mL) was treated portionwise with NaN₃ (4.64 g, 71.4 mmol), then the mixture was heated to 130°C for 16 h. On cooling, the reaction mixture was partitioned between EtOAc and H₂O. The aqueous phase was extracted with EtOAc, then the combined organic extracts were washed with H₂O (5x), before being dried (MgSO₄). Filtration and solvent evaporation furnished 2-azidomethyl-1-bromo-4-methoxybenzene: δ₁ (CDCl₃) 3.82 (s, 3H), 4.46 (s, 2H), 6.77 (dd, 1H), 6.97 (d, 1H), 7.48 (d, 1H). A stirred mixture of this aryl bromide (2.18 g, 9.0 mmol), 2-pyrrolidinone (829 µL, 10.8 mmol), trans-N,N-dimethyl-1,2-cyclohexyldiamine (142 µL, 0.9 mmol), CuI (86 mg), and K₂CO₃ (2.49 g, 18.0 mmol) in PhMe (10 mL) was heated under reflux for 24 h. Standard workup followed by flash chromatography (EtOAc–He, 4:1) furnished 1-(2-azidomethyl-4-methoxyphenyl)pyrrolidin-2-one: m/z (ES⁺) = 247.2 [M + H]⁺. A 0.05 M solution of this azide (50 mg, 203 µmol) in MeOH (4 mL) was reduced using an H-cube apparatus (ThalesNano Nanotechnology, Budapest, Hungary) under the following conditions: 10% Pd/C Catcart 30, 1 mL/min, full H₂ mode, 20°C. Solvent evaporation under reduced pressure yielded 1-(2-aminomethyl-4-methoxyphenyl)pyrrolidin-2-one: Rf (EtOAc) = 0.35. A stirred solution of this anisole (290 mg, 1.3 mmol) in 48% aqueous HBr (10 mL) was heated under reflux for 2.5 h. The mixture was concentrated under reduced pressure to furnish the hydrobromide salt of 1-(2-aminomethyl-4-hydroxyphenyl)pyrrolidin-2-one: δ₁ (D₂O) 2.29 (m, 2H), 2.99 (t, 2H), 3.95 (t, 2H), 4.71 (s, 2H), 6.66–6.67 (m, 1H), 6.78–6.81 (m, 1H), 6.91 (d, 1H). A solution of this ammonium salt (1.3 mmol) in dioxane (8 mL) and H₂O (4 mL) at 0°C was treated with Boc₂O (360 mg, 1.7 mmol) and NEt₃ (442 µL, 3.2 mmol), before being stirred for 1 h. The reaction mixture was partitioned between EtOAc and H₂O, then the organic layer was washed with 1M citric acid, H₂O, and brine, before being dried (MgSO₄). Filtration and solvent evaporation provided the title compound: RT = 2.62 min; m/z (ES⁺) = 307.3 [M + H]⁺ (Method A).

Preparation 27: [5-[(R)-3-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]butoxy]-2-(2-oxo-pyrrolidin-1-yl)benzyl]carbamic acid tert-butyl ester

A stirred solution of [5-hydroxy-2-(2-oxo-pyrrolidin-1-yl)benzyl]carbamic acid tert-butyl ester (Preparation 26, 125 mg, 0.41 mmol) and (R)-methanesulfonic acid-3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]butoyl ester (Preparation 25, 155 mg, 0.45 mmol) in DMF (4 mL) was treated with K₂CO₃ (113 mg, 0.82 mmol), before being heated to 80°C for
16 h. On cooling, the mixture was diluted with EtOAc and washed with H₂O (5×), 1 M citric acid, saturated aqueous NaHCO₃ (2×), 1 M NaOH (2×), and brine. The EtOAc solution was dried (MgSO₄), filtered, and concentrated, then the residue was purified by flash chromatography (EtOAc) to afford the title compound: RT = 4.03 min; m/z (ES⁻) = 556.5 [M + H]⁺ (Method A).

**Preparation 28:** 4-{3-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]propoxy}-2,6-dimethylbenzoic acid

![Chemical structure of 4-{3-[1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl]propoxy}-2,6-dimethylbenzoic acid](image)

The title compound was synthesized from 2,6-dimethyl-4-(3-piperidin-4-ylpropoxy)benzoic acid hydrochloride (Preparation 17) and 2-chloro-5-ethylpyrimidine, using a procedure similar to that delineated in Preparation 18: RT = 3.95 min; m/z (ES⁺) = 398.22 [M + H]⁺ (Method A).

**Preparation 29:** 3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]propan-1-ol

![Chemical structure of 3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]propan-1-ol](image)

A stirred solution of 3-piperidin-4-ylpropan-1-ol hydrochloride (15.0 g, 84 mmol) in DMSO (120 mL) was cooled to 0°C, before being treated dropwise with DBU (30.0 mL, 201 mmol) over 5 min. 2,5-dichloropyrimidine (17.4 g, 117 mmol) was added portionwise, then the reaction was heated to 110°C for 4 h. After cooling to 20°C, the reaction was poured into H₂O (200 mL) and extracted with EtOAc (3 × 500 mL). The combined organic extracts were washed with 1 M HCl (2 × 200 mL), before being dried (MgSO₄) and concentrated. The residue was purified by column chromatography (EtOAc–CH₂Cl₂, 4:6) to provide the title compound: ¹H NMR (CDCl₃) δ 1.10–1.23 (m, 2H), 1.30–1.38 (m, 2H), 1.48–1.57 (m, 2H), 1.58–1.66 (m, 2H), 1.78 (d, 2H), 2.86 (m, 2H), 3.66 (t, 2H), 4.67 (d, 2H), 8.20 (s, 2H).

**Preparation 30:** (4-{3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]propoxy}phenyl)acetic acid methyl ester

![Chemical structure of (4-{3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]propoxy}phenyl)acetic acid methyl ester](image)

A stirred solution of methyl-4-hydroxyphenylacetate (1.00 g, 6.0 mmol) and 3-[1-(5-chloropyrimidin-2-yl)piperidin-4-yl]propan-1-ol (Preparation 29, 1.53 g, 6.0 mmol) in THF (40 mL) was cooled to 0°C. ADDP (2.27 g, 9.0 mmol) and nBu₃P (1.82 g, 9.0 mmol) were added portionwise and the reaction mixture was allowed to warm to 20°C. After 16 h, the
reaction was concentrated and the residue treated with IH and filtered. The filtrate was
concentrated and the residue purified by column chromatography (EtOAc-IH, 1:9) to provide
the title compound: RT = 4.85 min; m/z (ES⁺) = 404.1 [M + H]⁺ (Method A).

**Preparation 31:** 2-(4-Hydroxy-2-methylphenyl)-1-morpholin-4-y lethanthione

![Chemical structure](image1)

1-(4-Hydroxy-2-methylphenyl)ethanone (9.0 g, 60 mmol), sulfur (4.8 g, 150 mmol) and
morpholine (10.4 mL, 120 mmol) were heated to 135°C for 4 h. The reaction was cooled and the
residue stirred with EtOAc (200 mL) and H₂O (100 mL). The mixture was decanted off and the
residue washed with a further portion of EtOAc (200 mL) and H₂O (100 mL). The organic
layers were separated, dried (MgSO₄) and concentrated. Recrystallisation of the residue from
MeOH (150 mL) gave a pale yellow solid which was filtered and washed with Et₂O. A second
crop was obtained from the filtrate and the material combined to provide the title compound: RT
= 2.62 min; m/z (ES⁺) = 252.1 [M + H]⁺ (Method A).

**Preparation 32:** 2-(4-[3-[1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy]-2-
methyl[phenyl]-1-morpholin-4-y lethanthione

![Chemical structure](image2)

Mitsunobu reaction of 2-(4-hydroxy-2-methylphenyl)-1-morpholin-4-y lethanthione
(Preparation 31, 2.20 g, 8.8 mmol) and 3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]-propan-1-ol (Preparation 3, 2.21 g, 8.8 mmol), by a procedure similar to that outlined in
Preparation 30, provided the title compound: RT = 4.50 min; m/z (ES⁺) = 487.2 [M + H]⁺
(Method A).

**Preparation 33:** (2-Fluoro-4-hydroxyphenyl)acetic acid methyl ester

![Chemical structure](image3)

A mixture of (2-fluoro-4-methoxyphenyl)acetic acid (4.50 g, 24.4 mmol) and aqueous
hydrobromic acid (48%, 60 mL) was stirred under reflux for 12 h. The solvent was removed in
vacuo and the residue was co-evaporated with MeOH several times, before being taken up in
PhMe (200 mL) and MeOH (50 mL). The mixture was cooled to 0°C, before being treated with
(trimethylsilyl)diazomethane (13 mL, 2 M solution in hexane). The reaction was stirred from
0°C to ambient temperature over 1 h, then quenched with AcOH (10 mL) and concentrated in
vacuo. Purification by column chromatography (IH–EtOAc, 2:1) afforded the title compound:
RT = 2.68 min; m/z (ES⁺) = 248.06 [M + CH₃CN + Na]⁺ (Method A).
Preparation 34: (2-Fluoro-4-((R)-3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl]piperidin-4-yl)butoxy)phenyl)acetic acid methyl ester

(2-Fluoro-4-hydroxyphenyl)acetic acid methyl ester (Preparation 33, 747 mg, 4.05 mmol), ADDP (950 mg, 3.77 mmol) and nBu3P (1.0 mL, 4.00 mmol) were added to a solution of (R)-3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]butan-1-ol (Preparation 14, 506 mg, 1.89 mmol) in PhMe (50 mL) and the mixture was stirred at ambient temperature for 18 h. After addition of IH (100 mL), the mixture was stirred for an additional hour before being filtered. The filtrate was concentrated in vacuo to afford a residue which was purified by column chromatography (IH:EtOAc, 3:1) to give the title compound: RT = 4.40 min; m/z (ES+) = 434.22 [M + H]⁺ (Method A).

Preparation 35: (R)-3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]butan-1-ol

TFA (75 mL) was added to a solution of tert-butyl 4-((R)-3-hydroxy-1-methylpropyl)piperidinc-1-carboxylate (Preparation 12, 30.0 g, 117 mmol) in CH2Cl2 (150 mL) at 0°C and the resulting solution was stirred at this temperature for 0.5 h. The solvent was removed in vacuo and the remainder dissolved in CH2Cl2, then the CH2Cl2 solution was washed with saturated aqueous NaHCO3 solution, dried (MgSO4), filtered and concentrated in vacuo to afford (R)-3-piperidin-4-ylbutan-1-ol. To a portion of this material (10.0 g, 63.7 mmol) in DMSO (65 mL) was added DBU (14.3 mL, 95.5 mmol) and 2,5-dichloropyrimidine (14.3 g, 95.5 mmol) and the resulting reaction mixture was heated at 100°C for 1.5 h. The reaction mixture was cooled to ambient temperature, quenched with H2O and extracted with EtOAc. The organic extracts were washed with 1M HCl and brine, before being dried (MgSO4), filtered and concentrated in vacuo. Purification by column chromatography (EtOAc-IF; 1:4 to 7:13) afforded the title compound: RT = 3.58 min, m/z (ES+) = 270.08 [M + H]⁺ (Method A).

Preparation 36: (4-{((R)-3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl)butoxy]-2-fluorophenyl}acetic acid methyl ester

(R)-3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]butan-1-ol (Preparation 35) and (2-fluoro-4-hydroxyphenyl)acetic acid methyl ester (Preparation 33) were coupled under
conditions similar to those of Preparation 34 to afford the title compound: RT = 5.09 min; m/z (ES^+) = 436.15 [M + H]^+ (Method A).

**Preparation 37**: 2-(2-Fluoro-4-hydroxyphenyl)-1-morpholin-4-ylethanthione

1-(2-Fluoro-4-hydroxyphenyl)ethanone was reacted with sulfur and morpholine, as described in Preparation 31, to provide the title compound: RT = 2.63 min; m/z (ES^+) = 256.2 [M + H]^+ (Method A).

**Preparation 38**: 2-(2-Fluoro-4-)[3-{1-[3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]-propoxy}phenyl]-1-morpholin-4-ylethanthione

Mitsunobu reaction of 2-(2-fluoro-4-hydroxyphenyl)-1-morpholin-4-ylethanthione (Preparation 37) and 3-{1-[3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propan-1-ol (Preparation 31), by a procedure similar to that outlined in Preparation 30, provided the title compound: RT = 4.14 min; m/z (ES^+) = 490.2 [M + H]^+ (Method A).

**Preparation 39**: 2-(4-{3-[1-[4-Chloropyrimidin-2-yl)piperidin-4-yl]propoxy}-2-(fluorophenyl)-1-morpholin-4-ylethanthione

Mitsunobu reaction of 2-(2-fluoro-4-hydroxyphenyl)-1-morpholin-4-ylethanthione (Preparation 37) and 3-[1-[4-Chloropyrimidin-2-yl)piperidin-4-yl]propan-1-ol (Preparation 39), by a procedure similar to that outlined in Preparation 30, provided the title compound: RT = 4.53 min; m/z (ES^+) = 493.2 [M + H]^+ (Method A)

**Preparation 40**: 4-{3-[3-Fluoro-4-(2-morpholin-4-yl)-2-thioxoethyl]phenoxypropyl}-piperidine-1-carboxylic acid tert-butyl ester
Mitsunobu reaction of 2-(2-fluoro-4-hydroxyphenyl)-1-morpholin-4-ylethanethione (Preparation 37) and tert-butyl 4-(3-hydroxypropyl)piperidine-1-carboxylate, by a procedure similar to that outlined in Preparation 30, provided the title compound: RT = 4.17 min; m/z (ES⁺) = 481.11 [M + H]⁺ (Method A).

Preparation 41: 4-[(3-(4-Methoxyacarbonylmethyl)phenoxy)propyl]piperidine-1-carboxylic acid tert-butyl ester

Mitsunobu reaction of methyl (4-hydroxyphenyl)acetate and tert-butyl 4-(3-hydroxypropyl)piperidine-1-carboxylate, by a procedure similar to that outlined in Preparation 19, provided the title compound: RT = 4.24 min; m/z (ES⁺) = 392.13 [M + H]⁺ (Method A).

Preparation 42: 2-(2-Fluoro-4-methoxyphenyl)propionic acid methyl ester

(2-Fluoro-4-methoxyphenyl)acetic acid methyl ester (1.98 g, 10 mmol) in anhydrous THF (30 mL) was added over 15 min to a stirred solution of LDA (2.0 M in THF/Heptane/PhMe, 6 mL, 12 mmol) at -78 °C. The reaction was stirred for 1.5 h at -78°C, after which MeI (0.76 mL, 12 mmol) was added. After stirring at -78°C for a further 2 h, the reaction was allowed to warm to -10°C and stirred at this temperature for 16 h. Saturated aqueous NH₄Cl (200 mL) and EtOAc (400 mL) were added to the reaction and the organic layer was separated. The aqueous phase was extracted with further EtOAc (400 mL), then the combined organic extracts were washed with brine (500 mL), before being dried (MgSO₄), filtered and concentrated. The residue was purified by column chromatography (EtOAc–iH₂O, 1:4) to provide the title compound: δᵢ (CDCl₃) 1.48 (d, 3H), 3.68 (s, 3H), 3.78 (s, 3H), 3.96 (q, 1H), 6.62 (dd, 1H), 6.68 (ddl, 1H), 7.19 (t, 1H).

Preparation 43: 2-(2-Fluoro-4-hydroxyphenyl)propionic acid methyl ester

(2-Fluoro-4-methoxyphenyl)propionic acid methyl ester (Preparation 42, 1.97 g, 9.29 mmol) in HBr (48%, 50 mL) was heated to 160°C with stirring for 16 h. The reaction mixture was cooled and concentrated, then the residue was redissolved in MeOH (50 mL). 12M HCl (1 drop) was added, then the reaction was heated to 80°C for 16 h, after which time it was concentrated. The residue was purified by column chromatography (EtOAc–iH₂O, 1:4) to provide the title compound: RT = 2.98 min; m/z (ES⁺) = 197.1 [M – H]⁻ (Method A).
Preparation 44: 2-(2-fluoro-4-[[3-[[1-(3-isopropyl-1,2,4]oxadiazol-5-yl]piperidin-4-yl]propoxy]phenyl]propionic acid methyl ester

Mitsunobu reaction of 2-(2-fluoro-4-hydroxyphenyl]propionic acid methyl ester (Preparation 43) and 3-[[1-(3-isopropyl-1,2,4]oxadiazol-5-yl]piperidin-4-yl]propan-1-ol (Preparation 3), by a procedure similar to that outlined in Preparation 30, provided the title compound: RT = 4.54 min; m/z (ES') = 434.2 [M + H]^+ (Method A).

Preparation 45: 3-[[1-(5-Ethylpyrimidin-2-yl]piperidin-4-yl]propan-1-ol

3-Piperidin-4-yl-propan-1-ol was reacted with 2-chloro-5-ethylpyrimidine, employing a procedure similar to that used for the synthesis of Preparation 29, to furnish the title compound: m/z (ES') = 250.15 [M + H]^+.

Preparation 46: Methanesulfonic acid 3-[[1-(5-ethylpyrimidin-2-yl]piperidin-4-yl]propyl ester

3-[[1-(5-Ethylpyrimidin-4-yl]propan-1-ol (Preparation 45) was reacted with methanesulfonyl chloride, utilising a procedure similar to that outlined in Preparation 25, to give the title compound: m/z (ES') = 328.18 [M + H]^+.

Preparation 47: 2-((4-(3-46-Chloropyridin-3-yl)oxy)propyl]piperidin-1-yl]-5-ethylpyrimidineline

Using a procedure similar to that outlined in Preparation 27, 6-chloropyridin-3-ol was condensed with methanesulfonyl acid 3-[[1-(5-ethylpyrimidin-2-yl]piperidin-4-yl]propyl ester (Preparation 46) to afford the title compound: RT = 4.20 min; m/z (ES') = 364.15 [M + H]^+ (Method A).

Preparation 48: 3-(4-[(R)-3-[[5-Chloropyrimidin-2-yl]piperidin-4-yl]butoxy]-2-methylphenyl]propionic acid ethyl ester
(R)-3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]butan-1-ol (Preparation 35) and 3-(4-hydroxy-2-methylphenyl)propionic acid ethyl ester were coupled under conditions similar to those of Preparation 34 to afford the title compound: m/z (ES⁺) = 460.2 [M + H]⁺.

Example 1: 4-[[3-Fluoro-4-(5-methyltetrazol-1-yl)phenoxy]propyl]piperidine-1-carboxylic acid tert-buty1 ester

DIAD (335 µL, 1.70 mmol) was added to a stirred solution of 3-fluoro-4-(5-methyltetrazol-1-yl)phenol (Preparation 5, 150 mg, 773 µmol), tert-butyl 4-(3-hydroxypropyl)piperidine-1-carboxylate (207 mg, 850 µmol) and PPh₃ (264 mg, 1.00 mmol) in THF (7 mL) at 0°C and the resulting solution was stirred at ambient temperature for 3.5 h. Further PPh₃ (80 mg, 309 µmol) was added, stirring at ambient temperature was continued for 1.5 h and then the reaction mixture was concentrated in vacuo. Purification by RP-HPLC afforded the title compound: RT = 4.13 min; m/z (ES⁺) = 426.14 [M + H]⁺ (Method A).

Example 2: 4-[[3-Fluoro-4-(3-methyl-1,2,4]oxadiazol-5-yl)phenoxy]propyl]piperidine-1-carboxylic acid isopropylester

NaH (60%, 24.0 mg, 572 µmol, washed with Et2O) was added to a solution of N-hydroxyacetanilide (40.0 mg, 630 µmol) in THF (4 mL) and the resulting solution stirred at ambient temperature for 10 min. 4-[[3-Fluoro-4-methoxy carbonylphenoxy]propyl]piperidine-1-carboxylic acid isopropylester (Preparation 6, 200 mg, 520 µmol) in THF (4 mL) was added and the resulting solution was stirred at ambient temperature for 20 h. The reaction was quenched with H₂O, diluted with EtOAc and the organic layer washed with brine, dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (EtOAc-Pe-H, 1:9 to 1:4) afforded the title compound: RT = 4.09 min; m/z (ES⁺) = 406.10 [M + H]⁺ (Method A).

Example 3: 4-[[4-(3-ethyl-1,2,4]oxadiazol-5-yl)-3-fluorophenoxy]propyl]piperidine-1-carboxylic acid isopropylester
The title compound was synthesized from N-hydroxypropionamide and 4-[3-(3-fluoro-4-methoxycarbonylphenoxy)propyl]piperidine-1-carboxylic acid isopropyl ester (Preparation 6) employing a procedure similar to that outlined in Example 2: RT = 4.31 min; m/z (ES⁺) = 420.10 [M + H⁺]⁺ (Method A).

**Example 4:** 4-[3-(Fluoro-4-(5-methyl-[1,3,4]oxadiazol-2-yl)phenoxy)propyl]piperidine-1-carboxylic acid isopropylester

Acetic anhydride (50.0 µL, 520 µmol) was added to a solution of 4-[3-(3-fluoro-4-hydrazinocarbonylphenoxy)propyl]piperidine-1-carboxylic acid isopropyl ester (Preparation 7, 100 mg, 260 µmol) in pyridine (2 mL) at 0°C and the resulting solution was stirred at ambient temperature for 72 h. The solvent was removed in vacuo to afford crude 4-[3-[4-(N'-acetylhydrazinocarbonyl)-3-fluorophenoxy]propyl]piperidine-1-carboxylic acid isopropyl ester which was heated under reflux conditions with P₂O₅ (205 mg, 1.44 mmol) in toluene (4 mL) for 6 h. The reaction mixture was cooled, poured into H₂O, basified with 1M NaOH and then extracted with EtOAc. The combined organic extracts were washed with H₂O, brine, dried (MgSO₄), filtered and concentrated in vacuo. Purification by RP-HPLC afforded the title compound: RT = 3.86 min; m/z (ES⁺) = 406.09 [M + H⁺]⁺ (Method A).

**Example 5:** 1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-4-[3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)phenoxy]propyl]piperidine

A mixture of 4-(5-methyl-[1,2,4]oxadiazol-3-yl)phenol (74.0 mg, 418 µmol) and K₂CO₃ (72.0 mg, 522 µmol) in anhydrous DMSO (0.5 mL) was stirred at ambient temperature for 10 mins, where after a solution of methanesulfonyl acid 3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propyl ester (Preparation 4, 115 mg, 348 µmol) in DMSO (1 mL) was added. The reaction mixture was stirred at ambient temperature for 48 h, diluted with DCM (10 mL), washed with H₂O and brine, dried (MgSO₄), filtered and concentrated in vacuo. Purification by RP-HPLC afforded the title compound: RT = 4.731 min; m/z (ES⁺) = 412.1 [M + H⁺]⁺ (Method B).
The compounds listed in Table 1 were synthesised from methanesulfonic acid 3-[[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propyl] ester (Preparation 4) and the appropriate phenol, employing a procedure similar to that outlined in Example 5.

Table 1

<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>Name</th>
<th>Spectra: LCMS Method B</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td><img src="image" alt="Structure 6" /></td>
<td>1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-4-[[3-(4-(5-methyltetrazol-1-yl)phenoxy)propyl]piperidin-4-yl]</td>
<td>RT = 4.104 min; m/z (ES⁺) = 412.4 [M + H]⁺</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Structure 7" /></td>
<td>1-(3-Isopropyl-[1,2,4]oxadiazol-5-yl)-4-[[3-(4-(4-methyltetrazol-2-yl)phenoxy)propyl]piperidin-4-yl]</td>
<td>RT = 5.077 min; m/z (ES⁺) = 427.1 [M + H]⁺</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Structure 8" /></td>
<td>6-(4-[[3-(1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy]-2-methoxyphenyl]pyridin-2-yl)amine</td>
<td>RT = 2.857 min; m/z (ES⁺) = 452.3 [M + H]⁺</td>
</tr>
</tbody>
</table>

Example 9: (R)-2-Aminomethylpyrrolidin-1-yl)-(4-[[3-(1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy]-2-methylphenyl)ethanone

HOBt (31.0 mg, 672 µmol) and EDCl (32 mg, 672 µmol) were added to a stirred solution of 4-[[3-[[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy]-2-methylbenzoic acid (Preparation 9, 200 mg, 517 µmol) in THF (12 mL). After 0.5 h, (R)-1-pyrrolidin-2-ylmethylcarbamic acid tert-butyl ester (207 mg, 1.033 mmol) was added and the resulting mixture was stirred at ambient temperature for 16 h. The THF was removed in vacuo and the residue was partitioned between EtOAc and 2M NaOH. The organic phase was separated and washed with 2M NaOH, 1M HCl and brine, before being dried (MgSO₄). Filtration, solvent evaporation, and purification by column chromatography (EtOAc:MeOH 1:1 to 1:0) afforded (R)-1-(4-[[3-[[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy]-2-methylbenzoyl]pyrrolidin-2-ylmethyl]carbamic acid tert-butyl ester: RT = 4.30 min; m/z (ES⁺) = 570.39 [M + H]⁺ (Method A). To a stirred solution of this compound in dioxane (5 mL) was added 4M HCl in dioxane (1.08 mL, 4.29 mmol) and the resulting solution was stirred at ambient temperature for 5 h. The solvent was removed in vacuo and the remainder was dissolved in H₂O and washed with EtOAc. The aqueous was basified to pH 12 with 2M NaOH and extracted with EtOAc.
The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo to afford the title compound: RT = 2.97 min; m/z (ES⁺) = 470.31 [M + H]⁺ (Method A).

**Example 10:** ((R)-3-Aminopiperidin-1-yl)-(2-fluoro-4-{3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}[phenyl)methanone

HOBr·H₂O (43.0 mg, 320 μmol) and EDCI (61.0 mg, 320 μmol) were added to a stirred solution of 2-fluoro-4-{3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}benzoic acid (Preparation 6, 100 mg, 258 μmol) in THF (3 mL). After 1 h, (R)-piperidin-3-ylcarbamic acid tert-butyl ester (102 mg, 512 μmol) was added and the resulting mixture was stirred at ambient temperature for 4 h. The THF was removed *in vacuo* and the residue was partitioned between DCM and 2M NaOH. The organic phase was separated and washed with 2M NaOH and 1M HCl. Solvent evaporation afforded ([R]-1-{(3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy})-2-methylbenzyl)piperidin-3-yl)carbamic acid tert-butyl ester. To a stirred solution of this compound in DCM (10 mL) was added trifluoroacetic acid (200 μL) and the resulting solution was stirred at ambient temperature for 2 h before quenching with saturated aqueous NaHCO₃ solution. The organic layer was separated and loaded onto a 2 g SCX column and washed with MeOH. Elution with 1% ammonia in MeOH afforded a crude product which was further purified by column chromatography (DCM–NEt₃, 99:1 to DCM–MeOH–NEt₃, 89:10:1) to afford the title compound: RT = 2.47 min; m/z (ES⁺) = 474.06 [M + H]⁺ (Method B).

The analogs listed in Table 2 were synthesised by condensing the appropriate acid with the appropriate Boc protected amine, followed by Boc deprotection, employing procedures similar to those outlined in Example 10.

**Table 2**

<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>Name</th>
<th>Spectra: LCMS Method B</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>((S)-3-Aminopyrrolidin-1-yl)-(2-fluoro-4-{3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}[phenyl)methanone</td>
<td>RT = 3.12 min; m/z (ES⁺) = 460.14 [M + H]⁺*</td>
</tr>
<tr>
<td>12</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>((R)-3-Aminopyrrolidin-1-yl)-(2-fluoro-4-{3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}[phenyl)methanone</td>
<td>RT = 3.17 min; m/z (ES⁺) = 460.00 [M + H]⁺*</td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Molecular Formula</td>
<td>Retention Time</td>
</tr>
<tr>
<td>-----</td>
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</tr>
<tr>
<td>13</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>(+)-Aminopiperidin-1-yl-(2-fluoro-4-{3-[1-[3-isopropyl]-1,2,4]oxadiazol-5-yl)-piperidin-4-yl)propoxy]-phenyl)methanone</td>
<td>RT = 2.07 min; m/z (ES*) = 473.97 [M + H]⁺</td>
</tr>
<tr>
<td>14</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>((S)-2-Aminomethyl-pyrrolidin-1-yl)-(2-fluoro-4-{3-[1-[3-isopropyl]-1,2,4]oxadiazol-5-yl)-piperidin-4-yl)propoxy]-phenyl)methanone</td>
<td>RT = 2.59 min; m/z (ES*) = 474.06 [M + H]⁺</td>
</tr>
<tr>
<td>15</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>((R)-2-Aminomethyl-pyrrolidin-1-yl)-(2-fluoro-4-{3-[1-[3-isopropyl]-1,2,4]oxadiazol-5-yl)-piperidin-4-yl)propoxy]-phenyl)methanone</td>
<td>RT = 2.47 min; m/z (ES*) = 474.06 [M + H]⁺</td>
</tr>
<tr>
<td>16</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>((S)-3-Aminopiperidin-1-yl)-(2-fluoro-4-{3-[1-[3-isopropyl]-1,2,4]oxadiazol-5-yl)-piperidin-4-yl)propoxy]-phenyl)methanone</td>
<td>RT = 2.13 min; m/z (ES*) = 474.01 [M + H]⁺</td>
</tr>
<tr>
<td>17</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td>(3-Aminooxazetidin-1-yl)-(2-fluoro-4-{3-[1-[3-isopropyl]-1,2,4]oxadiazol-5-yl)-piperidin-4-yl)propoxy]-phenyl)methanone</td>
<td>RT = 2.01 min; m/z (ES*) = 445.93 [M + H]⁺</td>
</tr>
<tr>
<td>18</td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>(+)-Aminopiperidin-1-yl)-(4-{3-[1-[3-isopropyl]-1,2,4]oxadiazol-5-yl)-piperidin-4-yl)propoxy]-2-methylphenyl)methanone</td>
<td>RT = 2.07 min; m/z (ES*) = 470.02 [M + H]⁺</td>
</tr>
<tr>
<td>19</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>((S)-3-Aminopyrrolidin-1-yl)-(4-{3-[1-[3-isopropyl]-1,2,4]oxadiazol-5-yl)-piperidin-4-yl)propoxy]-2-methylphenyl)methanone</td>
<td>RT = 2.03 min; m/z (ES*) = 456.02 [M + H]⁺</td>
</tr>
<tr>
<td>20</td>
<td><img src="image8" alt="Chemical Structure" /></td>
<td>((R)-3-Aminopiperidin-1-yl)-(4-{3-[1-[3-isopropyl]-1,2,4]oxadiazol-5-yl)-piperidin-4-yl)propoxy]-2-methylphenyl)methanone</td>
<td>RT = 2.45 min; m/z (ES*) = 470.11 [M + H]⁺</td>
</tr>
</tbody>
</table>
The amides listed in Table 3 were also synthesised by condensing the appropriate acid with the appropriate Boc protected amine, followed by Boc deprotection, employing procedures similar to those outlined in Example 10.

<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>Name</th>
<th>Spectra: LCMS Method A</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td><img src="structure23.png" alt="Image" /></td>
<td>(R)-2-Aminomethylpyrrolidin-1-yl(\cdot)4-(3-[1-(5-chloropyrimidin-2-yl)piperidin-4-yl]propoxy)-2,6-dimethylphenyl methanone</td>
<td>RT = 3.23 min; \textit{m/z} (ES(^+)) = 486.26 [M + H](^+)</td>
</tr>
<tr>
<td>24</td>
<td><img src="structure24.png" alt="Image" /></td>
<td>(S)-2-Aminomethylpyrrolidin-1-yl(\cdot)4-(3-[1-(5-chloropyrimidin-2-yl)piperidin-4-yl]propoxy)-2,6-dimethylphenyl methanone</td>
<td>RT = 3.25 min; \textit{m/z} (ES(^+)) = 486.25 [M + H](^+)</td>
</tr>
<tr>
<td>25</td>
<td><img src="structure25.png" alt="Image" /></td>
<td>(R)-2-Aminomethylpyrrolidin-1-yl(\cdot)4-(3-[1-(5-chloropyrimidin-2-yl)piperidin-4-yl]propoxy)-2-methylphenyl methanone</td>
<td>RT = 3.10 min; \textit{m/z} (ES(^+)) = 472.24 [M + H](^+)</td>
</tr>
<tr>
<td>26</td>
<td><img src="structure26.png" alt="Image" /></td>
<td>(S)-2-Aminomethylpyrrolidin-1-yl(\cdot)4-(3-[1-(5-chloropyrimidin-2-yl)piperidin-4-yl]propoxy)-2-methylphenyl methanone</td>
<td>RT = 3.07 min; \textit{m/z} (ES(^+)) = 472.24 [M + H](^+)</td>
</tr>
</tbody>
</table>
27  N-(3-Amino-2,2-dimethylpropyl)-4-[3-[1-(5-chloropyrimidin-2-yl)piperidin-4-yl]propoxy]-2,6-dimethylbenzamide

28  (3-Aminomethylazetidin-1-yl)-4-[3-[1-(5-chloropyrimidin-2-yl)piperidin-4-yl]propoxy]-2,6-dimethylphenylmethanone

29  (2-Aminoaazetidin-1-yl)-4-{3-[1-(5-chloropyrimidin-2-yl)piperidin-4-yl]propoxy}-2,6-dimethylphenylmethanone

30  (3-Amino-3-methylazetidin-1-yl)-4-{3-[1-(5-chloropyrimidin-2-yl)piperidin-4-yl]propoxy}-2,6-dimethylphenylmethanone

31  N-(3-Amino-2,2-dimethylpropyl)-4-[3-[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]propoxy]-2,6-dimethylbenzamide

RT = 3.02 min; $m/z$ (ES$^+$) = 488.26 [M + H]$^+$

RT = 2.92 min; $m/z$ (ES$^+$) = 472.22 [M + H]$^+$

RT = 2.92 min; $m/z$ (ES$^+$) = 458.20 [M + H]$^+$

RT = 2.95 min; $m/z$ (ES$^+$) = 472.23 [M + H]$^+$

RT = 2.72 min; $m/z$ (ES$^+$) = 482.33 [M + H]$^+$
The amides listed in Table 4 were synthesised by condensing the appropriate acid with an appropriate amine, employing an amide-forming reaction similar to that employed for the synthesis of Example 10.

<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>Name</th>
<th>Spectra: LCMS Method A</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td><img src="image1" alt="Image" /></td>
<td>4-[[3-Isopropyl-1,2,4]oxadiazol-5-yl]piperidin-4-yl[propoxy]-2-methyl-N-[2-(2-oxo-pyrrolidin-1-yl)methyl]benzamide</td>
<td>RT = 3.42 min; m/z (ES⁺) = 498.32 [M + H]⁺</td>
</tr>
<tr>
<td>33</td>
<td><img src="image2" alt="Image" /></td>
<td>4-[[3-Isopropyl-1,2,4]oxadiazol-5-yl]piperidin-4-yl[propoxy]-2-methyl-N-(1-methyl-5-oxo-pyrrolidin-3-yl)benzamide</td>
<td>RT = 3.37 min; m/z (ES⁺) = 484.30 [M + H]⁺</td>
</tr>
<tr>
<td>34</td>
<td><img src="image3" alt="Image" /></td>
<td>4-[[3-Isopropyl-1,2,4]oxadiazol-5-yl]piperidin-4-yl[propoxy]-2-methyl-N-(5)-(2-oxo-pyrrolidin-3-yl)benzamide</td>
<td>RT = 3.43 min; m/z (ES⁺) = 484.26 [M + H]⁺</td>
</tr>
<tr>
<td>35</td>
<td><img src="image4" alt="Image" /></td>
<td>4-[[3-Isopropyl-1,2,4]oxadiazol-5-yl]piperidin-4-yl[propoxy]-2-methyl-N-((R)-2-oxo-pyrrolidin-3-yl)benzamide</td>
<td>RT = 3.36 min; m/z (ES⁺) = 470.25 [M + H]⁺</td>
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</tr>
<tr>
<td><strong>36</strong></td>
<td>4-[2-[1-(3-Isopropyl-&lt;br&gt;[1,2,4]oxadiazol-5-yl)]-&lt;br&gt;piperidin-4-yl]propoxy]-2-&lt;br&gt;methyl-N-((S)-2-oxo-&lt;br&gt;pyrroolidin-3-yl)benzamide</td>
<td></td>
<td>RT = 3.30 min; m/z (ES&lt;sup&gt;+&lt;/sup&gt;) = 470.25 [M + H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>37</strong></td>
<td>4-[2-[1-(3-tert-Butyl-&lt;br&gt;[1,2,4]oxadiazol-5-yl)]-&lt;br&gt;piperidin-4-yl]propoxy]-2-&lt;br&gt;methyl-N-((S)-2-oxo-piperidin-&lt;br&gt;3-yl)benzamide</td>
<td></td>
<td>RT = 3.63 min; m/z (ES&lt;sup&gt;+&lt;/sup&gt;) = 498.28 [M + H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>38</strong></td>
<td>4-[3,1-(3-Isopropyl-&lt;br&gt;[1,2,4]oxadiazol-5-yl)]-&lt;br&gt;piperidin-4-yl]propoxy]-2-&lt;br&gt;methyl-N-((R)-1-methyl-2-oxo-&lt;br&gt;pyrroolidin-3-yl)benzamide</td>
<td></td>
<td>RT = 3.42 min; m/z (ES&lt;sup&gt;+&lt;/sup&gt;) = 484.27 [M + H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>39</strong></td>
<td>4-[3-[1-3-Isopropyl-&lt;br&gt;[1,2,4]oxadiazol-5-yl)]-&lt;br&gt;piperidin-4-yl]propoxy]-2-&lt;br&gt;methyl-N-((S)-1-methyl-2-oxo-&lt;br&gt;pyrroolidin-3-yl)benzamide</td>
<td></td>
<td>RT = 3.42 min; m/z (ES&lt;sup&gt;+&lt;/sup&gt;) = 484.27 [M + H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>40</strong></td>
<td>4-[3-[1-(3-tert-Butyl-&lt;br&gt;[1,2,4]oxadiazol-5-yl)]-&lt;br&gt;piperidin-4-yl]propoxy]-2-&lt;br&gt;methyl-N-((R)-2-oxo-&lt;br&gt;pyrroolidin-3-yl)benzamide</td>
<td></td>
<td>RT = 3.59 min; m/z (ES&lt;sup&gt;+&lt;/sup&gt;) = 484.24 [M + H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>41</strong></td>
<td>4-[3-[1-(3-tert-Butyl-&lt;br&gt;[1,2,4]oxadiazol-5-yl)]-&lt;br&gt;piperidin-4-yl]propoxy]-2-&lt;br&gt;methyl-N-((S)-2-oxo-&lt;br&gt;pyrroolidin-3-yl)benzamide</td>
<td></td>
<td>RT = 3.59 min; m/z (ES&lt;sup&gt;+&lt;/sup&gt;) = 484.24 [M + H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Example 45: 4-[(3-Fluoro-4-(3-methyl-2-oxo-imidazolidin-1-yl)phenoxyl)propyl]piperidine-1-carboxylic acid tert-butyl ester</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>To a solution of 4-[3-(4-bromo-3-fluorophenoxy)propyl]piperidine-1-carboxylic acid tert-butyl ester in 1,4-dioxane (4 mL) was added 1-methylimidazolidin-2-one (120 mg, 1.20 mmol), CuI (34.8 mg, 180 μmol), N,N-dimethylethane-1,2-diamine (15.3 mg, 174 μmol) and K₂CO₃ (299 mg, 2.16 mmol) and the resulting reaction mixture was heated under microwave irradiation at 140°C for 4 h. The reaction mixture was diluted with EtOAc and H₂O, then the aqueous was separated and extracted with EtOAc (2 ×). The combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (EtOAc-H₂O, 3:2) afforded the title compound. RT = 3.89 min; m/z (ES⁺) = 436.12 [M + H]⁺ (Method A).</td>
<td></td>
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</tr>
</tbody>
</table>

| Example 46: 4-[(2,3,4-tetrahydroquinolin-6-yl)oxyl]propyl]piperidine-1-carboxylic acid tert-butyl ester |

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104
To a solution of 6-hydroxy-3,4-dihydro-lH-quinolin-2-one (164 mg, 1.10 mmol) in THF (10 mL) was added tert-butyl 4-(3-hydroxypropyl)piperidine-1-carboxylate (243 mg, 1.00 mmol) and PPh₃ (341 mg, 1.30 mmol). The resulting reaction mixture was cooled to 0°C prior to the addition of DIAD (433 µL, 2.20 mmol). The reaction mixture was stirred at ambient temperature for 4 h, then the solvent was removed in vacuo. The remainder was triturated with Et₂O/H₂O, and the PPh₃ removed by filtration. The filtrate was concentrated in vacuo and purified by column chromatography (EtOAc/MeOH, 1:9) to afford the title compound; RT = 3.76 min; m/z (ES⁺) = 389.17 [M + H]⁺ (Method A).

**Example 47:** 5-{2-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}-2,3-dihydroisoindol-1-one

To a solution of 5-hydroxy-2,3-dihydroisoindol-1-one (100 mg, 0.671 µmol) in THF (7 mL) and DMAP (2 mL) was added 3-{1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl}propan-1-ol (Preparation 3, 165 mg, 0.652 µmol) and PPh₃ (444 mg, 1.67 mmol). The resulting reaction mixture was cooled to 0°C prior to the addition of DIAD (564 µL, 2.86 mmol). The reaction mixture was stirred at ambient temperature for 1.5 h, then the solvent was removed in vacuo. The reaction mixture was diluted with EtOAc (50 mL), washed with 2 M NaOH (20 mL), H₂O (20 mL) and brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (EtOAc/MeOH, 3:2 to 7:3 to 1:0) afforded the title compound; RT = 3.47 min; m/z (ES⁺) = 385.04 [M + H]⁺ (Method A).

**Example 48:** 5-{[(R)-3-{1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]butoxy}-2,3-dihydroisoindol-1-one

The title compound was synthesized from (R)-3-{1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl}butan-1-ol (Preparation 14) employing a procedure similar to that outlined in Example 47; RT = 3.65 min; m/z (ES⁺) = 399.3 [M + H]⁺ (Method A).
The compounds listed in Table 5 were synthesised employing the following general synthetic route:

A mixture of the appropriate phenol (237 µmol) and potassium tert-butoxide (3.5 mg, 296 µmol) in anhydrous DMSO (0.5 mL) was stirred at ambient temperature for 10 min followed by the addition of a solution of methanesulfonic acid 3-[1-(3-isopropyl-
[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propyl ester (Preparation 4, 65.5 mg, 198 µmol) in DMSO (0.5 mL). The resulting reaction mixture was stirred at ambient temperature for 2 h and then at 60°C for 16 h. The reaction mixture was diluted with DCM (10 mL), washed sequentially with H₂O and brine and then evaporated under reduced pressure. The crude product was purified by preparative HPLC.

<table>
<thead>
<tr>
<th>Eg</th>
<th>Structure</th>
<th>Name</th>
<th>Spectra: LCMS Method B</th>
</tr>
</thead>
<tbody>
<tr>
<td>49</td>
<td><img src="image" alt="Structure" /></td>
<td>7-[3-[(3-Isopropyl-&lt;br&gt; [1,2,4]oxadiazol-5-yl)-&lt;br&gt;piperidin-4-yl]propoxy]-1H-quinazolin-4-one</td>
<td>RT = 3.469 min; m/z (ES&lt;sup&gt;+&lt;/sup&gt;) = 398.3 [M + H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>50</td>
<td><img src="image" alt="Structure" /></td>
<td>7-[3-[(3-Isopropyl-&lt;br&gt;[1,2,4]oxadiazol-5-yl)-&lt;br&gt;piperidin-4-yl]propoxy]-3,4-&lt;br&gt;dihydro-1H-quinolin-2-one</td>
<td>RT = 3.945 min; m/z (ES&lt;sup&gt;+&lt;/sup&gt;) = 399.2 [M + H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>51</td>
<td><img src="image" alt="Structure" /></td>
<td>6-[3-[(3-Isopropyl-&lt;br&gt;[1,2,4]oxadiazol-5-yl)-&lt;br&gt;piperidin-4-yl]propoxy]-3,4-&lt;br&gt;dihydro-2H-isoquinolin-1-one</td>
<td>RT = 3.762 min; m/z (ES&lt;sup&gt;+&lt;/sup&gt;) = 399.2 [M + H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>52</td>
<td><img src="image" alt="Structure" /></td>
<td>7-[3-[(3-Isopropyl-&lt;br&gt;[1,2,4]oxadiazol-5-yl)-&lt;br&gt;piperidin-4-yl]propoxy]-3,4-&lt;br&gt;dihydro-2H-isoquinolin-1-one</td>
<td>RT = 3.830 min; m/z (ES&lt;sup&gt;+&lt;/sup&gt;) = 399.2 [M + H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>53</td>
<td><img src="image" alt="Structure" /></td>
<td>14-4-[(1-(3-Isopropyl-&lt;br&gt;[1,2,4]oxadiazol-5-yl)-&lt;br&gt;piperidin-4-yl)butoxy]-&lt;br&gt;phenylpyrroloidin-2-one</td>
<td>RT = 4.097 min; m/z (ES&lt;sup&gt;+&lt;/sup&gt;) = 413.3 [M + H]&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Example 54: 1-(2-Aminomethyl-4-[(R)-3-[(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-<br>y]butoxy]phenyl)pyrroloidin-2-one

![Structure](image)
TFA (0.95 mL) was added to a stirred solution of [5-{[R]-3-[1-3-isopropyl-1,2,4]oxadiazol-5-yl]piperidin-4-yl}butoxy]-2-(2-oxo-pyrrolidin-1-yl)benzyl]carbamic acid tert-butyl ester (Preparation 27, 153 mg, 275 μmol) in DCM (4.7 mL) at 0°C. After 2 h, the reaction was quenched with saturated aqueous NaHCO₃, then stirring was continued for a further 10 min. The mixture was treated with additional DCM, then the organic phase was washed with H₂O and brine, before being dried (MgSO₄), filtered and concentrated to afford the title compound: RT = 2.84 min; m/z (ES⁺) = 456.5 [M + H]⁺ (Method A).

**Example 55**: (4-{[3-{[1-5-Chloropyrimidin-2-yl]piperidin-4-yl}propoxy]phenyl}acetic acid

![Chemical structure of Example 55](image)

(4-{[3-{[1-5-Chloropyrimidin-2-yl]piperidin-4-yl}propoxy]phenyl}acetic acid methyl ester (Preparation 30, 370 mg, 0.92 mmol), LiOH·H₂O (77 mg, 1.83 mmol), THF (10 mL) and H₂O (5 mL) were stirred at 20°C for 16 h. The THF was removed *in vacuo* and the residue acidified with 2M HCl, then H₂O (10 mL) and CH₂Cl₂ (40 mL) were added. The organic layer was separated and concentrated to give the title compound: RT = 4.34 min; m/z (ES⁺) = 390.1 [M + H]⁺ (Method A)

**Example 56**: (4-{[1-[3-Isopropyl]-1,2,4]oxadiazol-5-yl]piperidin-4-yl}propoxy)-2-methylphenyl]acetic acid

![Chemical structure of Example 56](image)

A stirred solution of 2-{[4-{[3-{[1-3-isopropyl]-1,2,4]oxadiazol-5-yl]piperidin-4-yl}propoxy]-2-methylphenyl]-1-morpholin-4-ylethamine (Preparation 32, 3.3 g, 6.8 mmol), 10% aqueous NaOH (200 mL) and MeOH (200 mL) was heated to 90°C for 4 h. The MeOH was removed *in vacuo* and the pH adjusted to 2-3 with 12M HCl. EtOAc (200 mL) was added and the organic layer separated. The aqueous layer was extracted further with EtOAc (200 mL) and the combined organic extracts were dried (MgSO₄), filtered and concentrated to provide the title compound: RT = 3.88 min; m/z (ES⁺) = 402.2 [M + H]⁺ (Method A).

**Example 57**: (2-Fluoro-4-{[R]-3-[1-3-isopropyl]-1,2,4]oxadiazol-5-yl]piperidin-4-yl}butoxy]phenyl]acetic acid

![Chemical structure of Example 57](image)
(2-Fluoro-4-{(R)-3-[1-3-isopropyl-1,2,4]oxadiazol-5-yl)piperidin-4-yl[butoxy]phenyl)acetic acid methyl ester (Preparation 34) was saponified, using a procedure similar to that outlined in Example 55, to yield the title compound: RT = 4.05 min; m/z (ES') = 420.21 [M + H]^+ (Method A).

**Example 58:** (4-{(R)-3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl)butoxy]-2-fluorophenyl)acetic acid

![Chemical Structure of Example 58](image)

(4-{(R)-3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl)butoxy]-2-fluorophenyl)acetic acid methyl ester (Preparation 36) was saponified, using a procedure similar to that outlined in Example 55, to yield the title compound: RT = 4.57 min; m/z (ES') = 422.13 [M + H]^+ (Method A).

**Example 59:** (2-Fluoro-4-{3-[1-(3-isopropyl-1,2,4]oxadiazol-5-yl)piperidin-4-ylpropoxy}-phenyl)acetic acid

![Chemical Structure of Example 59](image)

2-(2-Fluoro-4-{3-[1-(3-isopropyl-1,2,4]oxadiazol-5-yl)piperidin-4-ylpropoxy}-phenyl)-1-morpholin-4-ylethanesulphone (Preparation 38) was reacted with NaOH, utilizing a procedure similar to that outlined in Example 56, to afford the title compound: RT = 3.73 min; m/z (ES') = 406.2 [M + H]^+ (Method A).

**Example 60:** (4-{3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl)propoxy]-2-fluorophenyl)acetic acid

![Chemical Structure of Example 60](image)

2-(4-{3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl)propoxy]-2-fluorophenyl)-1-morpholin-4-ylethanesulphone (Preparation 39) was reacted with NaOH, utilizing a procedure similar to that outlined in Example 56, to afford the title compound. RT = 4.14 min; m/z (ES') = 408.2 [M + H]^+ (Method A).
Example 61: 4-[[3-(4-Carboxymethyl-3-fluorophenoxy)propyl]piperidine-1-carboxylic acid tert-buty] ester

4-{{3-{3-Fluoro-4-(2-morpholin-4-yl-2-thiooxethyll)phenoxylpropylpiperidine-1-carboxylic acid tert-buty}ester (Preparation 49) was reacted with NaOH, utilizing a procedure similar to that outlined in Example 56, to afford the title compound: RT = 3.84 min; m/z (ES') = 396.11 [M + H]+ (Method A).

Example 62: 4-{{3-(4-Carboxymethylphenoxylpropylpiperidine-1-carboxylic acid tert-buty] ester

2M NaOH (2.5 mL, 5 mmol) was added to a stirred solution of 4-[[3-(4-methoxy carbonylmethylphenoxy)propylpiperidine-1-carboxylic acid tert-buty]ester (Preparation 41, 470 mg, 1.2 mmol) in MeOH (7 mL). After 1 h, the MeOH was removed under reduced pressure, then H2O was added along with sufficient saturated aqueous NaHCO3 to adjust the pH to 10. The solution was washed with Et2O (50 mL), then the aqueous phase was acidified to pH 2 with 12M HCl. The mixture was extracted with EtOAc (50 mL), then the EtOAc extracts were washed with brine (5 mL) and dried (MgSO4). Filtration and solvent evaporation furnished the title compound: RT = 3.76 min; m/z (ES') = 378.14 [M + H]+ (Method A).

Example 63: 2-(2-Fluoro-4-{{3-1,3-isopropyl[1,2,4]oxadiazol-5-yl]piperidin-4-yl]propoxy}phenylpropionic acid

2-(2-Fluoro-4-{{3-1,3-isopropyl[1,2,4]oxadiazol-5-yl]piperidin-4-yl]propoxy}phenylpropionic acid methyl ester (Preparation 44) was saponified, using a procedure similar
to that outlined in Example 55, to yield the title compound: RT = 4.07 min; m/z (ES\(^+\)) = 420.2 [M + H]\(^+\) (Method A).

The amides listed in Table 6 were synthesised by condensing 2-4-2-fluoro-4-[3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperdin-4-yl]propoxy|phenyl|propionic acid (Example 63) with an appropriate amine, employing an amide-forming reaction similar to that employed for the synthesis of Example 10.

<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>Name</th>
<th>Spectra: LCMS Method A</th>
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<tr>
<td>64</td>
<td><img src="image" alt="Structure" /></td>
<td>2-(2-Fluoro-4-[3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperdin-4-yl]propoxy</td>
<td>phenyl</td>
</tr>
<tr>
<td>65</td>
<td><img src="image" alt="Structure" /></td>
<td>N(-)(R)-2,3-Dihydroxypropyl(-)-2-(2-fluoro-4-[3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperdin-4-yl]propoxy</td>
<td>phenyl</td>
</tr>
<tr>
<td>66</td>
<td><img src="image" alt="Structure" /></td>
<td>N(-)(S)-2,3-Dihydroxypropyl(-)-2-(2-fluoro-4-[3-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperdin-4-yl]propoxy</td>
<td>phenyl</td>
</tr>
</tbody>
</table>

**Example 67:** 4-(3-[1-(5-Ethylpyrimidin-2-yl)piperdin-4-yl]propoxy|pyridin-2-yl|piperazin-2-one

![Diagram](image)

A mixture of piperazine-2-one (42 mg, 420 \(\mu\)mol), 2-[4-[3-[6-Chloropyrimidin-3-yl]oxy]propyl|piperidin-1-yl]-5-ethylpyrimidine (Preparation 47, 100 mg, 278 \(\mu\)mol), NaO\(_3\)Bu (67 mg, 698 \(\mu\)mol), 1,1-bis(di-tert-butylphosphino)ferrocene palladium dichloride (15 mg, 23 \(\mu\)mol), and PhMe (3 mL) was heated to 120°C for 30 min under microwave irradiation. On cooling to ambient temperature, the reaction mixture was partitioned between EtOAc (40 mL) and 10% aqueous citric acid (40 mL). The aqueous phase was carefully neutralized with saturated aqueous NaHCO\(_3\), before being extracted with EtOAc (2 × 30 mL). The combined organic layers were dried (MgSO\(_4\)), filtered, and concentrated to give a residue that was
triturated with EtO (3 × 20 mL) to furnish the title compound: RT = 2.73 min; m/z (ES^+) = 425.26 [M + H]^+ (Method A).

**Example 68**: 3-(4-[(R)-3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]butoxy]-2-methylphenyl)-propionic acid

![Chemical Structure](image)

3-(4-[(R)-3-[1-(5-Chloropyrimidin-2-yl)piperidin-4-yl]butoxy]-2-methylphenyl)-propionic acid ethyl ester (Preparation 48) was saponified, using a procedure similar to that outlined in Preparation 20, to furnish the title compound: RT = 4.68 min; m/z (ES^+) = 432.19 [M + H]^+ (Method A).

The biological activity of the compounds of the invention may be tested in the following assay systems:

**Yeast Reporter Assay**

The yeast cell-based reporter assays have previously been described in the literature (e.g., see Miret J. J. et al., 2002, J. Biol. Chem., 277:6881-6887; Campbell R.M. et al., 1999, Bioorg. Med. Chem. Lett., 9:2413-2418; King K. et al., 1990, Science, 250:121-123; WO 99/14344; WO 00/12704; and US 6,100,042). Briefly, yeast cells have been engineered such that the endogenous yeast G-alpha (GPA1) has been deleted and replaced with G-protein chimeras constructed using multiple techniques. Additionally, the endogenous yeast GPCR, Ste3 has been deleted to allow for heterologous expression of a mammalian GPCR of choice. In the yeast, elements of the pheromone signaling transduction pathway, which are conserved in eukaryotic cells (for example, the mitogen-activated protein kinase pathway), drive the expression of Fus1. By placing β-galactosidase (LacZ) under the control of the Fus1 promoter (Fus1p), a system has been developed whereby receptor activation leads to an enzymatic readout.

Yeast cells were transformed by an adaptation of the lithium acetate method described by Agatep et al. (Agatep, R. et al., 1998, Transformation of Saccharomyces cerevisiae by the lithium acetate/single-stranded carrier DNA/polyethylene glycol (LiAc/ss-DNA/PEG) protocol. Technical Tips Online, Trends Journals, Elsevier). Briefly, yeast cells were grown overnight on yeast tryptone plates (YT). Carrier single-stranded DNA (10 μg), 2 μg of each of two Fus1p-LacZ reporter plasmids (one with URA selection marker and one with TRP). 2 μg of GPR119 (human or mouse receptor) in yeast expression vector (2 μg origin of replication) and a lithium acetate/ polyethylene glycol/ TE buffer was pipetted into an Eppendorf tube. The yeast expression plasmid containing the receptor/ no receptor control has a LEU marker. Yeast cells were inoculated into this mixture and the reaction proceeds at 30°C for 60 min. The yeast cells were then heat-shocked at 42°C for 15 min. The cells were then washed and spread on selection plates. The selection plates are synthetic defined yeast media minus LEU, URA and TRP (SD-
LUT). After incubating at 30°C for 2-3 days, colonies that grow on the selection plates were then tested in the LacZ assay.

In order to perform fluorimetric enzyme assays for β-galactosidase, yeast cells carrying the human or mouse GPR119 receptor were grown overnight in liquid SD-LUT medium to an unsaturated concentration (i.e. the cells were still dividing and had not yet reached stationary phase). They were diluted in fresh medium to an optimal assay concentration and 90µl of yeast cells added to 96-well black polystyrene plates (Costar). Compounds, dissolved in DMSO and diluted in a 10% DMSO solution to 10X concentration, were added to the plates and the plates placed at 30°C for 4h. After 4h, the substrate for the β-galactosidase was added to each well. In these experiments, Fluorescein di (β-D-galactopyranoside) was used (FDG), a substrate for the enzyme that releases fluorescein, allowing a fluorimetric read-out. 20µl per well of 500µM FDG/2.5% Triton X100 was added (the detergent was necessary to render the cells permeable). After incubation of the cells with the substrate for 60min, 20µl per well of 1M sodium carbonate was added to terminate the reaction and enhance the fluorescent signal. The plates were then read in a fluorimeter at 485/535nm.

The compounds of the invention give an increase in fluorescent signal of at least ~ 1.5-fold that of the background signal (i.e. the signal obtained in the presence of 1% DMSO without compound). Compounds of the invention which give an increase of at least 5-fold may be preferred.

cAMP Assay

A stable cell line expressing recombinant human GPR119 was established and this cell line may be used to investigate the effect of compounds of the invention on intracellular levels of cyclic AMP (cAMP). The cell monolayers are washed with phosphate buffered saline and stimulated at 37°C for 30min with various concentrations of compound in stimulation buffer plus 1% DMSO. Cells are then lysed and cAMP content determined using the Perkin Elmer AlphaScreen™ (Amplified Luminescent Proximity Homogeneous Assay) cAMP kit. Buffers and assay conditions are as described in the manufacturer’s protocol.

In vivo feeding study

The effect of compounds of the invention on body weight and food and water intake may be examined in freely-feeding male Sprague-Dawley rats maintained on reverse-phase lighting. Test compounds and reference compounds are dosed by appropriate routes of administration (e.g. intraperitoneally or orally) and measurements made over the following 24 h. Rats are individually housed in polypropylene cages with metal grid floors at a temperature of 21±4°C and 55±20% humidity. Polypropylene trays with cage pads are placed beneath each cage to detect any food spillage. Animals are maintained on a reverse phase light-dark cycle (lights off for 8 h from 09.30-17.30 h) during which time the room was illuminated by red light. Animals have free access to a standard powdered rat diet and tap water during a two week acclimatization period. The diet is contained in glass feeding jars with aluminum lids. Each lid had a 3-4 cm hole in it to allow access to the food. Animals, feeding jars and water bottles are weighed (to the nearest 0.1 g) at the onset of the dark period. The feeding jars and water bottles are subsequently measured 1, 2, 4, 6 and 24 h after animals are dosed with a compound of the
invention and any significant differences between the treatment groups at baseline compared to vehicle-treated controls.

Anti-diabetic effects of compounds of the invention in an in-vitro model of pancreatic beta cells (HIT-T15)

Cell Culture

HIT-T15 cells (passage 60) were obtained from ATCC, and were cultured in RPMI1640 medium supplemented with 10% fetal calf serum and 30nM sodium selenite. All experiments were done with cells at less than passage 70, in accordance with the literature, which describes altered properties of this cell line at passage numbers above 81 (Zhang HJ, Walseth TF, Robertson RP. Insulin secretion and cAMP metabolism in HIT cells. Reciprocal and serial passage-dependent relationships. Diabetes. 1989 Jan;38(1):44-8).

cAMP assay

HIT-T15 cells were plated in standard culture medium in 96-well plates at 100,000 cells/0.1ml/well and cultured for 24 hr and the medium was then discarded. Cells were incubated for 15min at room temperature with 100μl stimulation buffer (Hanks buffered salt solution, 5mM HEPES, 0.5mM IBMX, 0.1% BSA, pH 7.4). This was discarded and replaced with compound dilutions over the range 0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30 μM in stimulation buffer in the presence of 0.5% DMSO. Cells were incubated at room temperature for 30min. Then 75μl lysis buffer (5mM HEPES, 0.3% Tween-20, 0.1% BSA, pH 7.4) was added per well and the plate was shaken at 900 rpm for 20 min. Particulate matter was removed by centrifugation at 3000rpm for 5min, then the samples were transferred in duplicate to 384-well plates, and processed following the Perkin Elmer AlphaScreen cAMP assay kit instructions. Briefly 25μl reactions were set up containing 8μl sample, 5μl acceptor bead mix and 12μl detection mix, such that the concentration of the final reaction components is the same as stated in the kit instructions. Reactions were incubated at room temperature for 150min, and the plate was read using a Packard Fusion instrument. Measurements for cAMP were compared to a standard curve of known cAMP amounts (0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30, 100, 300, 1000 nM) to convert the readings to absolute cAMP amounts. Data was analysed using XLfit 3 software.

Representative compounds of the invention were found to increase cAMP at an EC50 of less than 10 μM. Compounds showing an EC50 of less than 1 μM in the cAMP assay may be preferred.

Insulin secretion assay

HIT-T15 cells are plated in standard culture medium in 12-well plates at 106 cells/1 ml/well and cultured for 3 days and the medium then discarded. Cells are washed x 2 with supplemented Krebs-Ringer buffer (KRB) containing 119 mM NaCl, 4.74 mM KCl, 2.54 mM CaCl2, 1.19 mM MgSO4, 1.19 mM KH2PO4, 25 mM NaHCO3, 10mM HEPES at pH 7.4 and 0.1% bovine serum albumin. Cells are incubated with 1ml KRB at 37°C for 30 min which is then discarded. This is followed by a second incubation with KRB for 30 min, which is collected and used to measure basal insulin secretion levels for each well. Compound dilutions (0, 0.1, 0.3, 1, 3, 10 μM) are then added to duplicate wells in 1ml KRB, supplemented with 5.6 mM glucose. After 30 min incubation at 37°C samples are removed for determination of insulin
levels. Measurement of insulin is done using the Mercodia Rat insulin ELISA kit, following the manufacturers instructions, with a standard curve of known insulin concentrations. For each well insulin levels are corrected by subtraction of the basal secretion level from the pre-incubation in the absence of glucose. Data was analysed using XLfit 3 software.

Oral Glucose Tolerance Tests

The effects of compounds of the invention on oral glucose (Glc) tolerance were evaluated in male Sprague–Dawley rats. Food was withdrawn 16 h before administration of Glc and remained withdrawn throughout the study. Rats had free access to water during the study. A cut was made to the animals' tails, then blood (1 drop) was removed for measurement of basal Glc levels 60 min before administration of the Glc load. Then, the rats were weighed and dosed orally with test compound or vehicle (20% aqueous hydroxypropyl-β-cyclodextrin) 45 min before the removal of an additional blood sample and treatment with the Glc load (2 g kg\(^{-1}\) p.o.). Blood samples were then taken from the cut tip of the tail 5, 15, 30, 60, 120, and 180 min after Glc administration. Blood glucose levels were measured just after collection using a commercially available glucose-meter (OneTouch UltraTM from Lifescan). Representative compounds of the invention statistically reduced the Glc excursion at doses of ≤10 mg kg\(^{-1}\).

The effects of compounds of the invention on oral glucose (Glc) tolerance may also be evaluated in male C57Bl/6 or male ob/ob mice. Food is withdrawn 5 h before administration of Glc and remained withdrawn throughout the study. Mice have free access to water during the study. A cut is made to the animals' tails, then blood (20 μL) is removed for measurement of basal Glc levels 45 min before administration of the Glc load. Then, the mice are weighed and dosed orally with test compound or vehicle (20% aqueous hydroxypropyl-β-cyclodextrin or 25% aqueous Gelucire 44/14) 30 min before the removal of an additional blood sample (20 μL) and treatment with the Glc load (2–5 g kg\(^{-1}\) p.o.). Blood samples (20 μL) are then taken 25, 50, 80, 120, and 180 min after Glc administration. The 20 μL blood samples for measurement of Glc levels are taken from the cut tip of the tail into disposable micro-pipettes (Dade Diagnostics Inc., Puerto Rico) and the sample added to 480 μL of haemolysis reagent. Duplicate 20 μL aliquots of the diluted haemolysed blood are then added to 180 μL of Trinder's glucose reagent (Sigma enzymatic (Trinder) colorimetric method) in a 96-well assay plate. After mixing, the samples are left at rt for 30 min before being read against Glc standards (Sigma glucose/urea nitrogen combined standard set).
WHAT IS CLAIMED IS:

1. The present invention is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof:

   \[
   Z \rightarrow W \rightarrow X \rightarrow Y \rightarrow R \rightarrow G
   \]

   (I)

   wherein Z is phenyl or a 6-membered N containing heteroaryl group which phenyl or heteroaryl group is substituted by \(-(\text{CH}_2)_3\text{-C(O)NR}_1^1\), \(-\text{E}_1\text{-CO}_2\text{H}\), \(-\text{CH(CH}_3)\text{-C(O)NR}_1^1\), a 5- or 6-membered N containing heterocyclic ring, which ring is substituted with oxo and optionally substituted by methyl, or a 5- or 6-membered N containing heteroaryl ring optionally containing up to 3 additional heteroatoms selected from N, O and S, which ring is substituted by C\(_{1-\text{3}}\) alkyl or \(-\text{NH}_2\);

   or Z is 1H-quinazoline-4-one, 2,3-dihydroisoindol-1-one, 1,3-dihydroindol-2-one, 3,4-dihydro-1H-quinolin-2-one, or 3,4-dihydro-2H-isoquinolin-1-one, which is attached to W through an aromatic carbon atom;

   and wherein Z is further optionally substituted by one or more C\(_{1-\text{2}}\) alkyl, C\(_{1-\text{2}}\) alkoxy, CH\(_3\)NH\(_2\), or fluoro groups;

   \(j\) is 0, 1 or 2;

   \(E_1\) is \(-\text{CH}_2\), \(-\text{CH}_2\text{-CH}_2\), or \(-\text{CH}(\text{CH}_3)\);

   \(W\) and \(Y\) are independently a bond, an unbranched or a branched C\(_{1-\text{4}}\) alkyne optionally substituted by hydroxy or C\(_{1-\text{3}}\) alkoxy, or an unbranched or a branched C\(_{2-\text{4}}\) alkenylene;

   \(X\) is selected from CH\(_2\), O, S, CH(OH), CH(dialogen), CF\(_2\), C(O), C(O)O, C(O)S, SC(O), C(O)CH\(_2\)S, C(O)CH\(_3\)C(OH), C(O)CH\(_2\text{-C(O)}\), C(O)CH\(_3\)C(O), OC(O), NR\(^5\), CH\(_{2}\text{(NR}_2\text{R}^{55})\), C(O)NR\(^3\), NR\(^3\)C(O), S(O) and S(O)\(_2\);

   \(R^5\) is hydrogen or hydroxy;

   \(G\) is \(\text{CHR}_3^1\), N-C(O)OR\(^8\), N-C(O)NR\(^3\)R\(^2\), N-C\(_{1-\text{4}}\)alkylen-C(O)OR\(^8\), N-C(O)C(O)OR\(^8\), N-S(O)R\(^3\), N-C(O)R\(^1\) or N-P(O)(O-Ph)\(_2\); or N-heterocyclyl or N-heteroaryl, either of which may optionally be substituted by one or two groups selected from C\(_{1-\text{4}}\) alkyl, C\(_{1-\text{4}}\) alkoxy or halogen; provided that \(G\) is not optionally substituted N-pyridazinyl;

   \(R^1\) and \(R^\text{II}\) together with the N atom to which they are attached form a 4- to 6-membered ring substituted by \(-\text{N}(R_2^3)\text{-}\) or \(-\text{CH}_2\text{NH}_2\) and optionally further substituted with methyl; or \(R^1\) is hydrogen and \(R^\text{II}\) is C\(_{5-\text{6}}\) alkyl substituted by amino or \(-\text{CH}(\text{CH}_3)\text{-}L\);

   in addition, when Z is \(-\text{CH}(\text{CH}_3)\text{-C(O)NR}_1^1\), \(R^1\) may be hydrogen and \(R^\text{II}\) may be hydrogen, C\(_{1-\text{3}}\) alkyl, or C\(_{2-\text{3}}\) alkoxy substituted by one or two hydroxy groups;

   \(L\) is a \(\alpha\) or \(\delta\) lactam optionally substituted with methyl;

   \(k\) is 0, 1 or 2;

   \(R^2\) are independently hydrogen or C\(_{1-\text{4}}\) alkyl;

   \(R^2\) is C\(_{3-\text{5}}\) alkyl;

   \(R^4\) is C\(_{1-\text{4}}\) alkyl, C\(_{2-\text{8}}\) alkenyl or C\(_{2-\text{8}}\) alkynyl, any of which may be optionally substituted by one or more substituents selected from halo, NR\(^2\)R\(^5\), OR\(^3\), C(O)OR\(^3\), OC(O)R\(^3\) and CN, and
may contain a CH₂ group that is replaced by O or S; or a C₃₋₇ cycloalkyl, aryl, heterocyclyl, heteroaryl, C₁₋₄ alkyleneC₃₋₇ cycloalkyl, C₁₋₄ alkylenearyl, C₁₋₄ alkyleneheterocyclyl or C₁₋₄ alkyleneheteroaryl, any of which may be substituted with one or more substituents selected from halo, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, OR², CN, NR³R⁵⁺, SO₂Me, NO₂ and C(O)OR⁵⁺;

R⁵⁺ and R⁵⁻ are independently hydrogen or C₁₋₄ alkyl; or taken together R⁵⁺ and R⁵⁻ may form a 5- or 6-membered heterocyclic ring; or a group NR³ may represent NS(O)₂-(2-NO₂-C₆H₄);

d is 0, 1, 2 or 3; and
c is 1, 2, 3, 4 or 5, provided that d + c is 2, 3, 4 or 5.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein Z represents phenyl or a 6-membered heteroaryl group containing up to two N heteroatoms substituted as defined in claim 1.

3. A compound according to claim 2, or a pharmaceutically acceptable salt thereof, wherein Z represents phenyl substituted as defined in claim 1.

4. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein Z is substituted by -(CH₂)₃-C(O)NR³⁻R¹⁺ or -E¹⁻CO₂H.

5. A compound according to claim 4, or a pharmaceutically acceptable salt thereof, wherein E¹⁻ is -CH₂⁻.

6. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein -W-X-Y⁻ is -O-CH₂-CH₂-CHR⁻, where R⁻ is hydrogen or methyl.

7. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein G is N-C(O)OR⁴⁺ or N-heteroaryl.

8. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein d and e represent 2.

9. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R⁴⁺ is hydrogen.

10. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R⁻ is C₂₋₅ alkyl.

11. A compound of formula (Ia), or a pharmaceutically acceptable salt thereof:
wherein:
Z is as defined in claim 1;
R² is hydrogen or methyl;
R² is -C(O)OR⁴ or a 5- or 6-membered heteroaryl group optionally substituted by one or
two groups selected from C₁₋₄ alkyl, C₁₋₄ alkoxy or halogen; and
R⁴ is C₂₋₅ alkyl.

12. A compound of formula (I) as defined in any one of Examples 1 to 68, or a
pharmacologically acceptable salt thereof.

13. A pharmaceutical composition comprising a compound according to any one of claims
1 to 12, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

14. A method for the treatment of a disease or condition in which GPR119 plays a role
comprising a step of administering to a subject in need thereof an effective amount of a
compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof.

15. A method for the regulation of satiety comprising a step of administering to a subject in
need thereof an effective amount of a compound according to any one of claims 1 to 12, or a
pharmacologically acceptable salt thereof.

16. A method for the treatment of obesity comprising a step of administering to a subject in
need thereof an effective amount of a compound according to any one of claims 1 to 12, or a
pharmacologically acceptable salt thereof.

17. A method for the treatment of diabetes comprising a step of administering to a subject in
need thereof an effective amount of a compound according to any one of claims 1 to 12, or a
pharmacologically acceptable salt thereof.

18. A method for the treatment of metabolic syndrome (syndrome X), impaired glucose
tolerance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels or
hypertension comprising a step of administering to a patient in need thereof an effective amount
of a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt
thereof.

19. A compound according to any one of claims 1 to 12, or a pharmaceutically acceptable
salt thereof, for use as a medicament.

20. Use of a compound according to any one of claims 1 to 12 or a pharmaceutically
acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of a
disease or condition as defined in any one of claims 14 to 18.
21. A compound according to any one of claims 1 to 12 or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of a disease or condition as defined in any one of claims 12 to 16.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D211/32 C07D401/04 C07D401/12 C07D401/14 C07D413/04
C07D413/12 C07D413/14 A61K31/4525 A61K31/454 A61K31/4545

A61P3/04 A61P3/10

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K C07D

Documentation searched other than minimum documentation in the fields indicated in the front that such documents are included in the fields searched

Electronic data-base consulted during the international search (name of data base and, where practical, search parameters)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim no.</th>
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Further documents are listed in the continuation of this C:

See separate section

Special category of cited documents:

A. document defining the general state of the art which is not considered to be of particular relevance

B. document further to or after the international filing date

C. document containing no prior art

D. document which may be considered an equivalent for the claimed invention

E. document containing further information helpful to understand the invention

F. document containing prior art and not considered to be of particular relevance

G. document containing prior art and considered to be of particular relevance

H. document containing prior art and not considered to be of particular relevance

I. document containing prior art and considered to be of particular relevance

J. document containing prior art and not considered to be of particular relevance

K. document containing prior art and considered to be of particular relevance

L. document containing prior art and not considered to be of particular relevance

M. document containing prior art and considered to be of particular relevance

N. document containing prior art and not considered to be of particular relevance

O. document containing prior art and considered to be of particular relevance

P. document containing prior art and not considered to be of particular relevance

Q. document containing prior art and considered to be of particular relevance

R. document containing prior art and not considered to be of particular relevance

S. document containing prior art and considered to be of particular relevance

T. document containing prior art and not considered to be of particular relevance

U. document containing prior art and considered to be of particular relevance

V. document containing prior art and not considered to be of particular relevance

W. document containing prior art and considered to be of particular relevance

X. document containing prior art and not considered to be of particular relevance

Y. document containing prior art and considered to be of particular relevance

Z. document containing prior art and not considered to be of particular relevance

Other documents are listed in the continuation of this section:

Data of the actual completion of the international search

2 October 2009

Data of mailing of the international search report

14/10/2009

Name and mailing address of the ISA

European Patent Office, P B 5616 Palaisavenue 2
CH - 2230 Fribourg
Tel: +41 31 399 2000
Fax: +41 31 399 2046

Authorized officer

Sotoca Usina, E
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<td>WO 2008/081204 A (PROSIDION LTD [GB]; FYFE MATTHEW COLIN THOR [GB]; KELLY JOHN [GB]; SMA) 10 July 2008 (2008-07-10) the whole document</td>
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<td>CL 182008 A1</td>
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The Patents Act, 1970 (as amended)

SECTION 15

In the matter of an
Application for Patent Number
478/MUMNP/2015
Dated 05/03/2015

By
JANSSEN SCIENCES IRELAND UC

The Applicant

DECISION

In view of the outstanding objections as raised by the Examiner after further examination of the instant application on the basis of response to FER filed by the Agent of the Applicant, this Office offered the Applicant an opportunity of being heard under Section 14 of The Act before the undersigned on 18/11/2019. The applicant has attended the hearing and submitted his reply on 03/12/2019.

In view of the applicant’s submission to the objection u/s 2(1)(ja) & 3(d), the office has reached to the following conclusion:-

The instant application discloses a compound of formula (I) with the proviso that N-(2-amino-5-phenethylpyrimidine-4-yl)-N-pentylamine is excluded.

The cited prior arts (D1-D3) also discloses the same compounds and the present compounds differ from the prior art in R1 position where it is ‘Hydrogen’ atom (present claimed compounds). But, “Replacement of alkyl group/or other group” cannot be considered as ‘Technical advancement’. Therefore, the office considers that the applicant has not complied the objections raised in hearing notice, and the present claimed subject matter (claim 1-3) does not meet requirements of section 2(1)(ja) of the Patent Act, 1970.

For the same reason the claims no 1-3 are also not allowable u/s 3(d) of the Patent Act 1970.

Under this circumstance, I hereby refuse to proceed further with this instant patent application number 478/MUMNP/2015 for grant of patent in accordance with Section 15 of The Patents Act, 1970 (as amended).

Dated this 21st day of February 2020.

(Mr. Sudipta Dey)
Assistant Controller of Patents & Designs

Attachments:
Details of the objections raised in Hearing Notice
Applicant’s Written Submission after hearing
पेषण दिनांक / Date of Dispatch: 12 Jul 2019

संदर्भ सं. / Ref. No : POK/Application No/478/MUMNP/2015

लेखा वे, / To
GOWREE GOKHALE
GOWREE GOKHALE NISHITH DESAI ASSOCIATES, 93-B MITTAL COURT,
NARIMAN POINT, MUMBAI 400 021, INDIA.

विषय: आवेदन संख्या 478/MUMNP/2015 के संदर्भ में सुनवाई नोटिस
Sub: Hearing Notice in Reference of Application No. 478/MUMNP/2015

सुनवाई स्थल / Hearing Location: KOLKATA

आपके द्वारा पूर्व परीक्षण रिपोर्ट / अनुमोदन परीक्षण रिपोर्ट के उत्तर के संदर्भ में, दिनांक 30/07/2019 को 03:00 PM To 03:30 PM बजे तक इस मामले में Hearing U/S (14) सुनवाई तय की गई है। अतः, आपके उपरोक्त दिनांक व समय पर निवडतृत के समय सुनवाई हेतु उपस्थित होना है।

With reference to your reply to the First examination Report/Subsequent Examination Report, a Hearing U/S (14) hearing is fixed in the matter on 30/07/2019 at 03:00 PM To 03:30 PM . You are therefore, required to appear before the Controller for the hearing on said date and time.

इस आवेदन को पेटेंट अनुदान हेतु पूर्व / अंतिम विधि के पूर्व / अंतिम विधि के उपयोग से पूर्व, निर्दिष्ट आवश्यकताएँ अभी भी मैंने नहीं किया।
The following objection(s) are still outstanding before / after the expiry of last date for putting this application in order for grant of patent.

Sudipta Dey
Assistant Controller of Patents & Designs

Please refer to the following URL for: Date/Time, Venue, Status and other details about the Hearing
http://ipindiaservices.gov.in/PatentCauseList

* Hearing Objections are attached.
Objections

Clarity and Conciseness

1. 1. The term pharmaceutically acceptable salt etc in claims renders their scope unclear, since it is not known to the skilled reader which structures are intended to be encompassed by this term. Further, the uses of vague and imprecise statement like a pharmaceutically acceptable salt etc make the claims and description indefinite, thereby resulting in a lack of clarity of the claims. Therefore this statement should be amended to bring the clarity.

Invention u/s 2(1)(j)

1. 1. Claims of the alleged invention lacks inventive step in view of prior art documents u/s 2(1)(ja) of the Patents Act.

D1 : EP1110951A1 (27/06/2001)

D2: WO2012066335A1 (24/05/2012)

D3: WO2009067081A (28/05/2009)

The cited document D1 discloses synthesized various compounds and examined them on the effect to Th1 and Th2 immune responses. As a result, it was found that certain pyrimidine derivatives enhance Th1 immune responses and suppress Th2 immune responses and therefore, change the balance of Th1/Th2 into preferable direction. That is, the invention relates to: a pyrimidine derivative of the formula (1) or a salt thereof; wherein R<1> is a formula (2); ring A is substituted or unsubstituted C3-10 cycloalkane, substituted or unsubstituted C5-10 cycloalkene, substituted or unsubstituted C7-10 bicycloalkane, or substituted or unsubstituted heterocyclic ring containing O atom or S atom as a heteroatom, and said S atom may form sulfinyl or sulfonyl together with one or two oxygen atoms, and R<4> is straight or branched C1-10 alkyl, C2-6 alkenyl, C3-6 alkinyl, C3-6 cycloalkyl, C4-10 cycloalkyl-alkyl, or OR<8> (R<8> is straight or branched C1-10 alkyl, C3-6 alkenyl, C3-6 alkinyl, C3-6 cycloalkyl or C4-10 cycloalkyl-alkyl

The cited document D2 discloses novel phenol compounds and, more particularly, to novel phenol compounds that act as TLR7 agonists. This invention also relates to methods for the preparation of such compounds and novel intermediates in the preparation thereof, to pharmaceutical compositions containing such compounds, to the use of such compounds in the preparation of medicaments, and to the use of such compounds in the treatment of conditions mediated by TLR7, such as allergic diseases, autoimmune diseases, viral diseases and, in particular, cancer.

The cited document D3 discloses relates to pyrimidine derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

From the teachings of prior art documents D1-D3 alkylpyrimidine derivatives of and processes for their preparationpharmaceutical compositions and their use in therapy for the treatment of viral infections is very obvious to the person skilled in the art having common general knowledge hence the claims are not allowable u/s 2(1)(ja) of the Patents.

Non-Patentability u/s 3

1. 1. Claims 1-2 attract the provision of section 3(d) of the Act.
BEFORE THE LEARNED CONTROLLER SUDIPTA DEY

PATENT OFFICE, KOLKATA

IN THE MATTER OF APPLICATION NO. 478/MUMNP/2015 FOR GRANT OF PATENT

IN THE NAME OF APPLICANT JANSSEN SCIENCES IRELAND UC

WRITTEN SUBMISSIONS OF THE ORAL ARGUMENTS BY THE APPLICANT

MAY IT PLEASE THE LEARNED CONTROLLER:

These written submissions are in pursuance of the oral submissions made at the hearing held on November 18, 2019 on behalf of the Applicant. Should the Ld. Controller not be convinced by any argument herein below, the Applicant humbly prays that it be provided one more opportunity before the Ld. Controller proceeds towards granting an order.

Relevant Facts

1. The Indian Application No. 478/MUMNP/2015 was filed on March 5, 2015 by the Applicant Janssen Sciences Ireland UC. A first examination report ("FER") was issued on June 20, 2018. A response to the FER was filed by the Applicant on April 20, 2019.

2. A hearing notice was issued by the Ld. Controller on November 1, 2019 scheduling the hearing on November 18. The Agents/Attorney of the Applicant appeared before the Ld. Asst. Controller on the scheduled date to make initial oral submission regarding the outstanding objections and requested for an adjournment for making further oral submissions.

3. In addition to the submissions below, the Applicant reiterates all the submissions made by it in the FER.
**Invention**

This invention relates to alkylpyrimidine derivatives and pharmaceutical compositions comprising such derivatives used in the treatment of viral infections, immune or inflammatory disorders, whereby the modulation, or agonism, of toll-like-receptors (TLRs) is involved.

Toll-Like Receptors are primary transmembrane proteins characterized by an extracellular leucine rich domain and a cytoplasmic extension that contains a conserved region. The innate immune system can recognize pathogen-associated molecular patterns via these TLRs expressed on the cell surface of certain types of immune cells. Recognition of foreign pathogens activates the production of cytokines and upregulation of co-stimulatory molecules on phagocytes. This leads to the modulation of T cell behaviour.

Compounds indicating activity on Toll-Like receptors have been previously described such as heterocyclic derivatives in WO2000006577, adenine derivatives in WO 98/01448 and WO 99/28321, and pyrimidines in WO 2009/067081.

However, there exists a strong need for novel Toll-Like receptor modulators having preferred selectivity, and an improved safety profile compared to the compounds of the prior art and hence, the Applicant has arrived at the compounds of the present invention.

**Amendments**

At the outset, it is humbly submitted that the Applicant to expedite the grant of the patent application wishes to pursue the attached revised set of claims annexed herein as ‘Annexure A’ wherein the term “pharmaceutically accepted salt” has been deleted from the claims.

**Outstanding Objection 1 of the hearing notice – Clarity and Conciseness**

1. The Ld. Controller has stated that “The term pharmaceutically acceptable salt etc in claims renders their scope unclear, since it is not known to the skilled reader which structures are intended to be encompassed by this term. Further, the uses of vague and imprecise statement like a pharmaceutically acceptable salt etc make the claims and description indefinite, thereby resulting in a lack of clarity of the claims. Therefore this statement should be amended to bring the clarity.”
2. The Applicant respectfully submits that the claims have been amended

In light of the foregoing, the Applicant submits that the amended claims as enclosed herewith are inventive and hence, the Applicant requests the Ld. Controller to waive this objection.

**Outstanding Objection 2(A) of the hearing notice: Definitiveness**

1. In this objection, the Ld. Controller has stated that “Claims of the alleged invention lacks inventive step in view of prior art documents u/s 2(1)(ja) of the Patents Act.

**D1: EP1110951A1 (27/06/2001)**

**D2: WO2012066335A1 (24/05/2012)**

**D3: WO2009067081A (28/05/2009)**

The cited document D1 discloses synthesized various compounds and examined them on the effect to Th1 and Th2 immune responses. As a result, it was found that certain pyrimidine derivatives enhance Th1 immune responses and suppress Th2 immune responses and therefore, change the balance of Th1/Th2 into preferable direction. That is, the invention relates to: a pyrimidine derivative of the formula (1) or a salt thereof; wherein R is a formula (2); ring A is substituted or unsubstituted C3-10 cycloalkane, substituted or unsubstituted C5-10 cycloalkene, substituted or unsubstituted C7-10 bicycloalkane, or substituted or unsubstituted heterocyclic ring containing O atom or S atom as a heteroatom, and said S atom may form sulfinyl or sulfonyl together with one or two oxygen atoms, and R is straight or branched C1-10 alkyl, C2-6 alkenyl, C3-6 alkynyl, C3-6 cycloalkyl, C4-10 cycloalkyl-alkyl, or OR (R is straight or branched C1-10 alkyl, C3-6 alkenyl, C3-6 alkynyl, C3-6 cycloalkyl or C4-10 cycloalkyl-alkyl The cited document D2 discloses novel phenol compounds and, more particularly, to novel phenol compounds that act as TLR7 agonists. This invention also relates to methods for the preparation of such compounds and novel intermediates in the preparation thereof, to pharmaceutical compositions containing such compounds, to the use of such compounds in the preparation of medicaments, and to the use of
such compounds in the treatment of conditions mediated by TLR7, such as allergic diseases, autoimmune diseases, viral diseases and, in particular, cancer. The cited document D3 discloses relates to pyrimidine derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy. From the teachings of prior art documents D1-D3 alkylpyrimidine derivatives of and processes for their preparation pharmaceutical compositions and their use in therapy for the treatment of viral infections is very obvious to the person skilled in the art having common general knowledge hence the claims are not allowable u/s 2(1)(ja) of the Patents.”

D1: EP1110951A1 (27/06/2001)

2. D1 relates to relates to pyrimidine derivatives having activities for suppression of type 2 helper T cell (Th2) immune responses and enhancement of type 1 helper T cell (Th1) immune responses. D1 does not relate to compounds exhibiting activity as TLR modulators. Therefore, the application for the compounds are completely different and the compounds of D1 would not be the starting point for the compounds of the present invention.

3. The Applicant submits that Formula (1) of D1 (reproduced below) presents a very broad class of compounds, requiring many choices to be made in order to arrive at individual structures.

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{R}^2 & \quad \text{R}^3 \\
\text{NH}_2 & \quad \text{NHR}^1 \\
\end{align*}
\]

Variable R1 of formula (1) refers to a wide range of options defined under Formulae (2) and (3). These options include at least one hundred and twelve options for the
groups of choice in connection with formula (3), specifically, eight groups for R5, seven groups for R6, and two groups for R7.

Variable R2 of formula (1) includes at least four groups: H, C1-10 alkyl, C3-5 alkylene together with R3, and C3-5 alkylene together with R3 in which methylene is replaced by O. Variable R3 includes at least seven groups from which to choose (including formula (4)).

Specifically, to arrive at the compounds of the present invention, R1 would have to be the option in which a structure of formula (3) is chosen in which R5 is C1-10 alkyl, R6 is hydrogen, and R7 is hydrogen; R2 would have to be selected as hydrogen; and R3 would have to be selected as formula (4), with R11 being phenyl or pyridyl.

D1 does not in any manner direct the skilled person to making the combination of choices required to arrive at the instantly claimed compounds.

Further, if the examples of D1 are taken as guidance, it is clear that the reference teaches away from the compounds of the instant claims. For instance, Examples 1-13, 16, and 19-21 teach R2 and R3 of formula (1) are fused rings and, therefore, teach away from the claimed compounds, in which the position corresponding to R2 of D1 in the instant claims is unsubstituted. Further, Examples 14, 15, 17, 18, 22-26, and 29 all disclose compounds that are substituted at positions R2 and R3, again teaching away from the claimed compounds. Finally, Example 30 includes a list of 27 additional compounds, all of which contain either independent substituents or a fused ring at positions R2 and R3.

Thus, the examples in which R2 is not substituted are the exception, rather than the rule, of D1. Accordingly, one having skill in the art would understand that the main teaching of D1 is to have both positions R2 and R3 occupied with a substituent (either with two independent substituents or with a fused ring).
Further, D1 includes several test examples, one of which is specifically directed to the compounds of Examples 26, 27, and 28 (see test 4, with results presented in Table 2 on page 36 of D1, reproduced below with the structural formulae added).

<table>
<thead>
<tr>
<th>Example</th>
<th>Structure</th>
<th>IL-4 Inhibition (IC₅₀ in µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td><img src="image" alt="Structure 26" /></td>
<td>0.5</td>
</tr>
<tr>
<td>27</td>
<td><img src="image" alt="Structure 27" /></td>
<td>1</td>
</tr>
<tr>
<td>28</td>
<td><img src="image" alt="Structure 28" /></td>
<td>2</td>
</tr>
</tbody>
</table>

Compound 26 has both R2 and R3 substituted, and thereby falls outside the scope of the instant claims. Compound 27 also falls outside the scope of the instant claims, but is closer in the sense that R2 is selected to be hydrogen. Compound 28 is closer still to the present claims, in the sense that it is the compound disclaimed from claim 1.

From the results of test 4, one having skill in the art would understand that compound 26, in terms of IC₅₀, is twice as potent as compound 27, and four times as potent as compound 28. Test 4 of D1 thus confirms the aforementioned main teaching of D1: the clear preference to have both R2 and R3 substituted.

Accordingly, one having skill in the art would not have been motivated to arrive at the compounds of the instant claims from D1 because the main thrust of the teaching of D1 is away from the substitution patterns in the instant claims.
Therefore, the Applicant humbly submits that D1 neither independently nor in combination with the other prior arts motivates a person skilled in the art to arrive at the claims as claimed in the present invention from the general disclosures made in D1.

**D2: WO2012066335A1 (24/05/2012)**

4. D2 discloses phenol compounds whereas the present invention relates to alkylpyrimidine derivatives. The compounds of D2 contain a phenolic ring off the 5-position of the pyrimidine ring that would be impossible to accommodate in the instant claims given the variable definitions therein. In the instant claims, the corresponding position is substituted with a two-carbon linker which may terminate in an aryl group, wherein the aryl group may be optionally substituted with one or more C1-6 alkoxy groups. In contrast, formula (I) of D2 requires a one-carbon linker, culminating in a phenolic ring that is further substituted with an aminoalkoxy or aminoalkyl group. The Applicant humbly submits that D2 neither independently nor in combination with the other prior arts motivates a person skilled in the art to arrive at the claims as claimed in the present invention.

**D3: WO2009067081A (28/05/2009)**

5. D3 discloses pyrimidine compounds. The Applicant submits that the compounds of D3 differ from compounds of the present invention in the substituents R1 and R2. Variable R1 of D3 is different when compared to the corresponding position in the present compound. The compounds of the instant claims are unsubstituted at this position. In contrast, R1 of D3 must be either C1-C6 alkyl, C1-C6 alkoxy, or C1-C6 alkylthio. Further, R2 of D3, located at the 5-position of the pyrimidine, is restricted to
a substituent of formula (Ia) or (Ib). Both formula (Ia) and (Ib) contain a ring substituted with a group terminating in a carboxylic ester. In contrast, the instant claims specify that the corresponding position is substituted with a two-carbon linker which may terminate in a ring, wherein the ring may be optionally substituted with one or more C1-6 alkoxy groups. The carboxylic ester taught by D3 would, therefore, not be possible in the instantly claimed compounds.

6. The Applicant therefore respectfully submits that the teachings in references D1 to D3 individually or in combination, do not render obvious to a person skilled in the art, the present invention. There is no hint or teaching in D1-D3 (individually or in combination) that would give the skilled person a reasonable expectation of success. The question which must be asked is whether the person skilled in the art ‘would have’ investigated this possibility in the expectation of success and not whether they ‘could have’ which in the present case would not have as there is no motivation in the prior art to reach the present invention. Thus, D1- D3, neither individually nor in combination, suggest/ motivate a person skilled in the art to arrive at the claims as claimed in the original set and the amended set of claims of the instant application.

Outstanding Objection 3 of the hearing notice: Non-patentability

1. In this objection, the Ld. Controller has stated “Claims 1- 2 attract the provision of section 3(d) of the Act”.

2. It is submitted that Section 3(d) reads as under:

   “The mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known
process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.”

Explanation: For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy.

3. The Applicant further submits that, Section 3 (d) does not allow patenting of a mere discovery of a new form of known substances, unless it exhibits enhanced efficacy. It is submitted that in order to determine whether a substance is not patentable under Section 3 (d):

1. the first step is to identify the known substance;
2. second step is to determine whether the claimed substance is a new form of a known substance (as detailed in Explanation to Section 3(d));
3. if the answer is yes, then the third step is to determine whether the claimed substance exhibits enhanced therapeutic efficacy over the known substance, if the answer is no than the new form of the known substance is not patentable.

4. The Applicant humbly reiterates its submission made in Objection 1 and 2 with respect to the cited prior arts D1 – D3. In light of the differences in the compounds claimed in the present invention versus the prior arts, the Applicant submits that the present invention claims a completely new substance and not a new form of a known substance.

The Applicant submits that just because D1-D3 are cited in the complete specification of the present application or otherwise cited as purported prior art in the FER, it does not mean that the compounds as claimed in the present application are new forms of the compounds as claimed in D1-D3. The Applicant for this relies on Fresenius Kabi Oncology Limited v. Glaxo Group Limited¹ where the IPAB held that:

¹ OPR/17/2012/PT/KOL, Order No. 162 of 2013
“It is not enough to plead that because Ex1 and 2 are admitted prior arts, this is only a new form of those compounds. That is vague. It is only when the pleadings show how the invention is one kind of a derivative of known substance the patentee will have to explain how the grant of patent is justified because of the enhancement of therapeutic efficacy. In this case the pleadings are not adequate. We hold that the S.3 (d) ground has not been proved”. [Emphasis supplied]

5. The instant case is also cited in the Patent Manual at page 33 for the purpose of explaining Section 3(d).

6. Further, the Applicant places reliance on Gilead Pharmasset LLC, USA v. Optimus Pharma Ltd. and Ors 2 (“Gilead Case”), the Ld. Deputy Controller of Patent held that: “107…Nucleosides and Nucleoside analogues were known in the prior art. Any further research or new invention in this field will obviously include the basic structure of nucleoside i.e. a base and a sugar. Thus, there is bound to be similarity in the core structure of new nucleosides analogues with the prior art or known nucleosides. However, to my mind, this should not be understood as structure similarity in this field of chemistry….” In light of the differences justified above, it is humbly submitted that just because there is some similarity in the base structure of the compound as claimed in the present invention versus that of D1.”

7. From the above cases, for the purpose of Section 3(d), it can be inferred that it is essential to identify what is the substance to which the compound of the present invention is required to be compared with. Further, it can be inferred that since just

---

because the prior art is cited, it need not be the substance against which the comparison is required.

8. Without prejudice to the above, even if all the compounds cited in the prior art are considered to be the known substance, the present invention does not form a new form of such known substance, the Explanation to section 3(d) for the purpose of determining what forms are considered to be “new form” of known substance states as below:

“Explanation: For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy.”

9. The Applicant submits that the compound of Formula (I) as claimed in the present application are not: salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations of the compounds as claimed or disclosed in either of D1-D3.

10. Further, it is submitted that the term “other derivatives” used in the Explanation should be used in the context of “new form of a known substance” as illustrated in the explanation itself. Thus, other derivatives in the explanation to Section 3 (d) has to be construed and restricted only to new form of a known substance. It also has to be interpreted ejusdem generis with the other terms in the Explanation (i.e. salt, ethers, ester, etc of the known substance) and every new compound should not be treated as a derivative of any earlier compound.

11. Without prejudice to the above, the Applicant respectfully submits that the therapeutic efficacy of the claimed compounds is disclosed in the specification, as filed. Specifically, the table on page 13 of the complete specification discloses the activity of the claimed compounds.
12. In view of the above submission in the present objection coupled with the submissions for Objection (1) and (2) above and amendments, the Ld. Controller is requested to withdraw this outstanding objection.

**Prayer**

In light of the above submissions it is therefore humbly prayed that:

- the Application 478/MUMNP/2015 with amended set of claims filed herewith be put in order for grant.

On behalf of the Applicant

Dated: December 3, 2019
Place: Mumbai

(Advocate and Patent Agent)
We Claim:

1. A compound of formula (I)

\[
\begin{align*}
\text{R}_1 \quad & \quad \text{N} \quad \text{R}_2 \\
\text{N} \quad \text{N} & \quad \text{NH}_2
\end{align*}
\]

or a pharmaceutically acceptable salt thereof, wherein

R₁ is hydrogen, or R₁ is a C₄-7 heterocycle group, aryl, or a bicyclic heterocycle group, each of which is optionally substituted by one or more C₁-6 alkoxy;

R₂ is C₁-6 alkyl,

with the proviso that N-(2-amino-5-phenethylpyrimidine-4-yl)-N-pentylamine is excluded.

2. A compound as claimed in claim 1, selected from the group consisting of the following compounds:

\[
\begin{align*}
\text{N} \quad \text{N} & \quad \text{NH}_2, \\
\text{N} \quad \text{N} & \quad \text{NH}_2, \\
\text{N} \quad \text{N} & \quad \text{NH}_2, \\
\text{N} \quad \text{N} & \quad \text{NH}_2, \\
\text{N} \quad \text{N} & \quad \text{NH}_2, \\
\text{N} \quad \text{N} & \quad \text{NH}_2, \\
\text{N} \quad \text{N} & \quad \text{NH}_2, \\
\text{N} \quad \text{N} & \quad \text{NH}_2.
\end{align*}
\]

and

3. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in claim 1 or 2 together with one or more pharmaceutically acceptable excipients, diluents or carriers.
We Claim:

1. A compound of formula (I)

\[
\begin{align*}
    R_1 \quad \text{N} \quad \text{N} \\
    \quad \text{N} \quad \text{H} \\
    \quad \text{N} \quad \text{H} \\
    \quad \text{N} \quad \text{N} \quad \text{H}_2 \quad \text{(I)} \\
\end{align*}
\]

wherein

\( R_1 \) is hydrogen, or \( R_1 \) is a \( C_4-7 \) heterocycle group, aryl, or a bicyclic heterocycle group, each of which is optionally substituted by one or more \( C_{1-6} \) alkoxy;

\( R_2 \) is \( C_{1-6} \) alkyl,

with the proviso that \( N-(2\text{-amino-5-phenethylpyrimidine-4-yl})-N\text{-pentyamine} \) is excluded.

2. A compound as claimed in claim 1, selected from the group consisting of the following compounds:

\[
\begin{align*}
    &\text{N} \quad \text{N} \\
    &\quad \text{N} \quad \text{NH}_2, \\
    &\quad \text{N} \quad \text{NH}_2, \\
    \quad \text{O} \quad \text{O} \\
    &\quad \text{N} \quad \text{N} \quad \text{NH}_2, \\
    &\quad \text{N} \quad \text{NH}_2, \\
    &\quad \text{N} \quad \text{NH}_2, \\
    &\quad \text{N} \quad \text{NH}_2, \\
    &\quad \text{N} \quad \text{NH}_2, \\
    &\quad \text{S} \\
&\quad \text{N} \quad \text{NH}_2.
\end{align*}
\]

and

3. A pharmaceutical composition comprising a compound of formula (I) as claimed in claim 1 or 2 together with one or more pharmaceutically acceptable excipients, diluents or carriers.
No. 142/DELNP/2009/1270

Dated 04/03/2020

To,

1. RAJESWARI & ASSOCIATES
AMSOFT BUSINESS CENTRE
UNITECH TRADE CENTRE
SECTOR 43, GURGAON-122002
HARYANA, INDIA

2. M/S. ANAND & ANAND
PLOT NO. 17 A, SECTOR-16 A
FILM CITY NOIDA-20130


M/s PHARMACYCLICS, INC.........................The Applicant
M/s. LAURUS LABS PVT LTD.......................The Opponent

Sir/Madam

I am forwarding an order/Decision with regards to hearing held u/s 25(2) Post
grant opposition on 22nd November, 2019 for application no. 1642/DELNP/2009
Patent No. IN 262968.

[Signature]

N.R. MEENA
Joint Controller of Patents & Designs
Patent office New Delhi

Enclosed:- Copy of Decision
The Patents (Amended) ACT, 2005
And
The Patents (Amended) Rules, 2006

In the matter of Patent No. 262968
(Application No.1642/DELNP/2009)
In the matter of opposition u/s 25(2)

Pharmacyclics Inc of 995 East Arques Avenue,
Sunnyvale, CA 94086 (US) a US corporation .....................The Patentee

Laurus Labs Limited, Hyderabad-33, India,
An Indian company.......................................................The Opponent

Present
1. Sh. Praful Kumar Manwatkar...............Examiner of Patents and Designs,
   & Member of Opposition Board

Applicant
1. Ms. Archana Shanker .....................Agent of the Patentee
2. Mr. Devinder Rawat .......................Agent of the Patentee
3. Dr. Sachin Malik ..........................Agent of the Patentee

Opponent
1. Ms. Rajeshwari H...........................Agent of the Opponent
2. Ms. Pragya Singh Thakur ..................Agent of the Opponent
3. Mr. Ramana Rao .............................Agent of the Opponent
4. Mr. Salf Rahman Ansari ....................Agent of the Opponent
5. Dr. Shyam Gupta ...........................Agent of the Opponent

Page 1 of 47
Hearing held on 22/11/2019

DECISION

1. Indian patent application N. 1642/DENLP/2009 was filed as a national phase application by Pharmacycics Inc., USA on 12/3/2009. The application claimed priority of US Application no. 60/828,590 dated 6/10/2006 for grant of Patent on invention "inhibitors of Bruton's Tyrosine kinase". The Application 1642/DENLP/2009 is a national phase application of PCT/US2006/049626. The application was examined and FER was issued on 3rd Oct 2013. The reply was filed on 3rd Jan 2014. The patent then granted on 25th Sept 2014. The patent was granted with total of 2 claims.

2. A post-grant opposition was filed by Laurus Labs Ltd on 24th September 2015 opposing the patent IN262968 on many grounds such as lack of novelty, lack of inventive step etc. The Opposition was filed along with evidence of Mr Raman Rao. The patentee filed a reply statement to the opposition on 23rd December 2015 along with petition under rule 60 to file further evidence. The reply statement was filed with the evidence of Dr Bridges.

3. The agent for the Opponent filed certain documents along with evidence of Mr. Choudhary and a petition under Rule 137/138 praying for leave to file the evidence and for the same to be taken on record. Subsequently the Patentee filed two interlocutory petitions opposing the filing of documents and evidence and Opponent opposed the interlocutory petition and filed their reply.
4. On October 17, 2019 both parties have appeared and made their oral arguments and insisted that an order be passed on this issue before final arguments on the main opposition is heard; vide order dated 06th November 2019 for doing justice to both the parties, said documents and evidence were taken on record and the relevancy is discussed at length hereinafter in my final order.

5. As stated hereinabove the present post-grant opposition has been filed by the Opponent namely Laurus Labs Ltd. against Indian Patent No. 262968 titled “INHIBITORS OF BRUTON’S TYROSINE KINASE” and is drawn to a set of chemical compounds which are purportedly BTK inhibitors. The final set of claims encompasses various chemical compounds including a compound known as Ibrutinib as represented here below.

**Structure of Ibrutinib**

![Structure of Ibrutinib]

2-propen-1-one, 1-\(((3R)-3-(4-amino-3-(4-phenoxyphenyl)-1h-pyrazolo(3,4-d)pyrimidin-1-yl)-1-piperidinyl)\). The compounds of the impugned patent are Protein kinase inhibitors i.e. BTK inhibitors (bruton's tyrosine kinase).
1. GROUNDS OF THE OPPOSITION

All claims of the impugned patent including the claims for the compound Ibrutinib are sought to be revoked in this opposition on following grounds:

(a) Section 25(2)(b): Lack of novelty

(b) Section 25(2)(c): Lack of inventive step

(c) Section 25(2)(f): Invention is not patentable under section 3(d)

(d) Section 25(2)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

1.1 LACK OF NOVELTY [SECTION 25(2)(B)]

1.1(a) It was argued by the Patentee that there are two requirements for anticipation, each of which is very important to consider separately: (a) disclosure and (b) enablement and the disclosure has to be unambiguous clear and a direct disclosure.

This was supported with case law LallubhaiChakubhaiJariwala Vs. ChimanlalChunilal and Co. [AIR1936Bom 99], wherein at para 10 the High Court held that:

...the earlier publication must give the requisite knowledge clearly, and it is not enough that it merely gives the means of attaining such knowledge. It must give sufficient information to a workman skilled in the particular art or craft in order to enable him to carry out the invention. How far that knowledge anticipates the new invention is again a question of fact depending on the facts and circumstances of...
each case. Even where the prior document and the present specification are identical or nearly identical in language, it does not necessarily follow that the Court must conclude that the first is an anticipation of the second, and often expert evidence is necessary to help the Court to consider what knowledge the prior publication could have conveyed to the mind of a person who had not the knowledge given by the invention in dispute.

1.1 (b) The Patentee has argued that Incorrect Structure was made by Experts of the Opponent and both the experts of the Opponent, Mr. Ramana Rao vide figure 4 para 9 of his affidavit and Dr. B.M Choudhary vide para 7 of the affidavit derive an INCORRECT "generic and hypothetical" structure from US2004/0006083 (US '083) and WO2004/100868 (WO '868) in order to demonstrate lack of novelty.

![Chemical Structure Diagram]

Figure 4.
1.1 (c) It was further represented by the Patentee that incorrect scientific representations were made by the Opponent stating that:

a. Even after having the knowledge of the molecule, the Opponent created a pyridine ring, which cannot be further substituted, instead of piperidine ring as present in Ibrutinib

b. The Opposition Board finding in para 6.2 at page 15-16 and held novelty in favour of the Patentee.

c. That alkyl carbonyl is $\text{CO-CH=CH}_2$. Being not that of an alkyl carbonyl but of an alkylene carbonyl.

d. US'083 has a primary Markush structure with two fragments specified as shown below:

Finally it was concluded by the counsel for the Patentee that there is no disclosure in either US '083 or WO '868 for a person skilled in the art to arrive at Ibrutinib or its method of synthesis and. Further US '083 and WO' 868 are inchoate, confusing and have an indefinitely described Markush generic structure which covers an incalculably enormous and undefinable number of compounds. The attempt to derive Ibrutinib from the two cited documents by the Opponent is only in hindsight (a priori) after having knowledge of the structure of Ibrutinib, they went searching for substituent's from US'083 and WO '868 like a leaf in the Sherwood forest.
It was further argued that even after having knowledge of the structure, the Opponent, nor was both their experts able to derive the structure of Ibrutinib from said documents. Both the experts make an incorrect structure of substituent's from the said prior art document. It was also argued by the counsel for the patentee that any arguments/written submissions/evidence that are beyond the pleadings, evidence and arguments at the oral hearing be struck off.

1.1 (d) Opponent relied upon with respect to anticipation

WO'868, US'083 and evidence of their expert (Dr. Choudhary). WRT US 2004/0006083 (US '083) in order to establish lack of novelty and put forth figure 6 so as shown herein below

![Figure 6](image)

US'083 is drawn to and discloses various tyrosine kinase inhibitors and the patent recognizes that there are receptor ad non-receptor tyrosine kinases. From the perusal of para 0021 &para 0379 at page 30 it is evident that said patent discloses that the
Compounds are useful as non-receptor tyrosine kinase and one of them is Btk, therefore the compounds are also Btk inhibitors. Moreover all the compounds of US'083 have 4-amino pyrazolo[3,4] pyrimidine as basic scaffold or the backbone (refer para 0034 at page 133). Many of the compounds contain phenoxyphenyl substitution at 3rd position and some of them contain piperidin at 1st position. The activity of the compound shows significant protein kinase inhibitory activity.

Ibrutinib is disclosed by this patent as shown in the Comparative hereinafter

US 2004/0006083

Wherein

Where Z₁₀₀₀ is
**Z** \(^{110}\) is a covalent bond.

**Z** \(^{111}\) is a covalent bond.

\(R_a\) and \(R_1\) each represent one or more substituents for each occurrence independently selected from the group consisting of hydrogen.

\(R_3\) for each occurrence is, independently, hydrogen.

\(A\) is \(-\{C_1-C_6\}\), \(-O\);

\(R_2\) is a group of the formula \(-B-E\), wherein \(B\)...substituted or unsubstituted azacycloalkyl...E is substituted or unsubstituted alkylcarbonyl...

\(a\) is 1 and \(D_1, G_1, J_1, L_1\) and \(M_1\) are each independently selected from the group consisting of \(CR_3\) and \(N\), provided that at least two of \(D_1, G_1, J_1, L_1\) and \(M_1\) are \(CR_3\);

\(b\) is 1 and \(D_2, G_2, J_2, L_2\) and \(M_2\) are each independently selected from the group consisting of \(CR_3\) and \(N\), provided that at least two of \(D_2, G_2, J_2, L_2\) and \(M_2\) are \(CR_3\);

**IMPUGNED PATENT 262968**
1.1(e). Opponent also argued that the entire specification of US’083 is written in a generalized manner i.e. in Markush format, wherein the compounds are represented by a general structure and many alternative compounds are proposed and the compounds as well as the alternative compounds are very well known to a person skilled in the art especially chemists who are reading the patent application. It is very well known that each compound within the Markush is an individualized description of that compound and represented by a common structure only for convenience. Therefore, disclosure of compounds in the Markush formula amounts to putting each of the compounds within the Markush formula in public domain and amounts to disclosure of each compound.

1.1 (f) Opponent argued about expert of the Patentee that is Dr. Bridges, who considers that US’083 is a specification which discloses compounds within a Markush and endeavour that from the Markush structures disclosed, it is not possible to arrive at Ibrutinib being large numbers of compounds. On the other hand Dr. Bridges ignore the basic tenet of the law in India, especially Section 2(i)(l) read with Section 2(i)(j) and (j)(a) that a new invention is only that which is not anticipated by any publication or document i.e. already published in any document. In the present case, Ibrutinib stands published by US’083 and the same is not properly considered by Dr. Bridges.
2: LACK OF INVENTIVE STEP [SECTION 25 (2) (C)]

2.1 THE PATENTEE HAS RESPONDED IN A FOLLOWING MANNER IN RESPONSE TO THE GROUND OF LACK OF INVENTIVE STEP:

A. OBVIOUSNESS IS TO BE DETERMINED BY PERSON SKILLED IN THE ART (POSA) WITH REFERENCE TO THE Division Bench of Hon'ble Delhi High Court, in Roche vs CIPLA, 2015 wherein in para 112 it is held that “to test obviousness the first test required to be applied is to see who is an ordinary person skilled in art (POSA) and its characteristics. The features of a person skilled in the art are -

i. that of a person who practices in the field of endeavor,
ii. belongs to the same industry as the invention,
iii. possesses average knowledge and ability and
iv. is aware of what was common general knowledge at the relevant date.

B. The Hon'ble IPAB in OA/8/2009/PT/CH, held vide para 42 that POSA reads the prior arts as a whole and allows himself to be taught by what is contained therein. He is neither picking out the” teaching towards passages” like the challenger, nor is he seeking out the “teaching away passages” like the defender. ... (Emphasis added)

THE PATENTEE FURTHER ARGUED THAT The Opponent did not have any pleadings in relation to US ‘083 for obviousness in their written statement of opposition therefore no evidence, written submission in relation to US ‘083 for obviousness can be entertained.
Whereas the Opponent had relied upon the following documents for lack of inventive step:

(a) US5593997 (US '997)
(b) WO2002/080926 (WO '926)
(c) WO2003/000187 (WO '187)
(d) WO2004/100868 (WO '868)
(e) Chen Mao, Min Zhou, and Fatih M. Uckun; The Journal of Biological Chemistry, 2001 Vol. 276, No. 44 issue 2 pp. 41435-41443
(f) US 2005/0196851A1:
(g) Andrew F. Burchat et al., Bioorganic & Medicinal Chemistry Letters, 2002, 12, 1687-1690
(h) Robert A. Copeland, Evaluation of Enzyme Inhibitors in Drug Discovery, 2005 discloses irreversible enzyme in activators.
(i) US7459,554B2

C. POSA not defined by the Council of Opponent

In order to assess inventive step, the qualifications of a person skilled in the art have to be defined, which the Opponent failed to do so. Reference is made to Paras 17 and 18 of AB-I affidavit wherein POSA characteristics are defined as follows

"POSA for the present invention will have a PhD in Medicinal Chemistry specializing in either Organic or Pharmaceutical chemistry, and have worked with a multidisciplinary team in drug discovery in the pharmaceutical industry, for at least three years, or have at least equivalent drug discovery experience."

Page 12 of 47
D. Neither Dr. Choudhary nor Mr. Ramana Rao are POSA for the purpose of evaluating inventive step of the impugned patent and also referred to the scientific errors made in their affidavits.

E. No motivation/rationale outlined by the Opponent to target BTK as it was neither a potential nor a validated target as on the priority date. Mere knowledge of crystal structure does not make a kinase a validated target.

There was no reason for a POSA to target the BTK enzyme. At the relevant time, there were many different approaches to target cancers and immunological diseases. If a POSA focused on targeting kinases, a POSA would have had no reason to focus on inhibiting tyrosine kinases, which are ubiquitous in human cells and provide many normal needed functions. If one focused on tyrosine kinases (and there was no reason to do so), there were many potential options.

F. No rationale provided by the Opponent for selection of closest prior art as none relate to inhibition of BTK AND Opponent rely almost exclusively on non-analogous references for their theory of obviousness. None of the references relied on by Opponent for their lead compound selection involves inhibition of BTK.

G. No rationale provided by the Opponent for selection of lead compound as selection of lead compound is based on hindsight AND NOT SUPPORTED in the Opposition and evidence of experts on biological activity of any compound in prior art for an informed selection of lead compound.
H. On the analysis for inventive step and to select the lead compound it was argued that neither the written statement of the Opponent nor their experts stated about the biological activity of any of the compounds selected as lead compounds to enable POSA make a selection of a starting point and the selection of prior art and identification of compounds is all arbitrary without any scientific rationale.

I. Among the references, the Patentee addressed US '083, Burchat, WO '926, and WO '868 used by the Opponent, together since these documents originate from the same company (Abbott).
It was submitted that POSA would have read them together in order to determine the direction of research and identify the closest prior art and select lead compound based on some scientific rationale.

J. No reason provided by the Opponent as to why a POSA would select compounds with 4- phenoxyphenyl side chain on C-3 position

K. No reason provided by the Opponent as to why a POSA would select examples 57 and 58 / entries 241 and 244 as relevant examples or lead compounds

L. No reason provided by the Opponent as to why a POSA would select compounds with a piperidine substitution at the N-1 position
It was concluded by the counsel for the Patentee that entire case of the Opponent is without any scientific rationale and the submissions made by the Opponent are not even supported by their experts.
2.2 **THE OPPONENT HAS RESPOND TO THE GROUND OF INVENTIVE STEP**

2.2(a) **The opponent has relied upon WO 2002/080926:**

Said patent of Abbott was published in October, 2002 and describes various protein tyrosine kinase inhibitors including Btk inhibitors. (pg. 383) from the perusal of page 49, the patent specifically states that the preferred compounds are those where at 3rd position, the substitution is phenoxyphenyl (about 350 compounds). Many of the compounds (about 500-1000+ compounds) have piperidine substitution at 1st position and the activity of the compound shows significant protein kinase inhibitory activity. All compounds of WO'926 have 4-amino-pyrazolo[3,4]pyrimidine base scaffold substituted at 3rd and 1st position; some of the relevant compounds disclosed by this patent are as under:

![Chemical structures]

**Example 1**

**Example 2**

**Example 3**

**Example 4**

Page no. 471-473 of WO'926
2.2 (b) The opponent has relied upon US 2004/0006083 ("US'083")

Said patent of Abbott was published in January, 2004 and as discussed earlier, this patent discloses various tyrosine kinase inhibitors including potential Btk inhibitors (page no. 131). 4-amino-pyrazolo[3,4]pyrimidine base scaffold substituted at 3rd and 1st position i.e. Ibrutinib like compounds are disclosed by this patent application. Some of the relevant compounds disclosed by this patent are as under:

Example 57 page no. 187 Example 58 page no. 187 Entry 241 page no. 235 Entry 244 page no. 236

2.2 (c) The opponents has relied upon WO 2004/100868:

This patent is also a work of Abbott wherein the disclosed compounds are tyrosine kinase inhibitors with 4-amino pyrazolo [3,4] pyrimidine backbone. Many of the compounds disclosed herein are phenoxyphenyl based with piperidine or other heterocycle substitutions. The activity of the compound shows significant Lck inhibitory activity.
l-[(l-methyl-3-piperidyl)-3-(4-phenoxyphenyl)-lH-pyrazolo[3,4-d]pyrimidin-4-amine (Page No. 1636)

l-[(l-(2-methoxyethyl)-3-piperidyl)-3-(4-phenoxyphenyl)-lH-pyrazolo[3,4-d]pyrimidin-4-amine (Page No. 1636)

All the compounds disclosed by Abbott in WO'926, US'083 and WO'868 are built on a basic scaffold i.e. 4-amino-pyrazolo[3,4-d]pyrimidine;
All of these compounds are substituted at 3rd position with some group and one of the common substituents found all along is Phenoxypyphenyl group. Further, all of these compounds are substituted at 1st position with some group and one of the common substituents found at 1st position in these compounds is substituted Piperidine.

2.2 (d) The Opponent has relied on Andrew et al. 2002

This is also a paper published by Abbott Research Centre and describes certain compounds with 4 amino pyrazolo-3,4-pyrimidine as the backbone; such compounds were synthesized and evaluated as inhibitors of Lck. The authors prepared following two exemplified compounds (among other compounds evaluated):
2.2(e) It is noted that authors conducted several tests to evaluate these compounds:

1. in vitro test for determination of IC50 of inhibition of Lck (Table 1)
2. in vivo test in mice for determination of effective dose ED50 (Table 2)
3. pharmacokinetic evaluation in mice (Table 6)

The in vitro tests on compounds 1, 2 confirmed their efficacy (in vitro) & utility as effective Lck inhibitors:

![Chemical structures of Compound 1 and Compound 2]

<table>
<thead>
<tr>
<th></th>
<th>lck</th>
<th>src</th>
<th>kdr</th>
<th>tte-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.015</td>
<td>0.042</td>
<td>1.19</td>
<td>0.25</td>
</tr>
<tr>
<td>2</td>
<td>0.040</td>
<td>0.035</td>
<td>5.32</td>
<td>0.75</td>
</tr>
</tbody>
</table>

*Mean of two experiments performed with seven concentrations of test compound.

i. As a result of these tests, the authors found that compound 1 has a very high volume of distribution and high plasma clearance i.e. the
Compound is excreted from the body very quickly, leaving no time for imparting any curative effect, and state in second paragraph of second column on page 111 that –
“Compound 1 demonstrated sub-optimal pharmacokinetic characteristics such as a very high volume of distribution and high plasma clearance”.

ii. On the other hand, compound 2 was found to have low volume of distribution and low plasma clearance i.e. it remains in blood for a period sufficient to impart curative effect. Andrew et al states in third paragraph of second column on page 111 that –
“In order to reduce the volume of distribution of 1 by lowering its lipophilicity, we elected to probe the corresponding pyrazolo[3,4-d]pyrimidine, compound 2 “.

iii. Because compound 2 was found to have low plasma clearance it was short listed and taken forward for in vivo tests (efficacy tests)

<table>
<thead>
<tr>
<th>Table 2. Mouse in vivo data for 2</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ED_{50}^a (mg/kg)</td>
<td>ED_{50}^a (mg/kg)</td>
<td>Inhibition (%)^b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 h</td>
</tr>
<tr>
<td>1.5</td>
<td>6</td>
<td>84</td>
<td>49</td>
</tr>
</tbody>
</table>

^aOral dosing, measured 2.5 h. after dosing.
^bAfter dosing at ED_{50}.

Compound 2 was also evaluated for its pharmacokinetic parameters and found effective...
Table 6. Pharmacokinetic parameters for 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ ($\mu\text{mol/L}$)</td>
<td>0.62</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>1.5</td>
</tr>
<tr>
<td>$V_d$ (l/kg)</td>
<td>9.6</td>
</tr>
<tr>
<td>$Cl_p$ (l/h/kg)</td>
<td>1.2</td>
</tr>
<tr>
<td>$T_{1/2}$ (h)</td>
<td>5.2</td>
</tr>
<tr>
<td>F (%)</td>
<td>69</td>
</tr>
</tbody>
</table>

iv. The murine in vivo data (on mice) and human whole blood data as shown in Table 2 & 5 also confirms that compound 2 fares better than other compounds.

Table 2. Mouse in vivo data for 2

<table>
<thead>
<tr>
<th>Oral dosing, measured 2.5 h after dosing.</th>
<th>Inhibition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$ED_{50}$ (mg/kg)</td>
<td>8 h</td>
</tr>
<tr>
<td>1.5</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

b. After dosing at ED<sub>50</sub>.

In vivo test in mouse for Effective dose, ED50 & ED90, for compound 2

Table 5. Human whole blood and murine in vivo data

<table>
<thead>
<tr>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (μM)</th>
<th>&quot;ED&lt;sub&gt;50&lt;/sub&gt;&quot; (mg/kg)</th>
<th>&quot;ED&lt;sub&gt;90&lt;/sub&gt;&quot; (mg/kg)</th>
<th>Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0.135</td>
<td>2.5</td>
<td>10.7</td>
</tr>
<tr>
<td>5</td>
<td>0.050</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>0.002</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>11</td>
<td>0.038</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>13</td>
<td>0.008</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>15</td>
<td>0.006</td>
<td>8.5</td>
<td>12.5</td>
</tr>
</tbody>
</table>

b. Oral dosing measured 2.5 h after dosing.

For compound 2 the ED50 is 1.5 whereas all other compounds have ED50 greater than 1.5.
v. Thus compound 2 gives better pharmacokinetic profile and effective dose among all the compounds:

![Chemical Structure]

The authors provide elaborate reasons why compound 2 performed better – presence of phenoxyphenyl at 3rd position – “occupying the lipophilic pocket in lck with the phenoxyphenyl moiety resulted in increased potency”:

![Chemical Structure]

vi. 3rd position (of the pyrazolo pyrimidine scaffold) - Perusal from above, as it is established by Andrew et al that substitution at 3rd position (of the pyrazolo pyrimidine scaffold) with phenoxyphenyl group increases potency of the compound as such phenoxyphenyl group is required at the 3rd position.
vii. Pyrazolo-pyrimidine scaffold - Compound 2 which showed excellent efficacy as demonstrated by Andrew et al had a pyrazolo pyrimidine scaffold therefore, for a person skilled in the art desirous of making a new compound, pyrazolo pyrimidine scaffold was required to be retained as Andrew et al have demonstrated that it has excellent efficacy.

viii. 1st Position on the pyrazolo pyrimidine scaffold - Compound 1 and 2 prepared by Andrew et al had a N-methyl piperazine appended to a cyclohexyl group at 1st position:

![Compound 1 and Compound 2](image)

ix. However, after conducting various tests on compounds 1 and 2 as shown above, the authors concluded that - "Our results also indicated that an appended solubilizing heterocycle in the ribose pocket, such as the N-methyl piperazine in 1" [second para, second column, page 111].

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The authors thus suggest that mere presence of N-methyl piperazine at 1st position would be sufficient to facilitate oral dosing. In other words, presence of a substituted 6-membered aza-heterocyclic group at 1st position would be sufficient to enable oral dosing of the compound.

3. INVENTION IS NOT PATENTABLE U/S 3(D) [SECTION 25 (2) (F)]

The council of opponent argued that there is no therapeutic efficacy demonstrated in the impugned patent with regard to the compound Ibrutinib (Compound 4) or its R isomer (compound 13) or S isomer (compound 14) as compared to prior art compounds. Ibrutinib exists as a racemic mixture and includes R & S isomers. The racemic compound is denoted as compound 4 and the R isomer is compound 13 and S isomer is compound 14.

The cellular assay in Table 3 is shown for compound 4 and compound 13 and 14 are not even tested. Example 4 (para 413-415) provides the efficacy of compound 4 in a mouse model of rheumatoid arthritis whereas the patent is claimed for inhibition of different types of cancer.
Compound 10 shows the best efficacy in terms of IC50 value as well as with regard to cell lines i.e. value of 0.58 and 3. However, compound No. 4 and compound No. 13 and 14 which are claimed are as efficacious as compound No. 10. Yet, the Patentee claims that compound No. 4, 13 and 14 are efficacious.

The council of patentee argued that nothing of this nature has been stated in the written statement. Even otherwise, this is not a ground. The Patentee is not claiming cancer but is claiming the compound, which is the new chemical entity that can be used for inhibiting BTK signaling pathway and associated disorders. This ground should therefore be dismissed.

4. THE COMPLETE SPECIFICATION DOES NOT SUFFICIENTLY AND CLEARLY DESCRIBE THE INVENTION OR THE METHOD BY WHICH IT IS TO BE PERFORMED [SECTION 25 (2) (G)]

On this ground the council of opponent argued that the patent specification does not disclose how to isolate R and S form of compound of example 4. In terms of Section 10(4), the best mode for performing the invention must be set out in the specification. In said patent the compound Ibrutinib is claimed (Compound 4) and therefore, it is expected that the preparation of compound 4 and the isomer compounds 13 and 14 are set out in the specification.

When we read the specification it show's that there is a general example 1A (para 393-395, pg. 71), which demonstrates synthesis of compound 4. However, the synthesis of compound 13 and 14 and especially the process whereby the respective isomers are isolated from the racemate (compound 4) is not disclosed by the specification.
The council of patentee argued that notwithstanding the above, clearly example 1a, 1b and 1c clearly show how to prepare compound of the present invention and since the patent specification is addressed to a person skilled in the art who is not a dullard would easily know how to separate stereospecific enantiomer from a racemic mixture (even a graduate in organic chemistry would know this). Further, it is ironical that on one hand the Opponent alleges obviousness and on the other hand alleges insufficiency.

5. Preliminary objections:

Some few preliminary objections are raised by the Patentee and I shall deal with the same.

A. The first objection is that the written submissions are beyond the pleadings and evidence filed by the Opponent and this is an attempt to introduce a new postgrant opposition.

I have gone through the opposition as well as replies and the evidences filed. As per me, there are some new references no doubt that have come through the evidence of Dr. Choudhary. That is why I had given opportunity to the Patentee to respond to the same. And they have also filed their own evidence on November 15\textsuperscript{th} 2019 for responding to the evidence of Dr. Choudhary.

This issue was also taken up by the Patentee by filing writ petition No 12105/2019 in the Delhi High Court. Further the Delhi High court through order dated 17.12.2019 found that the molecules and averments made are in support of the original case and no new case is made out. The Patent office was directed to consider the matter on merits and pass orders. The relevant part of the order is as below:

"Since the Opponent specifically submits before the Court that all the molecules which have been objected to as being fresh evidence are only in support of the above argument made in the original notice of opposition, as extracted above, this Court is of the opinion that the same does not constitute fresh evidence."
However, since the molecules have been exemplified in the written submissions and in the PowerPoint presentation, the Patentee is granted an opportunity to rebut the same, on or before 10th January 2019. The Patentee may file written submissions or deal with these molecules in the form of a note and file the same before the Patent Office. It is submitted that the hearing already stands concluded on 22nd November 2019. Upon the filing of the written submissions/note by the Patentee, the Patent Office shall decide the post-grant opposition expeditiously, in accordance with law.

I therefore abide by the order of the High Court. Also as per me, no new case is made out by the Opponent in the written submissions or hearing. The same issues were argued before. I also find that the Patentee has been given opportunity to rebut to any new issues if raised. Therefore this objection does not survive.

B. Evidence cannot travel beyond pleadings:

It is argued by the Patentee that evidence of Dr. Choudhary filed by the Opponent cannot be entertained as it goes beyond the pleadings of he originally filed Opposition. For this I find that the Patentee took up this ground by filing writ petition No 12105/2019. In conclusion the Delhi High court vide order dated 20.11.2019

“The Opponent has filed documents and evidence prior to the hearing and the Patentee sought an adjournment of the hearing accordingly. However, now the Patentee has had an opportunity to respond to all the documents and evidence filed by the Opponent – which the Opponent has already done. Thus, this Court does not deem it appropriate to direct non-consideration of the said further evidence filed by the parties. The decision would now be rendered by the Controller after taking into consideration all the pleadings, documents and evidence including the additional evidence filed by the parties on record.”

I have also given sufficient opportunity to the Patentee to respond to any grounds, which the Patentee thinks has been newly raised. The Patentee has also considered the same and responded by filing its own evidence. Because sufficient opportunity has been given, this objection cannot survive. I shall also abide by the order of the Delhi High court and shall consider all the evidence produced by both parties.
C. Another objection was with regard to the presentation made by the Opponent at the time of hearing – it was argued that this is also new matter and should not be taken into account.

For this aspect I have already given detailed reasons above, and therefore I need not elaborate on the same. In any case, I am not going by the presentation- I am making my findings on the prior art. I am taking it that the presentation was only to show what is the Opponent’s case.

D. Evidence of Mr Raman Rao cannot be considered, as he is from Laurus labs the Opponent.
For this also I rely on the Delhi High judgement and I abide by the same. I have given reasons earlier and am not repeating the same. As for Mr Raman Rao I am only reading his technical part and to that the Patentee has not raised any objection. The Opponent has not only relied on this affidavit but also produced another evidence- of Mr. Choudhary.

E. Evidence of Dr. Choudhary not persuasive:
The Patentee contends that the affidavit of Dr. Choudhary is not persuasive. I am not answering this issue now as I am dealing with this later in my discussion below.

6. Novelty:
6.1. Discussion: - As I read the provisions, I find that basis for anticipation of invention is in section 2(1)(j) read with section 25(2)(b).

After going through the submissions and evidences of both the parties and careful examination of WO 868 and US Patent 2004/0006083 (hereinafter referred to as US’083) it is noted that

There is no disclosure of of Ibrutinib alone as such, however US’083 and WO 868 is admittedly a document published prior to the priority date of the impugned patent. Further US ‘083 and WO’ 868 are have an indefinitely described Markush generic structure which covers an incalculably enormous and undefinable number of compounds.
The opposition Board also admits that US'083 discloses 4-amino pyrazolo [3,4] pyrimidine compounds. However, I am of the opinion that the Opposition Board has taken a view that this document does not disclose the structure of Ibrutinib, which is correct. The view of the Board is that “D1 does not form subject matter of prior public knowledge as identical patent has not been in public domain” is also correct. Hence the ground u/s 25 (2)(b) is not maintainable.

7. **Inventive step:**

7.1. **Discussion:**

As I read the provisions, I find that basis for lack of inventive step is in section 2(1)(j) read with section 25(2)(e).

Section 25(1)(e):- that the invention as far as claimed in the claims of the complete specification is obvious and clearly does not involve any inventive step, having regard to matter published as mentioned in clause (b) or having regard to what was used in India before the priority date of the applicants claims;

The Opponent submitted that the subject matter of the invention as claimed in claims 1 to 2 lacks an inventive step and is obvious to a person skilled in the art in the light of the prior art known to a person skilled in the art. The prior art relied upon by the Opponent for this purpose are:

Robert Copeland et al, 2003. Reliance was also placed on the affidavit of Mr
Raman Rao and of Dr. Chaudhary. On the other hand the Patentee relies on the affidavit of Dr Bridges.

In sum, it is the contention of the Opponent that the prior art (especially WO’926, US083, WO868) taught various compounds for that would act as lck inhibitors which already have the 4-amino-pyrazolo-[3,4] pyrimidine core with substitutions at 3rd and 1st positions. It is contended that these patents disclose compounds which are tyrosine kinase inhibitors and have phenoxy-phenyl and piperidine substitutions. It is contended that there are many compounds with other substitutions, and among them are those compounds with phenoxy-phenyl and piperidine substitutions.

\[ \text{Diagram:} \]

The Opponent has also relied upon Andrew et al 2002. And other prior art to contend that Andrew et al paper discloses compounds that have been tested on mice and have been found to show good lck inhibition activity. As per the Opponent compound 2 is the closest prior art compound which has phenoxy phenyl and piperidine substitutions. Further as per the Opponent, the art taught how to make irreversible inhibitors – eg Robert Copeland et al – various moieties were being attached to compounds to make them irreversible inhibitors and vinyl ketone has been suggested to be added to compounds to make them irreversible inhibitors. It is contended that by combining the teachings of Andrew et al 2002 and Robert Copeland’s
suggestion of vinyl ketone, a person skilled in the art could have made the compound ibrutinib claimed by the Patenntee.
The patentee on the other hand has contended that ibrutinib is a btk inhibitor and there is a difference between Ick and btk inhibitors. It is also argued that there is no motivation for a person skilled in the art to choose WO868, WO’926, US083 and choose the compounds therein having phenoxy-phenyl only as lead compounds; as there is no suggestion in these patents to do so. It is also contended that Andrew et al, 2002 and Robert Copeland et al actually teach away from the compound claimed by their patent. Therefore, a person skilled in the art could not have arrived at the claimed compound at all.

As correctly pointed out by the patentee, all the prior art relied upon by the Opponent pertain to Ick inhibitors. But we have to see the prior art as a whole. All the prior arts seems to refer to these proteins as under the general tyrosine kinase family. The patent specification of IN868 itself states that 

"[005]. Further described are irreversible inhibitors of Btk that form a covalent bond with a cysteine residue on Btk. further described herein are irreversible inhibitors of other tyrosine kinases, wherein the other tyrosine kinases share homology with Btk by having a cysteine residue (including a Cys 481 residue) that can form a covalent bond with the irreversible inhibitor (such tyrosine kinases, are referred herein as "Btk tyrosine kinase cysteine homologs").

[0163] Further, the irreversible Btk inhibitor compounds described herein can be used to inhibit a small subset of other tyrosine kinases that share homology with Btk by having a cysteine residue (including a Cys 481 residue) that can
form a covalent bond with the irreversible inhibitor. See, e.g., protein kinases in FIG. 1. Thus, a subset of tyrosine kinases other than Btk are also expected to be useful as therapeutic targets in a number of health conditions.

[0039] In another aspect are methods for modulating, including irreversibly inhibiting the activity of Btk or other tyrosine kinases, wherein the other tyrosine kinases share homology with Btk by having a cysteine residue (including a Cys 481 residue) that can form a covalent bond with at least one irreversible inhibitor described herein, in a mammal comprising administering to the mammal at least once an effective amount of at least one compound having the structure of any of Formula (A), Formula (B), Formula (C), or Formula (D).

In figure 1 the patentee has shown how btk protein has homology with other tyrosine kinases, including lck. Therefore the patentee appears to state in its patent that the inhibitor compounds claimed are not only inhibitors of btk but they can be expected to inhibit other homologous tyrosine kinases of which lck is one. The Opponent has also shown that lck has some homology with btk, and crystal structure of btk was known. [Chen et al 2001: lines 6 to 10, para 3, page 3 and Fig 3, page 6] it is stated that Btk contains a cysteine residue in its ATP binding domain/Kinase domain Lck and Btk admittedly have similar structure, with cysteine residue, hence the notion that inhibitors of Lck are likely to act as inhibitors of Btk is not without any basis. The argument of the patentee that lck and btk are totally unrelated and all prior art regarding lck must be rejected does not appear fully correct as it goes against their
specification of IN968. Hence reliance on prior art pertaining to compounds that act as lck inhibitors is not barred for the Opponent.

The Opponent has relied on various prior art such as WO868, WO'926, US083 to show that the art was preparing inhibitor compounds and going towards amino-pyrazolo-pyrimidine core and stating that these compounds are tyrosine kinase inhibitors, including lck inhibitors.

The Opponent has also relied on Andrew et al 2002 to argue that this paper describes certain compounds with 4 amino pyrazolo-3,4-pyrimidine as the backbone; and that such compounds were synthesized and evaluated as inhibitors of Lck. If we go through this paper it seems to deal with compounds with 4 amino pyrazolo-3, 4-pyrimidine as core. Two of the compounds made are as under:

\[ \text{Diagram with molecular structures} \]

1. \( X = \text{CH} \)
2. \( X = \text{N} \)
Compound 1 has pyrrolopyrimidine core and Compound 2 has pyrazolopyrimidine core. These compounds have N-methyl piperazine appended to a cyclohexyl group at 1st position. It also has phenoxy-phenyl group at 3rd position.

The author appears to have made several compounds and tested the same invitro as well as invivo. With the invitro studies on compound 1 and 2 the efficacy of these compounds is shown; the in vitro tests are for lck, src, tie-2 inhibition.

<table>
<thead>
<tr>
<th></th>
<th>lck</th>
<th>src</th>
<th>kdr</th>
<th>tie-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.015</td>
<td>0.042</td>
<td>1.19</td>
<td>0.25</td>
</tr>
<tr>
<td>2</td>
<td>0.040</td>
<td>0.035</td>
<td>5.32</td>
<td>0.75</td>
</tr>
</tbody>
</table>

*Mean of two experiments performed with seven concentrations of test compound.

The author also writes in the paper that compound 1 has high volume of distribution but high plasma clearance i.e. it has the capacity to exit the body.
quickly and not enough of the compound would remain in the body for reaction. Obviously, this compound has to be discarded. This is stated in second paragraph of second column on page 111 that –

"compound 1 demonstrated sub-optimal pharmacokinetic characteristics such as a very high volume of distribution and high plasma clearance".

Then the author appears to have gone ahead for other tests with compound 2, especially for in vivo studies in mice.

"In order to reduce the volume of distribution of 1 by lowering its lipophilicity, we elected to probe the corresponding pyrazolo [3,4-d]pyrimidine, compound 2".

The ED50 value has been reported for this compound in table 2.

<table>
<thead>
<tr>
<th>Table 2. Mouse in vivo data for 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED$_{50}$ (mg/kg)</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>1.5</td>
</tr>
</tbody>
</table>

$^{a}$Oral dosing, measured 2.5 h. after dosing.

$^{b}$After dosing at ED$_{90}$.

Further the paper has evaluated the compound for pharmacokinetic parameters, which can be seen from table 6.
Table 6. Pharmacokinetic parameters for 2

<table>
<thead>
<tr>
<th>Cmax (μmol/L)</th>
<th>Tmax (h)</th>
<th>Vd (l/kg)</th>
<th>Clp (l/h/kg)</th>
<th>T1/2 (h)</th>
<th>F (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.62</td>
<td>1.5</td>
<td>9.6</td>
<td>1.2</td>
<td>5.2</td>
<td>69</td>
</tr>
</tbody>
</table>

The murine in vivo data (on mice) and human whole blood data as shown in Table 2 & 5 also confirms that compound 2 is better than other compounds.

Table 2. Mouse in vivo data for 2

<table>
<thead>
<tr>
<th>ED50a (mg/kg)</th>
<th>ED90a (mg/kg)</th>
<th>Inhibition (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>8 h</td>
</tr>
<tr>
<td>1.5</td>
<td>6</td>
<td>84</td>
</tr>
</tbody>
</table>

aOral dosing, measured 2.5 h. after dosing.
bAfter dosing at ED50.

In vivo test in mouse for Effective dose, ED50 & ED90, for compound 2

Table 5. Human whole blood and murine in vivo data

<table>
<thead>
<tr>
<th>Whole blood</th>
<th>Mouse in vivo data</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC50 (μM)</td>
<td>^aED50 (mg/kg)</td>
</tr>
<tr>
<td>3</td>
<td>0.135</td>
</tr>
<tr>
<td>5</td>
<td>0.050</td>
</tr>
<tr>
<td>6</td>
<td>0.002</td>
</tr>
<tr>
<td>11</td>
<td>0.038</td>
</tr>
<tr>
<td>13</td>
<td>0.008</td>
</tr>
<tr>
<td>15</td>
<td>0.006</td>
</tr>
</tbody>
</table>

aOral dosing measured 2.5 h after dosing.
bAfter dosing at ED50.

For compound 2 the ED50 is 1.5 whereas all other compounds have ED50 greater than 1.5.
The authors provide elaborate reasons why compound 2 performed better—they justify presence of phenoxyphenyl at 3rd position stating that it occupies the lipophilic pocket in lck protein and increases potency—

"occupying the lipophilic pocket in lck with the phenoxyphenyl moiety resulted in increased potency":

![Chemical structure diagram]

When the author has done so many studies including pharmacokinetic studies, and other studies, it shows that the author found this compound [2] efficacious.

Here the Patentee's argument that there is no reason why a POSA [person of ordinary skill in the art] would select pyrazolopyrimidine has no merit since in the entire paper of Andrew et al 2002 there are only two types of compounds—one that has pyrazolopyrimidine core and another that has pyrolopyrimidine core and the author has shown with experiments that the compound 2 has better efficacy. The compound 2 has pyrazolopyrimidine core. Therefore there is no reason why a person skilled in the art would not go with this core.

It is argued by the patentee that change from pyrolopyrimidine core to pyrazolopyrimidine core has made the compound of Andrew et al less potent.
in terms of inhibition of lck. This observation seems to be based on invitro studies at table 1. However we have to see the article as a whole; and that time we see other tables where in vivo activity is given and in that compound (2) having pyrazolopyrimidin core is found more active.

With regard to the substitution of phenoxy-phenyl group at 3rd position, there are no arguments from the patentee doubting this substitution. On the other hand the author of the paper Andrew has given reason that this group at 3rdposition increases potency. During the hearing or thereafter there are no reasons given as to why this substitution would not have been made. Hence placement of phenoxy-phenyl at this position is logical for a person skilled in the art. It is shown to beneficial and responsible for increasing potency. A person looking to make compounds would be expected to retain this group on the pyrazolopyrimidine core.

Now comes the substitution at 1st position of the pyrazolopyrimidine core. It is correct that compounds 1 and 2 made by Andrew et al have cyclohexylgroup at 1st position and to that is appended N-methyl piperazine. This is as below:
One conclusion that the author Andrew has made after their tests on compounds 1 and 2 is that the ribose pocket of the lck protein is occupied by N-methyl piperazine – therefore this group becomes important at position 1.

"Our results also indicated that an appended solubilizing heterocycle is in the ribose pocket, such as the N-methyl piperazine in 1" [second para, second column, page 111].

The inference that presence of N-methyl piperazine at 1st position would be sufficient to facilitate oral dosing and enabling efficacy of the compound cannot be ignored.

The argument of the patentee on this point is that the structure drawn by the Opponent in the hearing presentation is incorrect. To avoid any confusion, I am ignoring the presentation slides wholly. I am referring to the papers and documents cited. The Patentee’s argument is also that compounds 1 and 2 have a cyclohexyl group at 1st position and to that N-methyl piperazine is appended. And this is not similar to ibrutinib as it has pirperidinyl group. It is also argued that there is no reason to replace the cyclo-hexyl group coupled with N-methyl piperazine with a simple piperidine ring group at 1st position.
From the paper, one can gather that the relevance of cyclohexyl- group with N-methyl piperazine fills up the ribose pocket of the lck protein. If it is so, then a person skilled in the art when preparing a new compound would look for similar Nitrogen based heretocyclic group which is structurally similar to cyclohexyl group and that could similarly occupy the ribose pocket as N-methyl piperazine. There are few of them – of which piperidinyl group seems to be frequently used in the prior art as in WO868. In chemistry, there are only few aza-heterocyclic groups and piperidinyl is not uncommon. It is common knowledge that Piperidinyl group is closely similar to cyclohexyl group which was already present in the compound of Andrew et al. After having arrived at a certain structure, a POSA would only seek to make only minimum changes to that structure so as to maintain the effect. And here is a person [the POSA] trying to make a compound other than what is reported in the prior arts. [Otherwise he would be repeating the prior art]. Cyclohexyl with N-methyl piperazine is already suggested and experimented by Andrew et al. There is piperidine group which is found within the compounds made in other prior arts which also are of Abbott. Piperidinyl group is a smaller group. Since piperidinyl group seems to be used in the prior art compounds and such compounds of prior art do behave as tyrosine kinase inhibitors, hence one can expect a replacement of at this point with piperidinyl group and expect anti-tyrosine kinase activity. Apart from doubting whether a POSA would replace cyclohexyl -N-methyl piperazine with piperidinyl group, I have not seen any other specific reason from the patentee why a POSA would not take this obvious step. It is not stated that this step is not technically impossible or if such step is taken then no anti-tyrosine kinase activity will come.
The argument of the patentee that Andrew et al teaches away from using piperidine substitution cannot also be accepted because 'teaching away' means that there should be negative teaching in the article against using piperidine ring. There is no such negative finding by the author. On the other hand the N-methyl piperazine group is an example. Because the author has tried other groups also and has mentioned that N-methyl piperazine occupies the ribose pocket, a POSA would have to look for a similarly placed structurally and functionally similar nitrogen-based heterocyclic group. Piperidine group at that position could be considered as a natural choice made from various existing alternatives used in the prior art and that would be known to a POSA.

With regard to the Michael acceptor the Opponent has relied on Robert Copeland et al and has argued that the article proposes strategies to make irreversible inhibitors. The article has reviewed compounds wherein such Michael acceptors when added turn them into irreversible compounds. And several examples are given, including one compound CI-1033. To this the Patentee has argued that Michael acceptor is not described for or in the context of any of Andrew's compounds, there is no teaching to add the Michael acceptor to any specific structure, there is no reason to add the Michael acceptor to the piperidine ring instead of the main pyrazolopyrimidine scaffold at some other position.

I find that the Copeland article addresses the effect of reversible inhibitors. This article is aimed at making irreversible enzyme inactivation and strategies for this purpose. "Instead, we will focus our attention here on two general
mechanisms of irreversible enzyme inactivation that are based on covalent modification of the enzyme, or of a critical cofactor or substrate of the enzyme reaction. These mechanisms are referred to as affinity labeling and mechanism-based inactivation. We will see that there are examples of both mechanisms of inactivation among drugs that are in current clinical use.”

...For all irreversible enzyme inactivators, the inactivation of the target enzyme requires the chemistry of covalent bond formation. Therefore all irreversible enzyme inactivators display slow binding kinetics, as defined in Chapter 6, in progress curve analysis.

More recently attempts to generate highly selective quiescent affinity labels have been made for a number of protease and kinase targets. As example, inhibitors of the Rhinovirus 3C protease (Mathews et al., 1999) and of the epidermal growth factor receptors (Boschelli, 2002), both incorporating Michael acceptors to covalently inactive cysteine residues in their target enzymes (Lowry and Richardson, 1981; Figure 8.6), have entered human clinical trials for the treatment of rhinovirus infection and cancer, respectively.

Thus the strategy of making irreversible inhibitors has been proposed for many proteases as well as kinase targets and as per the article, some of the molecules using this strategy have entered clinical trials.

A variety of strategies have been put forth to lock the activity of these kinases, including antibody-based therapies, receptor antagonists, reversible small molecule kinase inhibitors, and irreversible kinase inactivators. Groups at Parke-Davis (now Pfizer) and Wyeth have independently incorporated a Michael
acceptor into compounds that bind to the ATP binding pocket of EGFR to covalently associate with Cys 773 within this pocket. The Wyeth compound, EKB-569 (Figure 8, 8A), irreversible inhibits EGFR in vitro and in cells.

As example of the strategy the author has shown the incorporation of such michael acceptor group to obtain irreversible kinase inactivators - the examples are EKB-569 and CI-1033. EGFR inhibitors proposes the use of Michael acceptors in general and not in the context of any specific compound. It is wrong to contend that there is no specific structure for which the Michael acceptor is proposed to be added. As examples of possible applications of Michael acceptor, the author has used them on CI-1033 and EKB-569 and shown that the compound has become irreversible inhibitor. Whether the compound reached the market or not, is not relevant for patenting purpose. The fact that adding Michael acceptor to the main compound was possible and success could be achieved (because these compounds passed in vivo studies and were being studied in trials) can be gathered from this article. Therefore there is sufficient basis for adopting of this strategy by a person skilled in the art.

If one would see the compound that has come from Andrew et al there is only one position that is available for further substitution – the nitrogen at the free end of the pirperidinyl group. The Michael acceptor cannot be added to the 3rd position as it is already occupied by phenoxy-phenyl group.

As reported by Robert Copeland et al, it seems to be conventional to add Michael acceptor to compound. In this paper, the author has stated that there
are many compounds where this strategy has been tried. Vinyl ketone is also one of the moieties that has been suggested to give the irreversible inhibitor effect. Therefore it would be natural for a POSA to try and use this moiety (vinyl ketone). One can also notice that adding the moiety only adds and makes the compound as irreversible inhibitor. Patentee has not said that this will anyway change the anti-tyrosine kinase property of the compound. It will only make it as irreversible inhibitor. And if POSA wants to make irreversible inhibitor he could very well use this approach.

Based on the record, it appears to me that modification required to the compound of Andrew et al into something structurally similar is not a major one: there are steps already stated in the art and it has to be followed. Further, the skilled artisan's reasonable expectation of success is measured only by the past experiences – with the immediate prior art which only tells how to get tyrosine kinase inhibitors.

I abide by the judgment of Honourable Supreme court, the principle as laid down in AIR 1981 SUPREME COURT 1444, Patents Act (39 of 1970), S.2 (1)(j), S.64, which is as follows: “It is important that in order to be patentable an improvement on something known before or a combination of different matters already known, should be something more than a mere workshop improvement; and must independently satisfy the test of invention or an 'inventive step'. To be patentable, the improvement or the combination must produce a new process or improved results. Mere collection of more than one integers or things not involving the exercise of any inventive faculty, does not qualify for the grant of a patent.”
I find that various cited documents clearly disclose or teaches all the features of the claimed invention and invention consist merely a combination of known features, which does not give rise to an inventive technical advance. It appears that these are obvious modifications that a POSA would make and could expect the compound coming out to have tyrosine kinase activity, especially against lck. The combination of features and making of ibrutinib as claimed in impugned patent is obvious and therefore lack of inventive step over the cited prior art documents. Hence the ground for obviousness is maintainable.

The Opposition Board has not considered all the matters in this much detail and therefore though I have read the recommendations, I have not agreed with the Board on this issue. After the recommendations of the Board have come, there were further affidavits filed by both parties. I have not sent all of this to the Board once again as this would consume another 6 months and delay the proceeding. This is also not necessary in procedure and none of the parties have requested for this also. Therefore I thought it fit to give sufficient opportunity to both parties to file all their documents and then I have considered the same. I have also gone through the expert affidavits of both parties; the expert affidavits do not state anything more than what was in the opposition statement/reply statement and the written submissions; I understand that the written submissions captures all the points made by the experts. Hence I have not dealt with these affidavits in detail here. The affidavits of Dr Bridges deals with all the documents for inventive step.
individually and shows how there is inventive step in preparing ibrutinib. The same issues were argued – therefore instead of individually dealing with each of the affidavits I have considered the written submissions, which capture all the issues stated by the experts of both sides.

I have also seen all the judgments given by both parties. However I have not made specific mention of each of the judgments – because the matter is more factual. For the legal aspects I have taken into account all the case laws.

8. INVENTION IS NOT PATENTABLE U/S 3(D) [SECTION 25 (2) (F)]:-

**Discussion:** Based on the records I found that table 3 is shown for compound 4 and compound 13 and 14 are not even tested. Example 4 (para 413-415) provides the efficacy of compound 4 in a mouse model of rheumatoid arthritis whereas the patent is claimed for inhibition of different types of cancer. In my opinion nothing of this nature has been stated in the written statement. Even otherwise, The Patentee is not claiming cancer but is claiming the compound, which can be used for inhibiting BTK signaling pathway and associated disorders. Therefore, the ground u/s 3(d) read with u/s 25 (2) (f) is not maintainable.

9. THE COMPLETE SPECIFICATION DOES NOT SUFFICIENTLY AND CLEARLY DESCRIBE THE INVENTION OR THE METHOD BY WHICH IT IS TO BE PERFORMED [SECTION 25 (2) (G)]

**Discussion:** I have analyzed the submissions of patentee as well as opponent and observed the patent specification is disclose how to isolate R and S form of compound of example 4. In terms of Section 10(4), the best
mode for performing the invention is set out in the specification. In said
patent the compound Ibrutinib is claimed (Compound 4) and therefore, the
preparation of compound 4 and the isomer compounds 13 and 14 are clearly
mentioned in specification.
I relay on statement of the of patentee that example 1a, 1b and 1c clearly show
how to prepare compound of the present invention and since the patent
specification is addressed to a person skilled in the art who can easily
understand how to separate stereospecific enantiomer from a racemic
mixture. Therefore, the ground u/s 25 (2)(g) is not maintainable.

10. Decision:-

Having considered all the submissions made by the applicant/patentee during
the hearing as well as submissions made by the opponent and also in view of
the above circumstances and observations, I hereby conclude that the instant
granted claims are obvious to a ordinary person skilled in the art therefore
lack of inventive step over the cited prior art documents. I hereby order
revocation of Patent No.IN262968 granted on the Patent Application
No.1642/DELNP/2009. There is no award of costs to either party.

Dated this 04rd, March, 2020

( N.R.MEENA)
Joint Controller of Patents and Designs.

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AMSOFT BUSINESS CENTRE
UNITECH TRADE CENTRE
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HARYANA,INDIA

(2) M/S.ANAND & ANAND
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(71) Applicant (for all designated States except MG, US): ASTRAZENECA AB (SE/SE); S-151 85 Sodertalje (SE).

(71) Applicant (for MG only): ASTRAZENECA UK LIMITED (GB/GB), 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

(72) Inventors:
and

(74) Agent: GLOBAL INTELLECTUAL PROPERTY. AstraZeneca AB, S-151 85 Sodertalje (SE).


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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOUNDS FOR THE TREATMENT OF MULTI-DRUG RESISTANT BACTERIAL INFECTIONS

(57) Abstract: The present invention relates to compounds that demonstrate antibacterial activity, processes for their preparation, pharmaceutical compositions containing them as the active ingredient, to their use as medicaments and to their use in the manufacture of medicaments for use in the treatment of bacterial infections in warm-blooded animals such as humans. In particular this invention relates to compounds useful for the treatment of bacterial infections in warm-blooded animals such as humans, more particularly to the use of these compounds in the manufacture of medicaments for use in the treatment of bacterial infections in warm-blooded animals such as humans.
COMPOUNDS FOR THE TREATMENT OF MULTI-DRUG RESISTANT BACTERIAL INFECTIONS

BACKGROUND OF THE INVENTION

The international health community continues to express serious concern that the evolution of antibacterial resistance will result in strains against which currently available antibacterial agents will be ineffective. For example, resistant strains of Gram-positive pathogens such as methicillin-resistant Staphylococcus aureus (MRSA), methicillin-resistant coagulase-negative staphylococci (MRCNS), penicillin-resistant Streptococcus pneumoniae and multiple resistant Enterococcus faecalis are both difficult to treat and difficult to eradicate. Consequently, in order to overcome the threat of widespread multi-drug resistant organisms, there is an on-going need to develop new antibiotics, particularly those with either a novel mechanism of action and/or containing new pharmacophoric groups.

SUMMARY OF THE INVENTION

These and other needs are met by the invention disclosed herein which is directed to a compound of formula I:

\[ \text{L} - \text{U}_1 - \text{M} - \text{U}_2 - \text{R} \]

I

or a pharmaceutically acceptable salt thereof, or N-oxides thereof, wherein:

\[ \text{L} \] is a group of formula L1-L15:

- [Diagram showing molecular structures]

1. L1
2. L2
3. L3
4. L4
5. L5
6. L6
7. L7
8. L8
wherein "..." indicates the point of attachment;

$Z_3$, $Z_4$, and $Z_5$ are C or N provided that when $Z_1$, $Z_4$, or $Z_5$ is N, then $R_{2a}$, $R_{2c}$, or $R_{2d}$ are absent;

$R_{2a}$, $R_{2b}$, $R_{2c}$, $R_{2d}$, $R_{2e}$, and $R_{2f}$ are each independently H, halo, cyano, carboxy, nitro, carbamoyl, $-\text{CO-}(\text{C}_1-\text{C}_6)\text{alkyl}$, $\text{CO}_2(\text{C}_1-\text{C}_6)\text{alkyl}$, $(\text{C}_1-\text{C}_6)\text{alkyl}$, hydroxy,

$\text{halo}(\text{C}_1-\text{C}_6)\text{alkyl}$, $\text{halo}(\text{C}_1-\text{C}_6)\text{alkoxy}$, $(\text{C}_1-\text{C}_6)\text{alkoxy}$, $\text{NHCO}(\text{C}_1-\text{C}_6)\text{alkyl}$, $\text{SO}_2(\text{C}_1-\text{C}_6)\text{alkyl}$, $\text{SO}_2\text{NH}(\text{C}_1-\text{C}_6)\text{alkyl}$, or $\text{SO}_2\text{N}((\text{C}_1-\text{C}_6)\text{alkyl})_{2}$;

$R_{2g}$, $R_{2g'}$, and $R_{2g''}$ are each independently H, $(\text{C}_1-\text{C}_6)\text{alkyl}$, or $\text{halo}(\text{C}_1-\text{C}_6)\text{alkyl}$;

$U_1$ is CRaRb—CRaRd or CRaRb—CRcRd—CReRf, wherein Ra, Rb, Rc, Rd, Re, and Rf are each independently hydrogen or $(\text{C}_1-\text{C}_6)\text{alkyl}$;

M is a group of formula M1–M5:

wherein $R_2$ is H or carboxy, and wherein "..." indicate points of attachment.
Ry and Ry' are each independently H, halo, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy,
CO₂R', wherein R' is H, (C₁-C₆)alkyl, or halo(C₁-C₆)alkyl, or Ry and Ry' together with the
carbon to which they are attached form C=O; or Ry and Ry' together form a bridge;
X and Y are each independently CH₃, O, or NR';
" " " is a bond or is absent;
n is 1, or 2, or 3;
when M is a group of formula M1 or M4, U₁ is NR'_W, wherein W is CH₂, CO, SO₂,
\[
\text{CH₂HC-CH, CH₂CH₂CH=CH, or CH₂C=CH, wherein each hydrogen may be optionally}
\text{replaced by halo or (C₁-C₆)alkyl;}
\]
when M is a group of formula M2, M3, or M5, U₂ is W wherein W is as defined
herein above;
R' at each occurrence is independently H, (C₁-C₆)alkyl, -(C₁-C₆)alkylcarboxy,
-CO-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl, -CO-NH(C₁-C₆)alkyl, -CO-N((C₁-C₆)alkyl)₂, or
SO₂(C₁-C₆)alkyl, any of which may be optionally substituted on carbon with halo, hydroxy,
(C₁-C₆)alkyl, (C₁-C₆)alkoxy, SO₂(C₁-C₆)alkyl, NH₂, NH(C₁-C₆)alkyl, or N((C₁-C₆)alkyl)₂;
when W is CH₂, CO or SO₂, R is aryl, heteroaryl, heterocyclyl or ortho-fused bicyclic
\[
\text{\text{CH₂HC-CH, CH₂CH₂CH=CH, or CH₂C=CH, R is aryl, heteroaryl, heteroaryloxy, heteroarylfthio, heteroarylsulfinyl, heteroarylsulfonyl, heteroarylamino; wherein any R may be optionally substituted on carbon; and wherein any}
\text{ring nitrogen in R may be optionally substituted by (C₁-C₆)alkyl; and}
\]
any of L, U₁, M, U₂, or R may be optionally substituted on carbon by one, two or three
substituents selected from halo, nitro, cyano, hydroxy, oxo, trifluoromethoxy, trifluoromethyl,
amino, carboxy, carbamoyl, mercapto, sulphanamyl, methyl, ethyl, ethylid, ethynyl, methoxy,
ethoxycarbonyl, ethoxycarbonyl, heterocarbyl, heterocyclyl, acetyl, acetoxyl,
methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylanino, or
acetylamino;
with the proviso that when L is a group of formula L₈ or L₁₅, W is not CO.
What is also provided is a compound of formula I which is a compound of formula II:

\[
\begin{align*}
&\text{or a pharmaceutically acceptable salt thereof, wherein} \\
&R_2a, R_2b, R_2c, \text{and } R_2d \text{ are each independently } H, \text{ fluoro, chloro, cyano, (C}_1-\text{C}_6\text{)alkyl}, \\
&\text{halo(C}_1-\text{C}_6\text{)alkyl, halo(C}_1-\text{C}_6\text{)alkoxy, (C}_1-\text{C}_6\text{)alkoxy; } \\
&\text{"-----" is a bond or is absent; } \\
&Z \text{ is CH or N when "-----" is a bond, or } Z \text{ is } O \text{ or NH when "-----" is absent; } \\
&U_1 \text{ is } CRaRb---CRcRd \text{ or } CRaRb---CRcRd---CRCeRf, \text{ wherein } Ra, Rb, Rc, Rd, Re \text{ and } \\
&Re \text{ are each independently hydrogen or } C_1-C_6 \text{ alkyl;} \\
&M \text{ is a group of formula M1a or M2-M5: }
\end{align*}
\]

in the trans configuration relative to "-----", wherein R2 is H or carboxy.

Ry and Ry' are each independently H, hydroxy, fluoro, chloro, methoxy, carboxy, CO2(C1-C6)alkyl, or (C1-C6)alkyl, or together with the carbon to which they are attached form 
C=O; or Ry and Ry' together form a bridge;

X is CH2, NH, N[CO-(C1-C6)alkyl], N[S02(C1-C6)alkyl], N(C1-C6)alkyl, or O;

Y is CH2, NH, N[CO-(C1-C6)alkyl], N[S02(C1-C6)alkyl], N(C1-C6)alkyl, or O;

"-----" is a bond or is absent;

n is 1, 2, or 3;

when M is a group of formula M1a or M4, U2 is NR'-W, wherein R' is H,

(C1-C6)alkyl, -(C1-C6)alkylcarboxy, -CO-(C1-C6)alkyl, -CO2(C1-C6)alkyl,
-CO-NH(C<sub>1</sub>-C<sub>6</sub>)alkyl, -CO-N(N((C<sub>1</sub>-C<sub>6</sub>)alkyl)), any of which may be optionally substituted on carbon with halo, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, SO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl, NH<sub>2</sub>, NH(C<sub>1</sub>-C<sub>6</sub>)alkyl, or N((C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub>;

W is CH<sub>2</sub>, CO, SO<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>, CH<sub>2</sub>CH=CH, or CH<sub>2</sub>C=C, wherein each hydrogen may be optionally replaced by halo or (C<sub>1</sub>-C<sub>6</sub>)alkyl;

when M is a group of formula M2, M3, or M5, U<sub>2</sub> is W; and

when W is CH<sub>2</sub>, CO or SO<sub>2</sub>, R is aryl, heteroaryl, heterocyclyl or ortho-fused bicyclic heteroaryl, or when W is CH<sub>2</sub>CH<sub>2</sub>, CH<sub>2</sub>CH=CH, or CH<sub>2</sub>C=C, R is aryl, heteroaryl, heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkylthio, heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkylsulfinyl, heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkylsulfonyl, heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkylamino, wherein any R may be optionally substituted on carbon, and wherein any ring nitrogen in R may be optionally substituted by (C<sub>1</sub>-C<sub>6</sub>)alkyl.

What is also provided is a compound of formula I which is a compound of formula III:

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III
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or a pharmaceutically acceptable salt thereof, wherein

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are each independently H, fluoro, chloro, cyano, (C<sub>1</sub>-C<sub>6</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy;

Z is CH or N when " " " " is a bond, or, when " " " " is absent, Z is O or NH;

Y' is N or CR<sub>2</sub>, wherein R<sub>2</sub> is H, hydroxy, or carboxy;

U<sub>2</sub> is NR'-W, wherein W is CH<sub>2</sub>, CO, SO<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>, CH<sub>2</sub>CH=CH, or CH<sub>2</sub>C=C, wherein each hydrogen may be optionally replaced by halo or (C<sub>1</sub>-C<sub>6</sub>)alkyl; and
What is also provided is a compound of formula I which is a compound of formula IV:

![Chemical Structure IV](image)

or a pharmaceutically acceptable salt thereof, wherein

R₁, R₂, R₃, and R₄ are each independently H, fluoro, chloro, cyano, nitro,

(C₁-C₆)alkanoyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy, (C₁-C₆)alkoxy, NHCO-(C₁-C₆)alkyl, SO₂(C₁-C₆)alkyl, SO₂NH(C₁-C₆)alkyl, or SO₂N((C₁-C₆)alkyl);  

Z is CH or N when "-----" is a bond, or, when "-----" is absent, Z is O or NH;  
R' is H or (C₁-C₆)alkyl;  
W is CO, SO₂, or CH₂, wherein each hydrogen may be optionally replaced by halo or (C₁-C₆)alkyl; and

![Chemical Structures](image)

What is also provided is a compound of formula I which is a compound of formula V:

![Chemical Structure V](image)

or a pharmaceutically acceptable salt thereof, wherein

R₁, R₂, R₃, and R₄ are each independently H, fluoro, chloro, cyano, nitro,

(C₁-C₆)alkanoyl, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy,
(C<sub>1</sub>-C<sub>6</sub>)alkoxy, NHCO-(C<sub>1</sub>-C<sub>6</sub>)alky, SO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl, SO<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub>)alkyl, or
SO<sub>2</sub>N(C<sub>1</sub>-C<sub>6</sub>)alkyl); Z is CH or N when "---" is a bond, or, when "---" is absent, Z is O or NH; and

R is

5

What is also provided by the invention is a compound which is:

1-<sup>1</sup>[2-(4-<sup>4</sup>[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl]ethyl)-7-methoxyquino[2](1H)-one;

1-<sup>2</sup>[2-(4-<sup>4</sup>[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl]ethyl)-7-methoxyquino[2](1H)-one;

10 Methyl 1-<sup>2</sup>[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl]ethyl]-6-methoxy-1H-indole-2-carboxylate;

6-<sup>6</sup>[(1-<sup>1</sup>[(2-(7-Methoxy-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;

1-<sup>9</sup>[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]pipiperidin-1-yl)ethyl]-2-oxo-1,2-dihydroquinoline-7-carbonitrile;

2-<sup>2</sup>OxO-1-<sup>2</sup>[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino]piperidin-1-yl)ethyl]-1,2-dihydroquinoline-7-carbonitrile;

6-<sup>6</sup>[(1-<sup>1</sup>[(2-(7,8-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;

15 6-<sup>6</sup>[(1-<sup>1</sup>[(2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;

6-<sup>6</sup>[(1-<sup>1</sup>[(2-(7-Fluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;

30 1-<sup>2</sup>[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl)ethyl]-7-fluoroquinolin-2(1H)-one;

6-<sup>6</sup>[(1-<sup>1</sup>[(2-(7-Methoxy-2-oxo-3,4-dihydroquinolin-1(2H)-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;

(3S,4R)-1-<sup>2</sup>[(2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]-4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidine-3-carboxylic acid;

(3S,4R)-1-<sup>2</sup>[(2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]-4-[(2E)-3-(2,5-difluorophenyl)prop-2-yn-1-yl]amino]piperidine-3-carboxylic acid;
Methyl (3S,4R)-1-[2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl]-4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino)piperidine-3-carboxylate;

Methyl (3S,4R)-1-[2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl]-4-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]amino)piperidine-3-carboxylate;

(3R,4R)-1-[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]-4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino)piperidine-3-carboxylic acid;

(3R,4R)-1-[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]-4-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]amino)piperidine-3-carboxylic acid;

Methyl (3R,4R)-1-[2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl]-4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino)piperidine-3-carboxylate;

Methyl (3R,4R)-1-[2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl]-4-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]amino)piperidine-3-carboxylate;

Cis(+)-6-[(1-[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]-3-hydroxy-piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;

4-(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl methyl)amino]piperidin-1-yl)ethyl)-6-methoxy-2H,1,4-benzoxazin-3(4H)-one;

6-[(1-[2-(6-Methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;

6-[(1-[2-(6-Methoxy-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl)ethyl]piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;

4-[(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl methyl)amino]piperidin-1-yl)ethyl]-6-methoxy-2H,1,4-benzothiazin-3(4H)-one;

6-[(1-[2-(6-Fluoro-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl)ethyl]piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;

4-[(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl methyl)amino]piperidin-1-yl)ethyl]-6-fluoro-2H,1,4-benzoxazin-3(4H)-one;

6-[(1-[2-(6-Chloro-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;

6-[(1-[2-(6-Methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;

3-Oxo-4-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino]piperidin-1-yl)ethyl]-3,4-dihydro-2H,1,4-benzoxazine-6-carboxitrile;
6-\{1-\{2-(3-Oxo-6-(trifluoromethoxy)-2,3-dihydro-\textsubscript{4}H-1,4-benzoazoxin-4-yl)ethyl\}piperidin-4-yl\}amino\}methyl\}2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
6-\{4-(1-\{2-(6-Fluoro-3-oxo-2,3-dihydro-\textsubscript{4}H-1,4-benzoazoxin-4-yl)ethyl\}piperidin-4-yl\}amino\}methyl\}2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
4-(2-\{4-(1-\{2-(3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl\}amino\}piperidin-1-yl)ethyl\}-3-oxo-3,4-dihydro-\textsubscript{2}H-1,4-benzoazoxine-6-carbonitrile;
6-\{1-\{2-(6-Bromo-3-oxo-2,3-dihydro-\textsubscript{4}H-1,4-benzoazoxin-4-yl)ethyl\}piperidin-4-yl\}amino\}methyl\}2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
6-\{1-\{2-(6-Hydroxy-3-oxo-2,3-dihydro-\textsubscript{4}H-1,4-benzoazoxin-4-yl)ethyl\}piperidin-4-yl\}amino\}methyl\}2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
4-(2-\{4-\{1-\{2-(2,5-Difluorophenyl)cyclopropyl\}methyl\}amino\}piperidin-1-yl\}ethyl\}-3-oxo-3,4-dihydro-\textsubscript{2}H-1,4-benzoazoxine-6-carbonitrile;
6-\{1-\{2-(6,8-Difluoro-3-oxo-2,3-dihydro-\textsubscript{4}H-1,4-benzoazoxin-4-yl)ethyl\}piperidin-4-yl\}amino\}methyl\}2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
4-(2-\{4-\{1-\{2-(2,5-Difluorophenyl)prop-2-en-1-yl\}amino\}piperidin-1-yl\}ethyl\}-3-oxo-3,4-dihydro-\textsubscript{2}H-1,4-benzoazoxine-6-carbonitrile;
6-\{\{trans-4-\{2-(6-Methoxy-3-oxo-2,3-dihydro-\textsubscript{4}H-1,4-benzoazoxin-4-yl)ethyl\}cyclohexyl\}amino\}methyl\}2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
3-Oxo-4-\{2-(\{trans-4-\{1-\{2-(3-oxo-3,4-dihydro-\textsubscript{2}H-1,4-benzoazoxin-6-carbonitrile;
6-Bromo-4-(2-(3-oxo-3,4-dihydro-\textsubscript{2}H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl\}amino\}piperidin-1-yl\}ethyl\}-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
6-\{1-\{2-(6-Nitro-3-oxo-2,3-dihydro-\textsubscript{4}H-1,4-benzoazoxin-4-yl)ethyl\}piperidin-4-yl\}amino\}methyl\}2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
3-Oxo-4-\{2-(3-oxo-3,4-dihydro-\textsubscript{2}H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl\}amino\}piperidin-1-yl\}ethyl\}-3,4-dihydro-\textsubscript{2}H-pyrido[3,2-b][1,4]oxazine-6-carbonitrile;
3-Oxo-4-\{2-\{3-oxo-3,4-dihydro-\textsubscript{2}H-pyrido[3,2-b][1,4]oxazin-6-yl\}methyl\}amino\}piperidin-1-yl\}ethyl\}-3,4-dihydro-\textsubscript{2}H-pyrido[3,2-b][1,4]oxazine-6-carboxamide;
6-[[1-(2-(6-Acetyl-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
6-Acetyl-4-(2-[4-[[2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-yl]methyl]amino]piperidin-1-yl)ethyl]-2H-1,4-benzoxazin-3(4H)-one;
4-(2-[4-[[2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl]methyl]amino]piperidin-1-yl)ethyl]-6-methyl-2H-1,4-benzoxazin-3(4H)-one;
3-Oxo-4-[2-(6-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl]methyl]amino]-3-azabicyclo[3.1.0]hex-3-yl)ethyl]-3,4-dihydro-2H-1,4-benzoxazin-6-carbonitrile;
4-(2-[4-[[2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl]methyl]amino]piperidin-1-yl)ethyl]-2H-1,4-benzoxazin-3(4H)-one;
6-[[1-(2-[6-(1-Hydroxyethyl)-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl]ethyl]piperidin-4-yl]amino]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
Ethyl N-[[1-(2-[6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl]ethyl]-2H-1,4-benzoxazin-3(4H)-one-2]-an-1-yl]glycinate;
6-[[1-(2-[6-(Methylsulfonyl)-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl]ethyl]piperidin-4-yl]amino]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
6-[[1-(2-[6-(Ethylsulfonyl)-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl]ethyl]piperidin-4-yl]amino]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
7-Methoxy-3-methyl-1-[[2-(4-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl]methyl]amino]piperidin-1-yl)ethyl]quinazoline-2,4(1H,3H)-dione;
4-(2-[4-[[2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl]methyl]amino]-2-oxopiperidin-1-yl)ethyl]-6-methoxy-2H-1,4-benzoxazin-3(4H)-one;
6-[[1-(2-[6-Methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl]ethyl]piperidin-4-yl]amino]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
3-Oxo-4-[2-(3-oxo-4-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl]methyl]amino]piperidin-1-yl)ethyl]-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile;
4-[[3-[4-(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl]methyl]piperazin-1-yl]propyl]-6-methoxy-2H-1,4-benzoxazine-3(4H)-one;
1-(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino)piperidin-1-yl)ethyl]-7,8-difluoroquinoxalin-2(1H)-one;
5
6-[(1-[(2,7,8-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
10
6-[(1-[(2-(6,7-Dimethoxy-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
15
6-[(1-[(2-(7-Methoxy-3-methyl-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
7
1-(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino)piperidin-1-yl)ethyl)quinolin-2(1H)-one;
12
1-(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino)piperidin-1-yl)ethyl)quinolin-4(1H)-one;

Cis(±)-6-[(1-{2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl]-3-methoxypiperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;

7-Fluoro-2-oxo-1-{2-(4-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino)piperidin-1-yl)ethyl]-1,2-dihydroquinoline-5-carbonitrile;

5-Fluoro-2-oxo-1-{2-(4-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino)piperidin-1-yl)ethyl]-1,2-dihydroquinoline-7-carbonitrile;

7-Fluoro-1-{2-(4-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino)piperidin-1-yl)ethyl]quinoxalin-2(1H)-one;

1-(2-[(2,2-Dimethyl-3,4-dihydro-2H-chromen-6-yl)methyl]amino)piperidin-1-yl)ethyl]-5,7-difluoroquinolin-2(1H)-one;

1-{2-(4-{[(1,3-Dimethyl-2-oxa-2,3-dihydro-1H-benzimidazol-5-yl)methyl]amino)piperidin-1-yl)ethyl]-5,7-difluoroquinolin-2(1H)-one;

5,7-Difluoro-1-{2-(4-[(5,6,7,8-tetrahydronaphthalen-2-yl)methyl]amino)piperidin-1-yl)ethyl]quinolin-2(1H)-one;

5,7-Difluoro-1-{2-(4-[(6-fluoro-4H-1,3-benzodioxin-8-yl)methyl]amino)piperidin-1-yl)ethyl]quinolin-2(1H)-one;

5,7-Difluoro-1-{2-(4-[(1H-indol-6-yl)methyl]amino)piperidin-1-yl)ethyl]quinolin-2(1H)-one;

1-(2-[(2,3-Dihydro-1H-inden-5-yl)methyl]amino)piperidin-1-yl)ethyl]-5,7-difluoroquinolin-2(1H)-one;
5,7-Difluoro-1-[(2-(4-[[1-methyl-1H-1,2,3-benzotriazol-5-yl]methyl]amino)piperidin-1-yl)ethyl]quinolin-2(1H)-one;
5,7-Difluoro-1-[(2-[(1H-indol-5-yl)methyl]amino)piperidin-1-yl]ethyl]quinolin-2(1H)-one;
5,7-Difluoro-1-[(2-[(4-methyl-3,4-dihydro-2H,1,4-benzoxazin-7-yl)methyl]amino)piperidin-1-yl]ethyl]quinolin-2(1H)-one;
1-(2-[(2,1,3-Benzoxadiazol-5-yl)methyl]amino)piperidin-1-yl)ethyl]-7-fluoroquinoxalin-2(1H)-one;
N-1-[2-(7-Fluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl]-2,3-dihydro-1,4-benzodioxine-6-sulfonamide;
N-1-[2-(7-Fluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl]-3-oxo-3,4-dihydro-2H,1,4-benzoxazine-6-sulfonamide;
5-Fluoro-N-1-[2-(7-Fluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl]-1H-indole-2-carboxamide;
N-1-[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl]-6-morpholin-4-yl)nicotinamide;
N-1-[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl]-2,3-dihydro-1,4-benzodioxine-2-carboxamide;
N-1-[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl]-1-methyl-1H-1,2,3-benzotriazole-5-carboxamide;
N-1-[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl]-3-(2-methyl-1,3-thiazol-4-yl)benzamide;
N-1-[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl]-4-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide;
3-Oxo-4-[(2R,5S)-5-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino)piperidin-2-yl]ethyl]-3,4-dihydro-2H,1,4-benzoxazine-6-carbonitrile;
3-Oxo-4-[(2R,5S)-5-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino)piperidin-2-yl]ethyl]-3,4-dihydro-2H,1,4-benzoxazine-6-carbonitrile;
6-[(1-[2-(5,7-Difluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
6-[(1-[2-(6,8-Difluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
2-Oxo-1-{2-(4-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b]1,4]oxazin-6-yl]methyl][amino]piperdin-1-yl}ethy]-1,2-dihydroquinoxaline-6-carbonitrile;
3-Oxo-4-{2-(4-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b]1,4]oxazin-6-yl]methyl][amino]piperidin-1-yl}ethyl]-3,4-dihydroquinoxaline-6-carbonitrile;
6-{{1-[(2-({6-Methoxy-3-oxopyrido[2,3-b]1,4]oxazin-4(3H)-yl}ethyl][piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
4-{{2-(4-{[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl]amino]piperidin-1-yl}ethyl]-6-methoxypyrrolo[2,3-b][1,4]pyrazin-3(4H)-one;
6-{{1-[(2-{{6-Chloro-1-oxo-3-oxo-1,2,4-benzoetriazin-4(3H)-yl}ethyl][piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
6-Chloro-4-{2-{{2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl]amino}piperidin-1-yl}ethyl]-1,2,4-benzoetriazin-3(4H)-one 1-oxide;
6-{{1-[(2-{{6-Chloro-1-oxo-3,2,4-benzoatriazin-4(3H)-yl}ethyl][piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
4-{{2-(4-{[(2,3,5S,5R)-5-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl]amino]piperidin-2-yl}ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoaxazine-6-carbonitrile;
6-{{1-[(2-{{7-Bromo-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-1-yl}ethyl][piperidin-4-yl]amino}methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
2-Oxo-1-{2-(4-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-7-carbonitrile;
2-Oxo-1-{2-(4-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl]methyl][amino]piperidin-1-yl}ethyl]-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine-7-carboxamide;
1-(2-{4-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl]amino]-2-methylpiperidin-1-yl}ethyl]-5,7-difluoroquinolin-2(1H)-one;
1-(2-{4-{[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl]amino}piperidin-1-yl}ethyl]-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
Cis-d{4-{[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]-4-{[(3-{6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propyl][piperidine-3-carboxylic acid;
Methyl (Cis-d{4-{[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]-4-{[(3-{6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propyl]piperidine-3-carboxylate;
Cis-1-(2-4-((2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino)-3-hydroxy-3-piperidin-1-yl)ethyl)-2-oxo-1,2-dihydroquinoline-7-carbonitrile;

Cis-1-(2-(3-hydroxy-4-((3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl)amino)piperidin-1-yl)ethyl)-2-oxo-1,2-dihydroquinoline-7-carbonitrile;

5,7-Difluoro-1-(2-4-((5,6,7,8-tetrahydro-1,8-naphthyridin-2-ylmethyl)amino)piperidin-1-yl)ethyl)quinolin-2(1H)-one;

Cis-1-(2-4-((2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino)-3-methoxy-3-piperidin-1-yl)ethyl)-2-oxo-1,2-dihydroquinoline-7-carbonitrile;

Cis-1-(2-4-((3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl)amino)piperidin-1-yl)ethyl)-2-oxo-1,2-dihydroquinoline-7-carbonitrile;

Cis-1-(2-4-((2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino)-3-fluoropiperidin-1-yl)ethyl)-2-oxo-1,2-dihydroquinoline-7-carbonitrile;

Cis-1-(2-(3-fluoro-4-((3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl)amino)piperidin-1-yl)ethyl)-2-oxo-1,2-dihydroquinoline-7-carbonitrile;

Cis-1-(2-4-((2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino)-3-hydroxy-3-piperidin-1-yl)ethyl)-7-fluoroquinoxalin-2(1H)-one;

Cis-6-((1-2-(7-fluoro-2-oxoquinolin-1(2H)-yl)ethyl)-3-hydroxy-3-piperidin-4-yl)methyl]pyrido[3,2-b][1,4]oxazin-3(4H)-one;

Cis-1-(2-4-((2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino)-3-fluoropiperidin-1-yl)ethyl)-7-fluoroquinoxalin-2(1H)-one;

Cis-6-((1-2-(7-fluoro-2-oxoquinolin-1(2H)-yl)ethyl)-3-fluoropiperidin-4-yl)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;

Cis-1-(2-4-((2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino)-3-hydroxy-3-piperidin-1-yl)ethyl)-7-methoxyquinoxalin-2(1H)-one;

Cis-6-((1-2-(7-methoxy-2-oxoquinolin-1(2H)-yl)ethyl)-3-hydroxy-3-piperidin-4-yl)methyl]pyrido[3,2-b][1,4]oxazin-3(4H)-one;

Cis-1-(2-4-((2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino)-3-methoxy-3-piperidin-1-yl)ethyl)-7-methoxyquinoxalin-2(1H)-one;
Cist06-[[1-2-(7-methoxy-2-oxoquinazolin-1(2H)-yl)ethyl]-3-methoxy-1-y1)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
Cist1-2-{4-[2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]-3-fluoropiperidin-1-yl]ethyl]-7-methoxyquinazolin-2(1H)-one;
Cist6-[[1-2-(7-methoxy-2-oxoquinazolin-1(2H)-yl)ethyl]-3-methoxy-1-y1)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one; 
Cist4-2-{3-2-hydroxy-4-[[3-oxo-3-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)amino) piperidin-1-yl]ethyl]-3-oxo-3,4-dihydro-2H-1, 4-benzoxazine-6-carbonitrile;
Cist4-[(2-3-methoxy-4-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6- 

y1)amino) piperidin-1-yl]ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile;
Cist4-2-{3-fluoro-4-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6- 

y1)amino) piperidin-1-yl]ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile;
1-(2-4-[2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)aminopiperidin-1- 

y1)ethyl]-7-methoxy-3,4-dihydroquinazolin-2(1H)-one;
5,7-Difluoro-1-{2-(4-[[1-oxo-1,3-dihydro-2-benzofuran-5- 

y1)amino) piperidin-1-yl]ethyl]quinolin-2(1H)-one; 
6-[[1-2-(7-Methoxy-2-oxoquinazolin-1(2H)-yl)propyl]piperidin-4- 

y1)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one; or 
5,7-Difluoro-1-{2-(4-[[5,6,7,8-tetrahydro-1,8-naphthyridin-2- 

y1)methyl]amino) piperidin-1-yl]ethyl]quinolin-2(1H)-one.

The invention also provides a pharmaceutical composition comprising a compound of formulas I-V admixed with a pharmaceutically acceptable adjuvant, carrier, or excipient.

The invention also provides a method of treating a bacterial infection comprising administering a therapeutically effective amount of a compound of formulas I-V to a mammal in need thereof.

The invention also provides a method of treating a bacterial infection in a warm-blooded animal, such as a human being, in need of such treatment, which comprises administering to said animal an effective amount of a compound of formulas I-V or a pharmaceutically acceptable salt thereof.

The invention also provides a method for inhibiting bacterial DNA gyrase in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formulas I-V or a pharmaceutically acceptable salt.
The invention also provides a compound of formulas I-V and pharmaceutically acceptable salts thereof for use as a medicament.

The invention also provides the use of a compound of formulas I-V or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an anti-bacterial effect in a warm-blooded animal such as a human being.

The invention also provides the use of a compound of formulas I-V or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of a bacterial infection in a warm-blooded animal such as a human being.

The invention also provides a process for making a compound of formulas I-V,

comprising one of the following:

(a) \( N \)-alkylation of \( L \) with \( X-U_1 M \), wherein \( X \) is a leaving group in the presence of a base to form \( L U_1 M \), wherein \( U_1 \) is \( CH_2 CH_2 \), followed by attachment of \( U_2 \) and \( R \) via functional group manipulation, alkylation, or reductive amination;

\[
\begin{align*}
L & \xrightarrow{X-U_1 M} L-U_1 M \xrightarrow{U_2} \\
\text{Base} & \\
\xrightarrow{R} & \\
L-U_1 M-U_2 & \xrightarrow{R} L-U_1 M-U_2-R
\end{align*}
\]

(b) \( N \)-alkylation of \( L \) with \( HO-U_1 M \), under Mitsunobu conditions to form \( L U_1 M \), followed by attachment of \( U_2 \) and \( R \) via functional group manipulation, alkylation, or reductive amination;

\[
\begin{align*}
L & \xrightarrow{HO-U_1 M} L-U_1 M \xrightarrow{U_2} \\
\text{Mitsunobu} & \\
\xrightarrow{R} & \\
L-U_1 M-U_2 & \xrightarrow{R} L-U_1 M-U_2-R
\end{align*}
\]

(c) \( N \)-alkylation of \( L \) with bromo- or chloroacetic acid or a derivative thereof to form \( L-CH_2 CO_2 H \) followed by

i) activation of the acid moiety in \( L-CH_2 CO_2 H \);

ii) amide coupling to form \( L U_1 M \), wherein \( U_1 \) is \( CH_2 CO_2 \);

iii) attachment of \( U_2 \) and \( R \) via functional group manipulation, alkylation, or reductive amination; and
iv) optional reduction of the carbonyl moiety in U₁ to form a compound wherein U₁ is CH₃CH₂:

\[ \text{XCH₂CO₂H} \]
\[ \text{X= Cl, Br} \]

Base

\[ \text{L-CH₂CO₂H} \quad \xrightarrow{M} \quad \text{L-CH₂COM} \]

\[ \text{L-CH₂COM-U₂-R} \quad \xrightarrow{R} \quad \text{L-CH₂CH₂M-U₂-R} \]

(d) N-alkylation of L with \( X-(\text{CH₂})ₙ\text{CH}=\text{CH₂} \) wherein X is a leaving group and n is 1 or 2 to form L-(\( \text{CH₂} \)ₙ\text{CH}=\text{CH₂}), followed by:

i) oxidative cleavage using an oxidant such as ozone or sodium periodate (with reductive workup) to form L-(\( \text{CH₂} \)ₙ\text{CH₃OH});

ii) conversion of the alcohol moiety in L-(\( \text{CH₂} \)ₙ\text{CH₃OH}) to a leaving group;

iii) reaction of L-(\( \text{CH₂} \)ₙ\text{CH₂}Y) with M, in the presence of a base to form LU₁M;

and

iv) attachment of U₂ and R via functional group manipulation, alkylation, or reductive amination:

\[ \text{L-CH₂COM-U₂-R} \quad \xrightarrow{R} \quad \text{L-CH₂CH₂M-U₂-R} \]

X, Y = leaving group  n = 1 or 2

(e) N-alkylation of L with \( X-(\text{CH₂})ₙ\text{CH}=\text{CH₂} \) wherein X is a leaving group and n is 0 or 1 to form L-(\( \text{CH₂} \)ₙ\text{CH}=\text{CH₂}), provided that when n is 0, a metal catalyst is optionally used, followed by:

i) hydroboration followed by an oxidative workup to form to form L-(\( \text{CH₂} \)ₙ\text{CH₂CH₃OH})
ii) conversion of the alcohol moiety in L-(CH₂)ₙCH₂CH₂OH to a leaving group;

iii) reaction of L-(CH₂)ₙCH₂CH₂-“LG” with M₁, in the presence of a base to form 

LU₁M; and

iv) followed by attachment of U₂ and R via functional group manipulation, 

alkylation, or reductive amination;

\[ \begin{align*}
L & \xrightarrow{X-(CH₂)ₙ-CH=CH₂, Base} L-\left(\text{CH₂}\right)ₙ \xrightarrow{\text{Hydroboration}} L-\left(\text{CH₂}\right)ₙ \xrightarrow{\text{Oxidative Workup}} L-\left(\text{CH₂}\right)ₙ \xrightarrow{\text{OH}} \\
& \xrightarrow{\text{U₂}} L-U₁M \xrightarrow{M} L-U₁M-U₂ \xrightarrow{R} L-U₁M-U₂R \n\end{align*} \]

\( X, Y = \text{leaving group} \quad n = 1 \text{ or } 2 \)

(f) Oxidation of the alcohol intermediate \( L-\text{OH} \) in d) and e) supra to the aldehyde 

, followed by

i) reductive amination with M₁U₂; to form LU₁M₂U₂, wherein U₁ is CH₃CH₂;

ii) reductive amination with R; or

\[ \begin{align*}
L & \xrightarrow{\text{OH}} \xrightarrow{[O]} L \xrightarrow{\text{MU₂}} \\
& \xrightarrow{\text{R}} L-U₁M-U₂ \xrightarrow{R} L-U₁M-U₂R \n\end{align*} \]

(g) N-alkylation of L with X-(CH₂)ₙCH₂CH₂OH, wherein X is a leaving group and n is 0 or 1 to form the intermediate L-(CH₂)ₙCH₂CH₂OH as depicted in (e), supra, followed by

\[ \begin{align*}
i) & \quad \text{conversion of the alcohol moiety in L-(CH₂)ₙCH₂CH₂OH to a leaving group;} \\
& \quad \text{reaction of L-(CH₂)ₙCH₂CH₂-“LG” with M, in the presence of a base to form} \\
& \quad LU₁M; \text{ and} \\
\end{align*} \]
iii) followed by attachment of $U_2$ and $R$ via functional group manipulation, alkylation, or reductive amination.

\[ \begin{align*}
    & L \overset{(-)}{\rightarrow} \overset{n}{\rightarrow} \overset{L \overset{(-)}{\rightarrow} \overset{n}{\rightarrow} M}{OH} \rightarrow L \overset{(-)}{\rightarrow} \overset{n}{\rightarrow} Y \\
    & L-U_1-M \rightarrow L-U_1-M-U_2 \rightarrow R \rightarrow L-U_1-M-U_2-R
\end{align*} \]

$X, Y = \text{leaving group}$  \hspace{0.5cm} $n = 1 \text{ or } 2$

**DETAILED DESCRIPTION OF THE INVENTION**

Unless otherwise stated, the following terms used in the specification and claims have the following meanings.

**Definitions**

"Alkyl" means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to six carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, pentyl, and the like, that may be optionally substituted.

"Alkenyl" means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms, containing at least one double bond, e.g., ethenyl (-CH=CH-), propenyl, and the like that may be optionally substituted.

"Alkylene" means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms, e.g., methylene (-CH$_2$-), ethylene (-CH$_2$CH$_2$-), propylene, 2-methylpropylene, pentylene, and the like that may be optionally substituted.

"Acyl" means a radical --C(=O)R where $R$ is hydrogen, alkyl, alkenyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, aralkyl, heteroaralkyl or heteroaryl, e.g., acetyl, benzoyl, thiocarbamoyl, and the like that may be optionally substituted.

"Acyloxy" means a radical --OC(=O)R where $R$ is hydrogen, alkyl, alkenyl, cycloalkyl, heteroalkyl, haloalkyl or optionally substituted phenyl, e.g., acetoxy, benzoyloxy, and the like that may be optionally substituted.

"Halo" means fluoro, chloro, bromo or iodo.
"Haloalkyl" means alkyl substituted with one or more same or different halo atoms, e.g., —CH₂Cl, —CF₃, —CH₂CF₃, —CH₂CCl₃, and the like.

"Cycloalkyl" means a saturated monovalent cyclic hydrocarbon radical of three to six ring carbons, e.g., cyclopropyl, cyclohexyl, and the like that may be optionally substituted. "Amine" or "amino" refers to radicals of the general formula —NR'R', wherein R and R' are independently selected from hydrogen or a hydrocarbyl radical, or wherein R and R' combined form a heterocycle. Examples of amino groups include: —NH₂, methyl amino, diethyl amino, anilino, benzyl amnio, piperidinyl, piperazinyl and indolyl.

"Monosubstituted amino" means a radical —NHR where R is alkyl, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl or optionally substituted phenyl, e.g., methylanino, (1-methylthylethyl)amino, phenylamino, and the like.

"Disubstituted amino" means a radical —NRR' where R and R' are independently alkyl, alkenyl, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl or optionally substituted phenyl. Representative examples include, but are not limited to, dimethylanino, methylthylethlamino, di(1-methylthylethyl)amino, methylbenzylamino, and the like.

"Aryl" means a monovalent monocyclic or bicyclic aromatic hydrocarbon radical of 6 to 10 ring atoms, and optionally substituted independently with one or more substituents, preferably one, two or three substituents selected from alkyl, haloalkyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, halo, cyano, nitro, acyloxy, alkoxyl, optionally substituted phenyl, heteroaryl, heteroaralkyl, amino, monosubstituted amino, disubstituted amino, acylanino, hydroxyamino, amidino, guanidino, cyanoguanidiny, hydrazino, hydrazido, —OR (where R is hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, cycloalkylalkyl, optionally substituted phenyl, heteroaryl or heteroaralkyl), —S(O)ₙR (where n is an integer from 0 to 2 and R is hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, cycloalkylalkyl, optionally substituted phenyl, heteroaryl or heteroaralkyl), —NR₂R' (where R is hydrogen or alkyl and R' is alkyl, amino, monosubstituted or disubstituted amino) —C(O)R (where R is hydrogen, alkyl, alkenyl, cycloalkyl, heteroalkyl, haloalkyl or optionally substituted phenyl), —COOR (where R is hydrogen, alkyl, optionally substituted phenyl, heteroaryl or heteroaralkyl), —(alkylene)-COOR (where R is hydrogen, alkyl, optionally substituted phenyl, heteroaryl or heteroaralkyl), methyleneedioxy, 1,2-ethylenedioxy, —CONR'R' or —(alkylene)CONR'R' (where R' and R'' are independently selected from hydrogen, alkyl, cycloalkyl, haloalkyl, cycloalkylalkyl, optionally substituted phenyl, heteroaryl and heteroaralkyl). More specifically the term aryl includes, but is not limited to,
phenyl, 1-naphthyl, 2-naphthyl, and derivatives thereof.

The term "ortho-fused" as used in the phrase "ortho-fused bicyclic subunit" means a bicyclic saturated, partially aromatic or fully aromatic, fully unsaturated or partially saturated, carbocyclic or heterocyclic ring system wherein the two rings have only two atoms and one bond in common. Both rings may be aromatic, for example, such as in naphthalene, pteridine, cincholine, quinoxaline, quinolizine, phthalazine, quinoline, isoquinoline, quinolizine, purine, indazole, indole, isoindole, indolizine, or pyrimidine and the like.

"Heteroaryl" means a monovalent monocyclic or bicyclic aromatic radical of 5 to 10 ring atoms containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C. For the avoidance of doubt, "heteroaryl" includes "ortho-fused bicyclic heteroaryl". The aromatic radical is optionally substituted independently with one or more substituents, preferably one or two substituents selected from oxo, alkyl, haloalkyl, heteroaalkyl, cycloalkyl, cycloalkylalkyl, halo, cyano, nitro, acyloxy, optionally substituted phenyl, amino, mono substituted amino, disubstituted amino, acylamino, hydroxymonoamino, amidino, guanidino, cyanoguanidinyl, hydrazino, hydrazido. —OR (where R is hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, cycloalkylalkyl or optionally substituted phenyl), —SO₃R (where n is an integer from 0 to 2 and R is hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, cycloalkylalkyl, optionally substituted phenyl, amino, mono or disubstituted amino), —C(OR) (where R is hydrogen, alkyl, alkenyl, cycloalkyl, heteroaalkyl, haloalkyl or optionally substituted phenyl), —COOR (where R is hydrogen, alkyl, or optionally substituted phenyl), —(alkylene)-COOR (where R is hydrogen, alkyl or optionally substituted phenyl), methylenedioxy, 1,2-ethylenedioxy, —CONR₂ or —(alkylene)-CONR₂ (where R' and R" are independently selected from hydrogen, alkyl, cycloalkyl, haloalkyl, cycloalkylalkyl or optionally substituted phenyl). The term heteroaryl includes, but is not limited to pyridyl, pyrrolyl, thiophene, pyrazolyl, thiazolyl, imidazolyl, pyrimidinyl, thiadiazolyl, indolyl, carbazolyl, azaindolyl, benzofuranyl, benzothiazolyl, benzisoxazolyl, purinyl, quinolinyl, benzopyranly, and derivatives thereof.

"Heterocycle" or "Heteroocyclyl" means a saturated, partially unsaturated or fully unsaturated cyclic radical of 3 to 8 ring atoms in which one or two ring atoms are heteroatoms selected from N, O, or S(O)ₙ (where n is an integer from 0 to 2). The heterocyclic ring may be optionally substituted independently with one, two or three substituents selected from alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaalkyl, halo, cyano, acy1, acylamino, amino, monosubstituted amino, disubstituted amino, —COOR (where R is
hydrogen or alkyl), —XR (where X is O or S(O), where n is an integer from 0 to 2 and R is hydrogen, alkyl, halalkyl, cycloalkyl, aralkyl, aryl, heteroaryl or heteroaralkyl) or —CONR" (where R' and R" are independently selected from hydrogen or alkyl).

Representative examples include, but are not limited to tetrahydropyranyl, piperidino, 1-(4-chlorophenyl)piperidino, and the like.

In one aspect of the invention "Ry and Ry' together form a bridge". A bridge is a bond, a carbon atom or two carbon atoms connecting two different ring atoms of M which are meta or para to each other. Particularly the bridge is a bond. Particularly the bridge is one carbon atom. Alternatively the bridge is two carbon atoms. Examples of M where "Ry and Ry' together form a bridge" are:

(M1, bridge is a bond, atoms of M are meta to each other),

(M2, bridge is one carbon atom, atoms of M are meta to each other),

(M4, bridge is two carbon atoms, atoms of M are para to each other),

and

(M5, bridge is a bond, atoms of M are meta to each other).

"Aralkyl" means a radical —R₄—R₆ where R₄ is bound to R₆ and R₄ is an alkylene group and R₆ is an aryl group as defined above e.g., benzyl, phenylethyl, 3-(3-chlorophenyl)-2-methylpentyl, and the like.

"Heteroaralkyl" means a radical —R₄—R₆ where R₄ is bound to R₆ and R₄ is an alkylene group and R₆ is a heteroaryl group as defined above e.g., pyridin-3-ylmethyl, 3-(benzofuran-2-yl)propyl, and the like.

"Alkoxy", "aryloxy" or "heteroaryloxy" means a radical —OR where R is an alkyl, aryl or heteroaryl, respectively as defined above e.g., methoxy, phenoxy, pyridin-2-ylloxy and the like.

"Alkylthio" and "heteroaryltthio" respectively mean an alkyl group or heteroaryl group attached via a thioether linkage.
"Alkylsulfanyl" and "heteroaryl-sulfanyl" respectively mean an alkyl group or heteroaryl group attached via a sulfanyl linkage.

"Alkylcarbonyloxy" refers to an alkyl group attached to a CO₂ group, as in alkyl-CO₂—, alkenyl-CO₂—, aryl-CO₂—, respectively, where alkyl is as defined herein. For example, alkylcarbonyloxy includes but is not limited to, acetoxyl, ethylcarbonyloxy, n- or iso-propylcarbonyloxy, n-, iso-, sec- or tert-butylcarbonyloxy, n-pentylcarbonyloxy, n-hexylcarbonyloxy.

"Optionally substituted" means that the group at issue is optionally substituted independently with one, two or three substituents selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphanamoyl, methyl, ethyl, ethenyl, ethynyl, methoxy, ethoxy, acetyl, acetoxyl, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, or any otherwise provided.

"Amino-protecting group" refers to those organic groups intended to protect nitrogen atoms against undesirable reactions during synthetic procedures e.g., benzyl, benzoxycarbonyl (CBZ), 1-butoxycarbonyl (BOC), trifluoroacetyl, and the like.

Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers".

Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. For example, if the Y and Y' substituents in a compound of formula I are attached to the same carbon are different, then the carbon to which they are attached is an asymmetric center and the compound of formula I can exist as an (R)- or (S)-stereoisomer relative to that
carbon. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 2001).

A “pharmacologically acceptable excipient” means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes an excipient that is acceptable for veterinary use as well as human pharmaceutical use. A “pharmacologically acceptable excipient” as used in the specification and claims includes both one and more than one such excipient.

A “pharmacologically acceptable counterion” means an ion having a charge opposite to that of the substance with which it is associated and that is pharmacologically acceptable.

Representative examples include, but are not limited to, chloride, bromide, iodide, methanesulfonate, p-tolylsulfonate, trifluoroacetate, acetate, and the like.

A “pharmacologically acceptable salt” of a compound means a salt that is pharmacologically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo(2.2.2)oct-2-ene-1-carboxylic acid, glucosoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfonic acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or
2) Salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

3) "Leaving group" has the meaning conventionally associated with it in synthetic organic chemistry i.e., an atom or group capable of being displaced by a nucleophile and includes halogen (such as chloro, bromo, iodo), alkanesulfonyloxy (such as mesyloxy or trifluorosulfonyloxy) or arenesulfonyloxy (such as tosyloxy), ester, or amino, and the like.

"Pro-drugs" means any compound which releases an active parent drug according to formula I in vivo when such prodrug is administered to a mammalian subject. Prodrugs of a compound of formula I are prepared by modifying functional groups present in the compound of formula I in such a way that the modifications may be cleaved in vivo to release the parent compound. Prodrugs include compounds of formula I wherein a hydroxy, thio or amino group in compound I is bonded to any group that may be cleaved in vivo to regenerate the free hydroxy, amino, or thio group, respectively. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate, and benzoate derivatives), carbamates (e.g., N,N-dimethyaminecarbonyl) of hydroxy functional groups in compounds of formula I, and the like.

"Treating" or "treatment" of a disease includes:

1) preventing the disease, i.e., causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease;

2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms; or

3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

A "therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to affect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.
Invention Compounds

Referring again to a compound of the invention, the following specific values are disclosed.

In a compound of formula I, a specific value for L is __________, wherein __________ indicates the point of attachment and Z is CH or N. Other specific values for L include the following structures, wherein __________ has the same meaning.

A specific value for $R_{2b}$ is H. Other specific values for $R_{2b}$ include halo, ($C_1-C_6$)alkanoyl, cyano, carboxy, ($C_1-C_6$)alkoxy carbonyl, ($C_1-C_6$)alkyl, hydroxy, halo($C_1-C_6$)alkyl, halo($C_1-C_6$)alkoxy, ($C_1-C_6$)alkoxy, $NHCO-($($C_1-C_6$)alkyl, SO$_2($($C_1-C_6$)alkyl, $SO_2NH($($C_1-C_6$)alkyl, or $SO_2N($($C_1-C_6$)alkyl).
To that end, specific values for $R_{2b}$ include H, methoxy, cyano, fluoro, chloro, trifluoromethoxy, bromo, hydroxy, CONH$_2$, CO$_2$Me, MeCO, methyl, 1-hydroxyethyl, 2-hydroxyethyl, SO$_2$Me, and SO$_2$Et.

A specific value for $R_{2a}$ is H. Other specific values for $R_{2a}$ include halo,

- $\text{(C}_1\text{-C}_8\text{)alkanoyl, cyano, carboxy, (C}_1\text{-C}_8\text{)alkoxy carbonyl, (C}_1\text{-C}_8\text{)alkyl, hydroxy,}$
- $\text{halo(C}_1\text{-C}_8\text{)alkyl, halo(C}_1\text{-C}_8\text{)alkoxy, (C}_1\text{-C}_8\text{)alkoxy, NHCO(C}_1\text{-C}_8\text{)alkyl, SO}_2\text{(C}_1\text{-C}_8\text{)alkyl,}$
- $\text{SO}_2\text{NH(C}_1\text{-C}_8\text{)alkyl, or SO}_2\text{N((C}_1\text{-C}_8\text{)alkyl)}_2.$

To that end, specific values for $R_{2a}$ include H, methoxy, cyano, fluoro, chloro, trifluoromethoxy, bromo, hydroxy, CONH$_2$, CO$_2$Me, MeCO, methyl, 1-hydroxyethyl.

2-hydroxyethyl, SO$_2$Me, and SO$_2$Et.

A specific value for $R_{2c}$ is H. Other specific values for $R_{2c}$ include halo,

- $\text{(C}_1\text{-C}_8\text{)alkanoyl, cyano, carboxy, (C}_1\text{-C}_8\text{)alkoxy carbonyl, (C}_1\text{-C}_8\text{)alkyl, hydroxy,}$
- $\text{halo(C}_1\text{-C}_8\text{)alkyl, halo(C}_1\text{-C}_8\text{)alkoxy, (C}_1\text{-C}_8\text{)alkoxy, NHCO(C}_1\text{-C}_8\text{)alkyl, SO}_2\text{(C}_1\text{-C}_8\text{)alkyl,}$
- $\text{SO}_2\text{NH(C}_1\text{-C}_8\text{)alkyl, or SO}_2\text{N((C}_1\text{-C}_8\text{)alkyl)}_2.$

To that end, specific values for $R_{2c}$ include H, methoxy, cyano, fluoro, chloro, trifluoromethoxy, bromo, hydroxy, CONH$_2$, CO$_2$Me, MeCO, methyl, 1-hydroxyethyl, 2-hydroxyethyl, SO$_2$Me, and SO$_2$Et.

A specific value for $R_{2d}$ is H. Other specific values for $R_{2d}$ include halo,

- $\text{(C}_1\text{-C}_8\text{)alkanoyl, cyano, carboxy, (C}_1\text{-C}_8\text{)alkoxy carbonyl, (C}_1\text{-C}_8\text{)alkyl, hydroxy,}$
- $\text{halo(C}_1\text{-C}_8\text{)alkyl, halo(C}_1\text{-C}_8\text{)alkoxy, (C}_1\text{-C}_8\text{)alkoxy, NHCO(C}_1\text{-C}_8\text{)alkyl, SO}_2\text{(C}_1\text{-C}_8\text{)alkyl,}$
- $\text{SO}_2\text{NH(C}_1\text{-C}_8\text{)alkyl, or SO}_2\text{N((C}_1\text{-C}_8\text{)alkyl)}_2.$

To that end, specific values for $R_{2d}$ include H, methoxy, cyano, fluoro, chloro, trifluoromethoxy, bromo, hydroxy, CONH$_2$, CO$_2$Me, MeCO, methyl, 1-hydroxyethyl, 2-hydroxyethyl, SO$_2$Me, and SO$_2$Et.

A specific value for $R_{2e}$ is H. Other specific values for $R_{2e}$ include halo,

- $\text{(C}_1\text{-C}_8\text{)alkanoyl, cyano, carboxy, (C}_1\text{-C}_8\text{)alkoxy carbonyl, (C}_1\text{-C}_8\text{)alkyl, hydroxy,}$
- $\text{halo(C}_1\text{-C}_8\text{)alkyl, halo(C}_1\text{-C}_8\text{)alkoxy, (C}_1\text{-C}_8\text{)alkoxy, NHCO(C}_1\text{-C}_8\text{)alkyl, SO}_2\text{(C}_1\text{-C}_8\text{)alkyl,}$
- $\text{SO}_2\text{NH(C}_1\text{-C}_8\text{)alkyl, or SO}_2\text{N((C}_1\text{-C}_8\text{)alkyl)}_2.$

To that end, specific values for $R_{2e}$ include H, methoxy, cyano, fluoro, chloro, trifluoromethoxy, bromo, hydroxy, CONH$_2$, CO$_2$Me, MeCO, methyl, 1-hydroxyethyl, 2-hydroxyethyl, SO$_2$Me, and SO$_2$Et.

A specific value for $R_{2f}$ is H. Other specific values for $R_{2f}$ include halo,

- $\text{(C}_1\text{-C}_8\text{)alkanoyl, cyano, carboxy, (C}_1\text{-C}_8\text{)alkoxy carbonyl, (C}_1\text{-C}_8\text{)alkyl, hydroxy,}$
halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, halo(C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, NHCO-(C<sub>1</sub>-C<sub>6</sub>)alkyl, SO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl, SO<sub>2</sub>NH(C<sub>1</sub>-C<sub>6</sub>)alkyl, or SO<sub>2</sub>N((C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub>.

To that end, specific values for R<sub>2f</sub> include H, methoxy, cyano, fluoro, chloro, trifluoromethoxy, bromo, hydroxy, CONH<sub>2</sub>, CO<sub>2</sub>Me, MeCO, methyl, 1-hydroxyethyl, 2-hydroxyethyl, SO<sub>2</sub>Me, and SO<sub>2</sub>Et.

A specific value for R<sub>2g</sub> and R<sub>2g'</sub> is H. Other specific values for R<sub>2g</sub> and R<sub>2g'</sub> include (C<sub>1</sub>-C<sub>6</sub>)alkyl, and halo(C<sub>1</sub>-C<sub>6</sub>)alkyl.

A specific value for U<sub>1</sub> is CH<sub>3</sub>CH<sub>2</sub>. Other specific values for U<sub>1</sub> include CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub> and CH<sub>2</sub>CH(Me). A further specific value for U<sub>1</sub> is CH(Me)CH<sub>2</sub>.

A specific value for M is , wherein Y is O, NH or CH<sub>2</sub> and "......" is absent or is a bend. Other specific values for M include a group of formula M5

which is , a group of formula M4 which is

or a group of formula M2 which is , wherein "......" indicates the point of attachment and [U<sub>1</sub>] and R2 is H or carboxy, n is 1, 2, or 3, and R <sub>y</sub> is H, F, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, or carboxy.

A specific value for M is a group of formula M4 which is

Other specific values for M include groups of formula M4 which are
When M is a group of formula M1 or M4, a specific value for [M]-U₂ is [M]-NHCH₂.

When M is a group of formula M1 or M4, other specific values for [M]-U₂ include

\[ [M] \text{--NH--} \]

, when M is a group of formula M2, M3, or M5, a specific value for [M]-U₂ is [M]-CH₂CH=CH- or [M]-CH₂CH₂-

A specific value for \( R \) is 2,1,3-benzothiadiazol-5-yl;

- 3-oxo-3,4-dihydro-2H-1,4-benzothiazin-6-yl;
- 2,3-dihydro-benzo[1,4]dioxin-6-yl;
- 1,2,3-benzothiadiazol-5-yl;
- 3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl;
- 7-fluoro-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl;
- 2-oxo-2,3-dihydro-1H-pyrido[3,2-b][1,4]thiazin-7-yl;
- 2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl;
- 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl;
- [1,2,3]thiadiazolo[5,4-b]pyridin-6-yl;
- 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][14]thiazin-6-yl;
- 7-chloro-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl;
- 7-fluoro-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl;
- 2-thienylthio; or
- 2,5-difluorophenyl.

More specifically \( R \) is

```
--N--
```

wherein "---" indicates the point of attachment.
A specific group of compounds of the invention are compounds wherein L is

\[ \text{structure} \]

wherein "\( \sim \sim \sim \)" indicates the point of attachment;

"\( \sim \sim \sim \)" is a bond or is absent;

Z is CH or N when "\( \sim \sim \sim \)" is a bond, or, when "\( \sim \sim \sim \)" is absent, Z is O or NH;

R\(_2a\), R\(_2b\), R\(_2c\), and R\(_2d\) are each independently H, halo, cyano, (C\(_1\)-C\(_6\))alkanoyl, carboxy, (C\(_1\)-C\(_6\))alkoxy, (C\(_1\)-C\(_6\))alkyl, halo(C\(_1\)-C\(_6\))alkyl, halo(C\(_1\)-C\(_6\))alkoxy, (C\(_1\)-C\(_6\))alkoxy, NHCO-(C\(_1\)-C\(_6\))alkyl, SO\(_2\)(C\(_1\)-C\(_6\))alkyl, SO\(_2\)NH(C\(_1\)-C\(_6\))alkyl, or SO\(_2\)N((C\(_1\)-C\(_6\))alkyl)\(_2\).

A specific group of compounds of the invention are compounds wherein U\(_1\)=M=U\(_2\)

\[ \text{structure} \]

is

Y is O, NH, N(C\(_1\)-C\(_6\))alkyl, N[CO-(C\(_1\)-C\(_6\))alkyl], N[SO\(_2\)(C\(_1\)-C\(_6\))alkyl] or CH\(_2\) and "\( \sim \sim \sim \)" is absent or is a bond. Other specific groups of compounds of the invention are compounds wherein U\(_1\)=M=U\(_2\) is

\[ \text{structure} \]

"[L] \( \sim \sim \sim \)" indicates the point of attachment to L and "\( \sim \sim \sim \)" indicates the point of attachment to R, and wherein R\(_2\) is H or carboxy and n is 1, 2, or 3;

R\(_a\), R\(_b\), R\(_c\), R\(_d\), R\(_e\), and R\(_f\) are each independently H or (C\(_1\)-C\(_6\))alkyl;

R\(_y\) is H, F, hydroxy, (C\(_1\)-C\(_6\))alkyl, (C\(_1\)-C\(_6\))alkoxy, or carboxy;
R' is H, (C₁₋₆)alkyl, or -(C₁₋₆)alkylcarboxy; and
W is CH₂, CO, SO₂, CH₂CH₂, CH₂CH=CH₂, or CH₂C=CH₂, wherein each hydrogen may be optionally replaced by halo or (C₁₋₆)alkyl;
X is CH₂, NH, N(C₁₋₆)alkyl, N[C(O)(C₁₋₆)alkyl], N[S(O)₂(C₁₋₆)alkyl] or O.

A specific group of compounds of the invention are compounds of formula I which are compounds of formula II:

or a pharmaceutically acceptable salt thereof, wherein
R₁a, R₁b, R₁c, and R₁d are each independently H, fluoro, chloro, cyano, (C₁₋₆)alkyl,
halo(C₁₋₆)alkyl, halo(C₁₋₆)alkoxy, (C₁₋₆)alkoxy;
" --- " is a bond or is absent;
Z is CH or N when " --- " is a bond, or Z is O or NH when " --- " is absent;
U₁ is C(Ra-Rb)-C(Rc-Rd) or C(Ra-Rb)-C(Rc-Rd)-C(Re-Rf), wherein Ra, Rb, Rc, Rd, Re and Rf are each independently hydrogen or (C₁₋₆)alkyl;
M is a group of formula M1a or M2-M5:

in the trans configuration relative to " --- " wherein R2 is H or carboxy;
Ry and Ry' are each independently H, halo, (C₁₋₆)alkyl, or together with the carbon to which they are attached form C=O; or Ry and Ry' together form a bridge;
X is CH₂, or provided n is 2 or 3, X is NH, N(C₁₋₆)alkyl, or O;
Y is CH₂, NH, N(C₁₋₆)alkyl, or O.
"-----" is a bond or is absent;

n is 1, 2, or 3;

when M is a group of formula M1a or M4, U₂ is NR—W, wherein R′ is H,

\[(\text{C}_1\text{C}_6\text{alkyl})_2, (\text{C}_1\text{C}_6\text{alkyl})_3, \text{or} \quad (\text{C}_1\text{C}_6\text{alkyl})_4, \quad \text{and} \quad W \equiv \text{CH}_2, \text{CO}, \text{SO}_2, \text{CH}_2\text{HC-CH}_2\text,\]

5 CH₂CH₂, CH₂CH=CH, or CH₂C=CH, wherein each hydrogen may be optionally replaced by
halo or (C₁-C₆)alkyl, provided that when M is a group of formula M₂, M₃, or M₅, U₂ is W,
and

when W is CH₂, CO or SO₂, R is aryl, heteroaryl, heterocyclyl or ortho-fused bicyclic
heteroaryl, or when W is

\[\text{CH}_2\text{HC-CH} \quad \text{CH}_2\text{CH}_2, \quad \text{CH}_2\text{CH}=\text{CH}, \quad \text{or} \quad \text{CH}_2\text{C}=\text{C}, \quad \text{R is aryl,}\]

10 heteroaryl, heteroaryl(C₁-C₆)alkyloxy, heteroaryl(C₁-C₆)alkythio,
heteroaryl(C₁-C₆)alkylsulfanyl, heteroaryl(C₁-C₆)alkylsulfonyl, heteroaryl(C₁-C₆)alkylamino
wherein any R may be optionally substituted on carbon; and wherein any ring nitrogen in R
may be optionally substituted by (C₁-C₆)alkyl.

A specific group of compounds of the invention are compounds of formula I which are
15 compounds of formula III:

![Diagram of compound III](attachment:image.png)

or a pharmaceutically acceptable salt thereof, wherein

R₂a, R₂b, R₂c, and R₂d are each independently H, fluoro, chloro, cyano, (C₁-C₆)alkyl,
halo(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy, (C₁-C₆)alkoxy;

20 Z is CH or N when "-----" is a bond, or, when "-----" is absent, Z is O or NH;
Y′ is N or CR₂, wherein R₂ is H or carboxy;
Ry is H, fluoro, hydroxy, methoxy, carboxethoxy, or carboxy;
U₂ is NR₁—W, wherein R₁ is H, (C₁–C₆)alkyl, or
O(C₁–C₆)alkyl, or, and W is CH₂, CO₂, SO₂, CH₂CH₂, CH₂CH=CH, or CH₂C≡C, wherein each hydrogen may be optionally replaced by halo or (C₁–C₆)alkyl; and

R is 2,1,3-benzothiadiazol-5-yl;

5 3-oxo-3,4-dihydro-2H-1,4-benzothiazin-6-yl;
2,3-dihydro-benze[1,4]dioxin-6-yl;
1,2,3-benzothiadiazol-5-yl;
3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl;
7-fluoro-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-yl;
10 2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl;
2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl;
3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl;
[1,2,3]thiadiazolo[5,4-b]pyridin-6-yl;
3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl;
15 7-chloro-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl;
7-fluoro-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl;
2-thienylthio; or
2,5-difluoro-phenyl.

A specific group of compounds of the invention are compounds of formula I which are compounds of formula IV:

IV

or a pharmaceutically acceptable salt thereof, wherein
R is H, halo, cyano, nitro, (C₁-C₆)alkanoyl, carboxy, (C₁-C₆)alkyloxycarbonyl, (C₁-C₆)alkyl, hydroxy, halo(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy, (C₁-C₆)alkoxy, NHCO-(C₁-C₆)alkyl, SO₂(C₁-C₆)alkyl, SO₂NH(C₁-C₆)alkyl, or SO₂N((C₁-C₆)alkyl)₂;
Z is CH or N when "-----" is a bond, or, when "-----" is absent, Z is O or NH;
Ry is H, fluoro, hydroxy, methoxy, carboxymethoxy, or carboxy;
R' is H or (C₁-C₆)alkyl;
W is CO, SO₂, or CH₂, wherein each hydrogen may be optionally replaced by halo or (C₁-C₆)alkyl; and

A specific group of compounds of the invention are compounds of formula V:

or a pharmaceutically acceptable salt thereof, wherein
R₁, R₁ is H, halo, cyano, nitro, (C₁-C₆)alkanoyl, carboxy, (C₁-C₆)alkyloxycarbonyl, (C₁-C₆)alkyl, hydroxy, halo(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy, (C₁-C₆)alkoxy, NHCO-(C₁-C₆)alkyl, SO₂(C₁-C₆)alkyl, SO₂NH(C₁-C₆)alkyl, or SO₂N((C₁-C₆)alkyl)₂;
Z is CH or N when "-----" is a bond, or, when "-----" is absent, Z is O or NH;
Ry is H, fluoro, hydroxy, methoxy, carboxymethoxy, or carboxy;
R' is H or (C₁-C₆)alkyl; and

A specific group of compounds of the invention are compounds wherein L is a group of formula L₁.

A specific group of compounds of the invention are compounds wherein L is a group of formula L₂.
A specific group of compounds of the invention are compounds wherein L is a group of formula L1.

A specific group of compounds of the invention are compounds wherein L is a group of formula L2.

A specific group of compounds of the invention are compounds wherein L is a group of formula L3.

A specific group of compounds of the invention are compounds wherein L is a group of formula L4.

A specific group of compounds of the invention are compounds wherein L is a group of formula L5.

A specific group of compounds of the invention are compounds wherein L is a group of formula L6.

A specific group of compounds of the invention are compounds wherein L is a group of formula L7.

A specific group of compounds of the invention are compounds wherein L is a group of formula L8.

A specific group of compounds of the invention are compounds wherein L is a group of formula L9.

A specific group of compounds of the invention are compounds wherein L is a group of formula L10.

A specific group of compounds of the invention are compounds wherein L is a group of formula L11.

A specific group of compounds of the invention are compounds wherein L is a group of formula L12.

A specific group of compounds of the invention are compounds wherein L is a group of formula L13.

A specific group of compounds of the invention are compounds wherein L is a group of formula L14.

A specific group of compounds of the invention are compounds wherein L is a group of formula L15.

A specific group of compounds of the invention are compounds wherein M is a group of formula M1.

A specific group of compounds of the invention are compounds wherein M is a group of formula M1a.

A specific group of compounds of the invention are compounds wherein M is a group of formula M2.
A specific group of compounds of the invention are compounds wherein \( M \) is a group of formula M3.

A specific group of compounds of the invention are compounds wherein \( M \) is a group of formula M4.

A specific group of compounds of the invention are compounds wherein \( M \) is a group of formula M5.

A specific group of compounds of the invention are compounds wherein when \( M \) is a group of formula M1 or M2, \( W \) is \( \text{CH}_2 \), \( \text{CO} \) or \( \text{SO}_3 \).

**Preparation of Invention Compounds**

In a further aspect, the present invention provides a process for preparing a compound of the invention or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof. It will be appreciated that during certain of the following processes, certain substituents may require protection to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place and later removed.

Examples of protecting groups are disclosed in, for example, ‘Protective Groups in Organic Synthesis’ by Theodore Green (John Wiley & Sons, 1999). Protecting groups may be removed by any convenient method described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxyacarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or \( t \)-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzoxycarbonyl, or an aronyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group.

Thus, for example, an acyl group such as an alkanoyl or alkoxyacarbonyl group or an aronyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a \( t \)-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid.
as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an aryloxalkoxycarbonyl group such as a benzoxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group that may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aryl group, for example benzoyl, or an arylmethy1 group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aryl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a $t$-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon. Resins may also be used as a protecting group.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

A compound of the invention, or a pharmaceutically-acceptable salt or an in vivo hydrolysable ester thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a compound of the invention, or a pharmaceutically-acceptable salt or an in vivo hydrolysable ester thereof, are provided as a further feature of the invention and are illustrated by the following representative examples. Necessary starting materials may be obtained by standard procedures of organic chemistry (see, for example, Advanced Organic Chemistry (Wiley-Interscience, 2001), Jerry March or Houben-Weyl, Methoden der Organischen Chemie). The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively, necessary starting materials are obtainable by analogous procedures to those illustrated that are within the ordinary skill of an organic
chemist. Information on the preparation of necessary starting materials or related compounds (which may be adapted to form necessary starting materials) may also be found in the certain Patent Application Publications, the contents of the relevant process sections of which are incorporated herein by reference; for example WO2004/058144; US2004/0224946;  

WO2004/002992.

The skilled organic chemist will be able to use and adapt the information contained and referenced within the above references, and accompanying Examples therein and also the Examples herein, to obtain necessary starting materials, and products.

Thus, the present invention also provides that the compounds of the invention and pharmaceutically-acceptable salts and in vivo hydrolysable esters thereof, can be prepared by a process (a) to (h); and thereafter if necessary:

i) removing any protecting groups;

ii) forming a pro-drug (for example an in-vivo hydrolysable ester); and/or

iii) forming a pharmaceutically-acceptable salt;

wherein said processes (a) to (h) are as follows (wherein the variables are as defined above unless otherwise stated):

Thus, the present invention also provides that the compounds of the invention and pharmaceutically-acceptable salts and in vivo hydrolysable esters thereof, can be prepared by a process (a) to (h); and thereafter if necessary:

i) removing any protecting groups;

ii) forming a pro-drug (for example an in-vivo hydrolysable ester); and/or

iii) forming a pharmaceutically-acceptable salt;

wherein said processes (a) to (g) are as follows (wherein the variables are as defined above unless otherwise stated):

a) By modifying a substituent in, or introducing a substituent into another compound of the invention by using standard chemistry (see for example, Comprehensive Organic Functional Group Transformations (Pergamon), Katritzky, Meth-Cohn & Rees). For example:

• a hydroxy group may be converted into a fluoro group, an acyloxy group (for instance an acetoxy group), an amino group, a heterocyclic group linked through nitrogen (optionally substituted on a carbon other than a carbon atom adjacent to the linking nitrogen ring atom—for instance an optionally substituted amino group). The skilled artisan understands that such reactions of the hydroxy group take place directly
(for instance by acylation or Mitsunobu reaction) or through the intermediacy of one or more derivatives (for instance a mesylate or an azide);

- an acyloxy group may be converted into a hydroxy group or into the groups that may be obtained from a hydroxy group (either directly or through the intermediacy of a hydroxy group); an alkyl halide group may be converted to a hydroxy group, an amino group, a thioalkyl group or a heterocyclic group linked through nitrogen; a keto group may be reduced to a hydroxy group or an saturated alkyl group.

b) as depicted in Scheme 1, by alkylation of a suitable bicyclic ring system containing a NH group in the ring with a suitable alkylating reagent containing a leaving group (such as an O-mesylate, chloro, bromo or iodo) in the presence of a base. Alkylation may be followed by functional group manipulations and/or further alkylations or reductive aminations.

Scheme 1

As depicted in Scheme 2, by reaction of a suitable bicyclic ring system containing a NH group in the ring with a suitable aldehyde under Mitsunobu conditions, followed by deprotection and reductive amination with an aldehyde. This sequence may be followed by functional group manipulations and/or further alkylations or reductive aminations.
d) As depicted in Scheme 3, by alkylation of a suitable bicyclic ring system containing a NH group in the ring with bromo- or chloroacetic acid or with a derivative thereof, followed by activation of the acid and amide coupling. The amide coupling reaction may be followed by functional group manipulations and/or further alkylation or reductive aminations and optional reduction of the amide moiety.

Scheme 3

1) BrCH₂COOH
2) Peptide coupling with amine
1. HCl
2. 3A Mol Sieves.
3. NaBH₄(OAc)₃

10

e) As depicted in Scheme 4, by alkylation of a suitable bicyclic ring system containing a NH group in the ring with allylbromide, followed by oxidative cleavage of the double bond with a suitable oxidizing agent, such as ozone or periodate and subsequent
manipulation of the resulting alcohol, e.g., by conversion to a mesylate, followed by alkylation. The alkylation reaction may be followed by functional group manipulations and/or further alkylations or reductive aminations.

**Scheme 4**

![Scheme 4 Diagram]

1) Allyl bromide/ NaH  
2) NaO4  

1) Mesyl chloride/ NEt3  
2) 

1. HCl  
2. 3A Mol Sieves, O  
3. Na(BOAc)3H

1) As depicted in Scheme 5, by alkylation of a suitable bicyclic ring system containing a NH group in the ring with allyl bromide, followed hydroboration and subsequent manipulation of the resulting alcohol, e.g. by conversion to a mesylate, followed by alkylation. The alkylation reaction may be followed by functional group manipulations and/or further alkylations or reductive aminations.
Scheme 5

1. Allylbromide/NaH
2. borane, H₂O₂

1. Mesyl chloride/NEt₃
2. H₂S

1. HCl
2. 3A Mol Sieves, O
3. NaBH₄(OAc)₃

Alternatively, as depicted in Scheme 6, the alcohol intermediate in Scheme 5 may be oxidized to the aldehyde, followed by reductive amination to arrive at the same intermediate.

Scheme 6

1. HCl
2. 3A Mol Sieves, O
3. NaBH₄(OAc)₃

h) Using essentially the procedure described under c), by reaction of a suitable bicyclic ring system containing a NH group in the ring with an alcohol.
(II) under Mitsunobu conditions; or by alkylation of a suitable bicyclic ring system containing a NH group with a derivative of (II), where the alcohol moiety is converted to a leaving group, such as O-mesylate, followed by deprotection and reductive amination with an aldehyde. This sequence may be followed by functional group manipulations and/or further alkylations or reductive aminations, also using essentially the procedure described under c).

For example, as depicted in Scheme 7, an O-mesylate alkylating reagent may be prepared from the alcohol, by reaction with mesyl chloride, in the presence of a base, such as a trialkyl amine or an immobilized version thereof on a resin. It is understood, that such an alkylating reagent is potentially unstable and needs to be prepared fresh under careful, controlled conditions.

![Scheme 7](image)

With respect to (a)-(g) and Schemes 1-5 above, the removal of any protecting groups, formation of pharmaceutically-acceptable salts and/or formation of in-vivo hydrolyzable esters or amides are within the skill of an ordinary organic chemist using standard techniques. Furthermore, details regarding these transformations, for example, the preparation of in-vivo hydrolysable ester prodrugs has been described in the section above on such esters.

When an optically active form of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using an optically active starting material (formed, for example, by asymmetric induction of a suitable reaction step), or by resolution of a racemic form of the compound or intermediate using a standard procedure, or by chromatographic separation of diastereoisomers (when produced). Enzymatic techniques may also be useful for the preparation of optically active compounds and/or intermediates.
Similarly, when a pure regioisomer of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using a pure regioisomer as a starting material, or by resolution of a mixture of the regioisomers or intermediates using a standard procedure.

Biological Activity

According to a further feature of the invention there is provided a compound of the invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof for use in a method of treatment of the human or animal body by therapy.

According to a further feature of the present invention there is provided a method for producing an antibacterial effect in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof.

The ability of the invention compounds disclosed herein to achieve an antibacterial effect is demonstrated by the following tests.

Enzyme Potency Testing Methods

Supercoiling assay description:

Compounds were tested for inhibition of Escherichia coli DNA supercoiling activity as follows. Assays were performed in polypropylene multiwell plates in 50 μl reactions containing 35 mM Tris-HCl (pH 7.5), 24 mM KCl, 4 mM MgCl₂, 2 mM dithiothreitol, 1.8 mM spermidine, 5% (v/v) glycerol, 200 mM bovine serum albumin, 1.25% (w/v) DMSO, 3 mM ATP, 10 μg/ml relaxed pBR322 plasmid, 0.6 mM DNA gyrase, and test compound. Reactions were quenched after 1 hour by the addition of 10 μl of 30% (w/v) Ficoll-400, 10 mM EDTA, and 5% sodium dodecyl sulfate. Twenty-five μl of each sample was loaded onto a 0.8% (w/v) agarose gel and electrophoresed. The gel and gel buffer contained 1X TBE buffer (89 mM Tris base, 89 mM boric acid, and 2 mM EDTA at pH 8.3). After electrophoresis for 3 hours at 70V, the gel was stained with ethidium bromide and visualized by excitation with ultraviolet light. The fluorescence intensity of the most supercoiled plasmid band was used to measure gyrase activity. Compound potency was based IC₅₀ measurements determined from reactions performed with eight 2-fold serial dilutions of each compound and a control without compound.

Compounds of the Examples generally have an IC₅₀ of <20μg/ml.
ATPase assay description:

Compounds were tested for inhibition of GyrB ATPase activity using an ammonium molybdate/malachite green-based phosphate detection assay (Lanzetta, P. A., L. J. Alvarez, P. S. Reinsach, and O. A. Candia, 1979, 100: 95-97). Assays were performed in multiwell plates in 100 µl reactions containing: 50 mM TRIS buffer pH 7.5, 75 mM ammonium acetate, 5.5 mM magnesium chloride, 0.5 mM ethylenediaminetetraacetic acid, 5% glycerol, 1 mM 1,4-dithio-DL-threitol, 200 mM bovine serum albumin, 16 µg/ml sheared salmon sperm DNA, 4 nM E. coli GyrA, 4 nM E. coli GyrB, 250 µM ATP, and compound in dimethylsulfoxide. Reactions were quenched with 150 µL of ammonium molybdate/malachite green detection reagent containing 1.2 mM malachite green hydrochloride, 8.5 mM ammonium molybdate tetrahydrate, and 1 M hydrochloric acid. Plates were read in an absorbance plate reader at 625 nm and percent inhibition values were calculated using dimethylsulfoxide (2%) containing reactions as 0% inhibition and novobiocin-containing (2 µM) reactions as 100% inhibition controls. Compound potency was based on IC₅₀ measurements determined from reactions performed in the presence of 10 different compound concentrations.

Compounds of the invention generally have an IC₅₀ of <20 µg/ml.

Bacterial Susceptibility Testing Methods

Compounds were tested for antimicrobial activity by susceptibility testing in liquid media in a 96 well format. Compounds were dissolved in dimethylsulfoxide and tested in 10 doubling dilutions in the susceptibility assays. The organisms used in the assay were grown overnight on suitable agar media and then suspended in a liquid medium appropriate for the growth of the organism. The suspension was a 0.5 McFarland and a further 1 in 10 dilution was made into the same liquid medium to prepare the final organism suspension in 100 µL. Plates were incubated under appropriate conditions at 37 °C for 24 hours prior to reading. The Minimum Inhibitory Concentration (MIC) was determined as the lowest drug concentration able to reduce growth by 80% or more.

Compounds were evaluated against a panel of Gram-positive species, including Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes, and Enterococcus faecium. In addition, compounds were evaluated against a panel of Gram-negative species including Haemophilus influenzae, Escherichia coli and Moraxella catarrhalis. Compounds of the present invention have MIC's less than or equal to 8 µg/ml versus one or more of the organisms named above.

Data for several compounds of the invention are depicted below:
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**Pharmaceutical Formulations**

In another embodiment the present invention provides a pharmaceutical composition which comprises a compound of formula (I) admixed with a pharmaceutically-acceptable carrier, diluent, or excipient.

The invention compositions may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration as eye-drops, for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, sub-lingual, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

In addition to the compounds of the present invention, the pharmaceutical composition of this invention may also contain (i.e. through co-formulation) or be co-administered (simultaneously, sequentially or separately) with one or more known drugs selected from other clinically useful antibacterial agents (for example, β-lactams, macrolides, quinolones or aminoglycosides) and/or other anti-infective agents (for example, an antifungal triazole or amphotericin). These may include carbapenems, for example meropenem or imipenem, to broaden the therapeutic effectiveness. Compounds of this invention may also be co-formulated or co-administered with bactericidal/permeability-increasing protein (BPI) products or efflux pump inhibitors to improve activity against gram negative bacteria and bacteria resistant to antimicrobial agents.

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical diluents, carriers, or excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more coloring, sweetening, flavoring and/or preservative agents. A pharmaceutical composition to be dosed
intravenously may contain advantageously (for example to enhance stability) a suitable bactericide, antioxidant or reducing agent, or a suitable sequestering agent.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or alginic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional costing agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), coloring agents, flavoring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such
as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil in water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean lecithin, am esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavoring and/or coloring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butane-diol. Solubility enhancing agents, for example cyclodextrins may be used.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.
For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form. For example, a formulation intended for oral administration to humans will generally contain, for example, a therapeutically effective amount of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 1 to about 98 percent by weight of the total composition. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection. Each patient may receive, for example, a daily intravenous, subcutaneous or intramuscular dose of a compound of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively, the intravenous dose may be given by continuous infusion over a period of time. Alternatively, each patient may receive a daily oral dose which may be approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

Examples

The invention will now be illustrated by the following non-limiting examples.

Example 1

1-(2-(4-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino[1]piperidin-1-yl)ethyl)-7-methoxyquinolin-2(1H)-one

A solution of 1-(2-(4-aminopiperidin-1-yl)ethyl)-7-methoxyquinolin-2(1H)-one

(Intermediate 1, crude, 60 mg, 0.20 mmol) and 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde (WO 2004/053144) (33 mg, 0.20 mmol) in dry chloroform/methanol (5 mL, 1:1) was heated over 3 Å molecular sieves at 70°C for 3 hours. The reaction mixture was cooled to 0°C, and sodium trimetoxycarborohydride (127 mg, 0.6 mmol) was added. The
resulting reaction mixture was stirred at room temperature for 30 minutes and then was filtered through a 0.45 μm membrane and concentrated to dryness under reduced pressure. The residue was taken up in dichloromethane (50 mL) and saturated aqueous sodium hydrogen carbonate solution (5 mL). The pH of the aqueous phase was adjusted to a pH of 10 with 1M aqueous sodium hydroxide solution. The aqueous phase was back extracted twice with dichloromethane (2 x 20 mL) and the combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. Chromatography on silica gel with dichloromethane/ methanol (8:1 to 4:1) gave the free base of the title compound as a colorless oil. The free base was taken up in dichloromethane (2 mL), ethanol (7 mL) was added, followed by addition of 1M HCl in ether (0.3 mL). The colorless precipitate was collected by filtration and gave 50 mg (48%) of the bis-hydrochloride salt of the product, mp 243°C.


1H-NMR (DMSO-d6) δ (ppm): 2.00-3.80 (m, 11H); 3.96 (s, 3H); 4.20-4.45 (m, 6H); 4.68 (m, 2H); 6.45 (d, 1H); 6.93 (d, 1H); 7.18 (s, 1H); 7.30 (s, 1H); 7.68 (d, 1H); 7.88 (d, 1H); 8.25 (s, 1H); 9.74 (brs, 2H); 11.18 (brs, 1H).

**Intermediate 1**: 1-[(2-4-Aminopiperidin-1-yl)ethyl]-7-methoxyquinolin-2(1H)-one

A solution of tert-butyl (1-[(2-7-methoxy-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl) carbamate (Intermediate 1, 150 mg, 0.37 mmol) in dioxane (4 mL) was treated at room temperature under vigorous stirring with a solution of HCl in dioxane (4M, 2 mL). After 18 hours, the reaction mixture was concentrated under reduced pressure. The residue was taken up in dichloromethane (60 mL) and saturated aqueous sodium hydrogen carbonate solution (10 mL). The aqueous phase was extracted three times with dichloromethane (3 x 50 mL) and the combined organic phases were dried over sodium sulfate and concentrated under reduced pressure to give 113 mg (100% yield) of the crude product as an oil.

MS (ES): 302.24 (MH+*) for C17H23N2O2

1H-NMR (DMSO-d6) δ: 1.21 (m, 2H); 1.65 (m, 2H); 2.04 (t, 2H); 2.40-2.52 (m, 2H); 2.89 (m, 2H); 3.69 (m, 1H); 3.88 (s, 3H); 4.31 (t, 2H); 6.40 (m, 1H); 6.88 (m, 1H); 6.94 (m, 1H); 7.63 (m, 1H); 7.80 (m, 1H). (The NH2 protons were not observed)
**Intermediate 2: tert-Butyl (1-[2-(7-methoxy-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl)ethanesulfonate**

A solution of 7-methoxyquinolin-2(1H)-one (Intermediate 3, 340 mg, 2.2 mmol) in dry dimethylformamide (DMF) (10 mL) was treated at 0°C with a cooling bath under stirring with sodium hydride (88 mg, 60% in oil, 2.2 mmol). The cooling bath was removed and the mixture was stirred for 30 minutes at room temperature. A solution of 2-{4-[(tert-butoxycarbonyl)amino]piperidin-1-yl} ethyl methanesulfonate in N,N-dimethylformamide (DMF) (Intermediate 6, 0.58 mmol/mL, 3.5 mL, 2.03 mmol) was then added and the resulting mixture was stirred overnight at room temperature. Thin Layer Chromatography (TLC): Rf = 0.1 (hexanes/acetone, 1:1) (the O-alkylated product was observed as a minor product and has a RF value of 0.3). The DMF was removed under reduced pressure, and the residue was taken up in ethyl acetate (100 mL) and saturated aqueous sodium hydrogen carbonate solution (30 mL). The aqueous phase was back extracted once with ethyl acetate (50 mL). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. Chromatography on silica gel with hexanes/acetone (1:1) gave 153 mg (20% yield) of the product as a colorless hard foam.

**MS (ES):** 402.25 (MH⁺) for C₂₉H₃₁N₅O₄

**¹H-NMR (DMSO-d₆) δ: 1.30-1.42 (m, 2H); 1.36 (s, 9H); 1.66 (m, 2H); 2.04 (m, 2H); 2.45-2.53 (m, 2H); 2.92 (m, 2H); 3.15 (m, 1H); 3.38 (s, 3H); 4.31 (s, 2H); 6.39 (m, 1H); 6.76 (m, 1H); 6.88 (m, 1H); 6.93 (m, 1H); 7.62 (d, 1H); 7.80 (d, 1H). (The structure was confirmed by an HMBC-NMR experiment)

**Intermediate 3: 7-Methoxyquinolin-2(1H)-one**

A solution of methyl (2E)-3-(2-amino-4-methoxyphenyl)acrylate (Intermediate 4, 500 mg, 2.4 mmol) in acetonitrile (600 mL) was deoxygenated under vacuum, purged with nitrogen and irradiated at 365 nm with a long wave UV lamp (B-100AP, Blak Ray) for 28 hours. The solvent was removed under reduced pressure and the product was precipitated from dichloromethane (20 mL) by the addition of hexanes (100 mL) to give 357 mg (76% yield) of the crude product as a colorless solid, 90% pure by ¹H-NMR (together with 10% dimer), mp 190°C.

**MS (ES):** 176.21 (MH⁺) for C₁₆H₁₄NO₂

**¹H-NMR (DMSO-d₆) δ: 3.79 (s, 3H); 6.28 (d, 1H); 6.75-6.81 (m, 2H); 7.55 (d, 1H); 7.79 (d, 1H); 11.59 (s, 1H).
Intermediate 4: Methyl (2E)-3-(2-amino-4-methoxyphenyl)acrylate

To a solution of methyl (2E)-3-(4-methoxy-2-nitrophenyl)acrylate (Intermediate 5, 4.9 g, 20.66 mmol) in acetic acid (150 mL) at room temperature under nitrogen was added zinc powder (7.7 g, 118 mmol) in portions. After 4 hours, another 5 g of zinc was added and the resulting reaction mixture was heated at 50°C for two hours. The reaction mixture was then cooled to room temperature, filtered, and the filtrate was concentrated to dryness under reduced pressure. The residue was chromatographed on silica gel with hexanes/ethyl acetate (3:1) to give 1.0 g (23% yield) of product as a yellow solid, mp 149°C.

**MS (ES):** 208.17 (MH⁺) for C₁₇H₁₅NO₃

**¹H-NMR (DMSO-d₆):** δ: 3.67 (s, 3H); 3.68 (s, 3H); 5.68 (bs, 2H); 6.14 (dd, 1H); 6.21 (d, 1H); 6.23 (s, 1H); 7.40 (d, 1H); 7.82 (d, 1H).

Intermediate 5: (2S)-4-Methoxy-2-nitrophenyl Acrylate

A solution of 4-iodo-3-nitroanisole (10 g, 36 mmol), methyl acrylate (3.87 mL, 43 mmol), tris(4-methoxyphenyl)phosphine (1.1 g, 3.6 mmol) and triethylamine (6.05 mL, 43 mmol) was degassed and flushed with nitrogen. Palladium(II) acetate (1.2 g, 1.8 mmol) was added and the mixture was heated at 70°C overnight. It was filtered through a 0.45 μm membrane and the solvent was removed under reduced pressure. The residue was taken up in ethyl acetate (300 mL), it was washed with potassium phosphate buffer (1M, pH 7, 2x 300 mL) and dried over sodium sulfate. Chromatography on silica gel with dichloromethane, followed by precipitation from dichloromethane (50 mL) with hexanes (500 mL) gave 4.96 g (58% yield) of product as a yellow solid.

**MS (ES):** 260.20 (MNa⁺) for C₁₇H₁₅NO₃

**¹H-NMR (DMSO-d₆):** δ: 3.73 (s, 3H); 3.88 (s, 3H); 6.59 (d, 1H); 7.33 (dd, 1H); 7.57 (d, 1H); 7.78 (d, 1H); 7.94 (d, 1H).

Intermediate 6: 2-{[(tert-Butyloxycarbonylamino)piperidin-1-yl]ethyl}methanesulfonate

A mixture of tert-butyl [1-(2-hydroxyethyl)piperidin-4-yl]carbamate (Intermediate 7, 1.7 g, 7 mmol) in dry dichloromethane (20 mL) and triethylamine (1.4 mL, 9.8 mmol) was treated at 0°C with methanesulfonyl chloride (0.65 mL, 8.4 mmol). After 45 minutes the reaction was complete by TLC (chloroform/methanol 6:1, Rf 0.54). Potassium phosphate buffer (pH 7, 1M, 50 mL) was added, dichloromethane was removed under reduced pressure
and it was extracted with ice-cold ethyl acetate (2 x 100 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude preparation of the mesylate was used without delay for the next step.

**MS (ES):** 323.18 \((M^+\)) for C\textsubscript{14}H\textsubscript{12}N\textsubscript{2}O\textsubscript{3}S

**Intermediate 7: tert-Butyl [1-(2-hydroxyethyl)piperidin-4-yl]carbamate**

A mixture of tert-butyl piperidin-4-ylcarbamate (5 g, 25 mmol), 2-bromoethanol (1.77 mL, 25 mmol) and triethyamine (3.86 mL, 27.5 mmol) in acetonitrile (20 mL) was heated in a sealed tube at 50°C for 16 hours. The solvent was removed under reduced pressure, and the residue was taken up in ethyl acetate (300 mL) and washed with saturated aqueous sodium hydrogen carbonate solution (100 mL). The aqueous phase was back-extracted once with ethyl acetate (100 mL) and the combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. Chromatography on silica gel with dichloromethane/methanol (4:1) gave 4.04 g (66% yield) of product as a colorless solid, mp 66°C.

**MS (ES):** 245.28 \((M^+\)) for C\textsubscript{12}H\textsubscript{14}N\textsubscript{2}O\textsubscript{2}

**\(^1\)H-NMR (DMSO-\textsubscript{d6})**: 1.33 (m, 2H); 1.36 (s, 9H); 1.62 (m, 2H); 1.92 (t, 2H); 2.32 (t, 2H); 2.77 (m, 2H); 3.17 (m, 1H); 3.43 (m, 2H); 4.34 (t, 1H); 6.73 (d, 1H).

**Example 2**

1-(2-(4-[2,3-Dihydro[1,4]dioxino[2,3-\(c\)]pyrimidin-7-ylmethyl]amino)piperidin-1-\(y\)l)ethyl)-7-methoxyquinolino-4(1H)-one

A solution of 1-[2-(4-aminoquinoline-1-\(y\)l)ethyl]-7-methoxyquinolino-4(1H)-one (Intermediate 8, 60 mg, 0.20 mmol) and 2,3-dihydro[1,4]dioxino[2,3-\(c\)]pyridine-7-carbaldehyde (WO 2004/058144) (33 mg, 0.20 mmol) in dry chloroform/methanol (5 mL, 1:1) was heated over 3 Å molecular sieves at 70°C for 3 hours. The reaction mixture was cooled to 0°C, and sodium triacetoxyborohydride (1.27 mg, 0.6 mmol) was added and the resulting mixture was stirred at room temperature for 30 minutes. The mixture was then filtered through a 0.45 \(\mu\)m membrane, acidified with conc. HCl to pH 1 and concentrated to dryness under reduced pressure. The residue was taken up in dichloromethane (50 mL) and saturated aqueous sodium hydrogen carbonate solution (5 mL). The pH of the aqueous phase was adjusted to pH 10 with 1M aqueous sodium hydroxide solution. The aqueous phase was back extracted twice with dichloromethane (2 x 20 mL) and the combined organic phases were dried over sodium sulfate. Chromatography on silica gel with dichloromethane/methanol
(4:1), containing 0.125% ammonium hydroxide, gave the free base of the title compound as a colorless oil. The free base was taken up in dichloromethane (2 mL), ethanol (7 mL) was added, followed by addition of 1M HCl in ether (0.45 mL). The colorless precipitate was collected by filtration and gave 84 mg (81% yield) of the bis-hydrochloride salt of the product, mp 260°C.

**MS (ES):** 451.21 (MH+) for C_{22}H_{30}N_{4}O_{4}

**{H-NMR (DMSO-d_6) δ:** 2.00-3.80 (m, 11H); 4.07 (s, 3H); 4.30-4.46 (m, 6H); 5.06 (m, 2H); 6.83 (d, 1H); 7.28 (d, 1H); 7.45-7.58 (m, 2H); 8.22 (d, 1H); 8.37 (s, 1H); 8.61 (d, 1H); 9.94 (brs, 2H); 11.90 (brs, 1H).

**Intermediate 8: 1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-methoxyquinolin-4(1H)-one**

A mixture of tert-butyl [1-{2-(7-methoxy-4-oxoquinolin-1(4H)-yl)ethyl]piperidin-4-yl} carbonate (Intermediate 9, 370 mg, 0.92 mmol) in dioxane (10 mL) was treated at room temperature under vigorous stirring with a solution of HCl in dioxane (4M, 4 mL). After 18 hours, the reaction mixture was diluted with isopropanol (10 mL) and with water (4 mL) and more HCl in dioxane (4M, 5 mL) was added. After 1 hour, the reaction mixture was concentrated under reduced pressure to give the hydrochloride of the product as a colorless solid. The hydrochloride salt was taken up in aqueous sodium hydroxide solution (1M, 10 mL) and extracted with dichloromethane (60 mL). The aqueous phase was extracted three times with dichloromethane (3 x 60 mL) and the combined organic phases were dried over sodium sulfate to give 278 mg (100% yield) of the crude product as an oil.

**MS (ES):** 302.24 (MH+) for C_{17}H_{23}N_{4}O_{2}

**{H-NMR (DMSO-d_6) δ:** (data for the hydrochloride salt) δ: 1.80-2.30 (m, 4H); 3.14 (m, 2H); 3.36 (m, 1H); 3.48 (m, 2H); 3.68 (m, 2H); 4.06 (s, 3H); 5.03 (m, 2H); 6.74 (d, 1H); 7.24 (d, 1H); 7.45 (s, 1H); 8.21 (d, 1H); 8.46 (brs, 2H); 8.55 (d, 1H); 8.60 (brs, 1H); 11.95 (brs, 1H).

**Intermediate 9: tert-Butyl [1-{2-(7-methoxy-4-oxoquinolin-1(4H)-yl)ethyl]piperidin-4-yl} carbonate**

A solution of 7-methoxyquinolin-4-ol (Intermediate 10, 500 mg, 2.85 mmol) in dry DMF (10 mL) was treated at 0°C with a cooling bath under stirring with sodium hydride (114 mg, 60% in oil, 2.85 mmol). The cooling bath was removed and the mixture was stirred for 30 minutes at room temperature. A solution of 2-{4-[(tert-butoxycarbonyl)amino]piperidin-1-...
yl)ethyl methanesulfonate in DMF (Intermediate 6, 0.58 mmol/mL, 5 mL, 2.9 mmol) was added and the resulting solution was stirred overnight at room temperature. DMF was removed under reduced pressure, the residue was taken up in ethyl acetate (100 mL) and saturated aqueous sodium hydrogen carbonate solution (30 mL) and the aqueous phase was back extracted three times with ethyl acetate (3 x 70 mL). The combined organic phases were dried over sodium sulfate. Some starting 7-methoxyquinolin-4-ol precipitated from dichloromethane (30 mL) with hexanes (20 mL) and removed by filtration. The filtrate was concentrated to dryness under reduced pressure. Chromatography of the residue on silica gel with acetonitrile/water (15:1 to 10:1) gave 373 mg (33% yield) of the product as a colorless solid, mp 207°C.

MS (ES): 402.36(MH+) for C_{28}H_{21}N_{2}O_{4}

^1H-NMR (DMSO-d_6): 6: 1.25-1.37 (m, 2H); 1.35 (s, 9H); 1.63 (m, 2H); 2.02 (m, 2H); 2.60 (t, 2H); 2.82 (m, 2H); 3.16 (m, 1H); 3.89 (s, 3H); 4.28 (t, 2H); 5.92 (d, 1H); 6.75 (d, 1H); 6.96 (dd, 1H); 7.00 (d, 1H); 7.82 (d, 1H); 8.06 (d, 1H).

Intermediate 10: 7-Methoxyquinolin-4-ol

5-[[3-Methoxyphenyl]amino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (Intermediate 11, 43.5 g, 157 mmol) was added in small portions to phenylether (200 mL) at 225-260°C under stirring. The reaction mixture was stirred for an additional 5 minutes, until the evolution of gas had stopped. The reaction mixture was cooled to room temperature and the precipitate was collected by filtration and washed with hexanes. Purification by recrystallization from methanol gave 12.4 g (45% yield) of product as a green solid, mp 210°C.

MS (ES): 176.21 (MH+) for C_{16}H_{11}NO_{2}

^1H-NMR (DMSO-d_6): 6: 3.83 (s, 3H); 5.93 (d, 1H); 6.85-6.95 (m, 2H); 7.80 (m, 1H); 7.97 (d, 1H); 11.55 (bs, 1H).

Intermediate 11: 5-[[3-Methoxyphenyl]amino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione

A mixture of m-anisidine (22 g, 178 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (30.75 g, 214 mmol) and triethyl orthoformate (30 mL, 178 mmol) in ethanol (200 mL) was heated at 85°C for two hours. The mixture was allowed to cool to room temperature and the
precipitate was collected by filtration and washed with ethanol to give 43.7 g (89% yield) of product as a pale yellow solid, mp 108°C.

**MS (ES):** 276.12 (M-H) for C_{14}H_{13}NO_{3}

**{H-NMR (DMSO-d$_6$):}** δ: 1.66 (s, 6H); 3.78 (s, 3H); 6.81 (d, 1H); 7.09 (d, 1H); 7.19 (m, 1H); 7.32 (dd, 1H); 8.59 (d, 1H); 11.19 (d, 1H).

**Example 3**

Methyl 1-(2-[4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)amino][piperidin-1-yl]ethyl]-6-methoxy-1H-indole-2-carboxylate

A solution of methyl 1-[2-[(4-amino[1-piperidin-1-yl]ethyl]-6-methoxy-1H-indole-2-carboxylate (Intermediate 12, 200 mg, 0.60 mmol) and 2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-carbaldehyde (W0 2004/058144) (100 mg, 0.60 mmol) in dry chloroform/methanol (10 mL, 1:1) was heated over 3 Å molecular sieves at 70°C for 3 hours. The reaction mixture was cooled to 0°C, sodium triacetoxo borohydride (284 mg, 1.8 mmol) was added and the resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was filtered through a 0.45 µm membrane and concentrated to dryness under reduced pressure. The residue was taken up in dichloromethane (150 mL) and saturated aqueous sodium hydrogen carbonate solution (30 mL), the aqueous phase back extracted once with dichloromethane (70 mL) and the combined organic phases were dried over sodium sulfate. Chromatography on silica gel with dichloromethane/methanol (5:1), containing 0.125% ammonium hydroxide, gave the free base of the title compound, 239 mg (82% yield), as a colorless solid, mp 130°C.

**MS (ES):** 481.15 (M+H) for C_{28}H_{33}N_{4}O_{3}

**{H-NMR (DMSO-d$_6$):}** δ: 1.10-1.25 (m, 2H); 1.70 (m, 2H); 1.96 (t, 2H); 2.12 (m, 1H); 2.30 (m, 2H); 2.79 (m, 2H); 3.62 (s, 3H); 3.80 (s, 3H); 3.82 (s, 3H); 4.22-4.35 (m, 4H); 4.58 (1, 2H); 6.75 (m, 1H); 6.91 (s, 1H); 7.01 (s, 1H); 7.17 (s, 1H); 7.52 (d, 1H); 7.98 (s, 1H).

**Intermediate 12:** Methyl 1-[2-[(4-amino[1-piperidin-1-yl]ethyl]-6-methoxy-1H-indole-2-carboxylate

A solution of methyl 1-[2-[(tert-butoxycarbonyl)amino][piperidin-1-yl]ethyl]-6-methoxy-1H-indole-2-carboxylate (Intermediate 13, 520 mg, 1.2 mmol) in dioxane (4 mL) was treated at room temperature under vigorous stirring with a solution of HCl in dioxane (4M, 2 mL). After 3 days, the reaction mixture was concentrated under reduced pressure. The
residue was taken up in dichloromethane (60 mL) and saturated aqueous sodium hydrogen carbonate solution (10 mL), the aqueous phase was extracted three times with dichloromethane (3x 50 mL) and the combined organic phases were dried over sodium sulfate to give 407 mg (100% yield) of the crude product as colorless solid, mp 101°C.

**MS (ES):** 332.23 (MH⁺) for C₁₅H₂₂N₂O₃

**1H-NMR (DMSO-d₆):** 8: 1.15 (m, 2H); 1.61 (m, 2H); 1.99 (t, 2H); 2.51 (m, 2H); 2.79 (m, 2H); 3.49 (m, 1H); 3.81 (s, 3H); 3.83 (s, 3H); 4.59 (t, 2H); 6.76 (m, 1H); 7.02 (brs, 1H); 7.18 (s, 1H); 7.53 (d, 1H). (The NH₂ protons were not observed)

**Intermediate 13: Methyl 1-[(2-[(1 tert-butoxy carbonyl) amino]piperidin-1-yl) ethyl]-6-methoxy-1H-indole-2-carboxylate**

A solution of methyl 6-methoxy-2-indole-carboxylate (574 mg, 2.8 mmol) in dry DMF (10 mL) was treated at 0°C with a cooling bath under stirring with sodium hydride (123 mg, 60% in oil, 3.08 mmol). The cooling bath was removed and the mixture was stirred for 30 minutes at room temperature. A solution of 2-{[(1 tert-butoxy carbonyl) amino]piperidin-1-yl} ethyl methanesulfonate in DMF (Intermediate 6, 0.58 mmol/mL, 3.4 mL, 2.0 mmol) was added and the resulting mixture was stirred overnight at room temperature. The DMF was removed under reduced pressure, the residue was taken up in ethyl acetate (100 mL) and saturated aqueous sodium hydrogencarbonate solution (30 mL) and the aqueous phase was back extracted once with ethyl acetate (70 mL). The combined organic phases were dried over sodium sulfate. Chromatography on silica gel with hexanes/ethyl acetate (1:1 to pure ethyl acetate) gave 523 mg (43% yield) of the product as a colorless solid, mp 158°C.

**MS (ES):** 432.25 (MH⁺) for C₂₁H₂₃N₂O₅

**1H-NMR (DMSO-d₆):** 8: 1.23-1.37 (m, 2H); 1.35 (s, 9H); 1.63 (m, 2H); 1.99 (t, 2H); 2.51 (m, 2H); 2.81 (m, 2H); 3.15 (m, 1H); 3.81 (s, 3H); 3.83 (s, 3H); 4.58 (t, 2H); 6.72-6.78 (m, 2H); 7.01 (brs, 1H); 7.17 (s, 1H); 7.53 (d, 1H).

**Example 4**

6-{[(1-[2-(7-Methoxy-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl)amino]methyl}2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

1-[2-{4-Aminopiperidin-1-yl}ethyl]-7-methoxyquinolin-2(1H)-one (Intermediate 1, crude, 60 mg, 0.20 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carboxaldehyde (WO 2004/058144) (43 mg, 0.24 mmol) in dry dichloromethane/methanol (10 mL, 1:1) were
heated over 3 Å molecular sieves at reflux for 4 hours. The reaction mixture was cooled to 0°C, and sodium cyanoborohydride (19 mg, 0.30 mmol) was added and it was stirred at room temperature for 2 hours. The mixture was filtered through a fritted funnel and concentrated to dryness under reduced pressure. The residue was taken up in ethyl acetate and washed with saturated sodium bicarbonate followed by saturated sodium chloride. The saturated sodium bicarbonate was extracted with chloroform, and the chloroform was washed with saturated sodium chloride. The ethyl acetate and chloroform extracts were combined, dried over sodium sulfate and concentrated to dryness under reduced pressure. Silica gel chromatography with dichloromethane/methanol/ammonia ammonia (8:2:0.01) gave title compound as a colorless oil, 27 mg (30%).

**MS** (ES): 464.34 (MH⁺) for C₂₅H₂₆N₄O₄

**¹H-NMR (CDCl₃-d) δ: 1.93 (m, 4H); 2.94 (m, 3H); 3.38 (m, 2H); 3.48 (s, 2H); 4.02 (m, 6H); 4.64 (s, 2H); 4.66 (m, 1H); 6.51 (d, J = 9.4 Hz, 1H); 6.83 (dd, J = 6.5, 2.1 Hz, 1H); 7.22 (d, J = 8.1 Hz, 1H); 7.46 (m, 2H); 7.62 (m, 2H).

**Example 5**

1-[(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)ethy]amino)piperidin-1-yl]ethyl)-2-oxo-1,2-dihydroquinoline-7-carbonitrile

1-[(2-[(4-Amino)piperidin-1-yl]ethyl]-2-oxo-1,2-dihydroquinoline-7-carbonitrile (Intermediate 14, 70 mg, 0.24 mmol), 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde (WO 2004/058144) (40 mg, 0.24 mmol) and sodium triacetoxy borohydride (150 mg, 0.75 mmol) were reacted as described for Example 1, but the aqueous workup was omitted. Chromatography on silica gel with dichloromethane/methanol (6:1) and crystallization from dichloromethane/ether/hexanes gave the monooacetate salt of the product as a colorless solid, 69 mg (58%), mp 130-135°C.

**MS** (ES): 446.24 (MH⁺) for C₂₃H₂₈N₄O₃.

**¹H-NMR (DMSO-d₆) δ: 1.19 (m, 2H); 1.73 (m, 2H); 1.89 (s, 3H); 2.00 (t, 2H); 2.34 (m, 1H); 2.51 (m, 2H, under solvent peak); 2.88 (m, 2H); 3.65 (s, 2H); 4.24-4.37 (m, 6H); 6.76 (d, 1H); 6.92 (s, 1H); 7.63 (dd, 1H); 7.90 (d, 1H); 7.97-8.00 (m, 2H); 8.07 (brs, 1H).
Intermediate 14: 1-(2-(4-Aminopiperidin-1-yl)ethyl)-2-oxo-1,2-dihydropyridazinone-7-carbonitrile

A solution of tert-butyl [1-{2-(7-cyano-2-oxoquinolin-1-(2H)-yl)ethyl]piperidin-4-yl}carbamate (Intermediate 15) (6.57 g, 16.57 mmol) in dichloromethane (100 mL) was treated with trifluoroacetic acid (40 mL) at 0°C for 30 minutes. The solvent was removed under reduced pressure and the residue was distilled once with dichloromethane, then taken up in dichloromethane (200 mL) and washed with saturated sodium hydrogen carbonate solution (50 mL, pH adjusted to 10 with sodium hydroxide). The aqueous phase was back-extracted three times with dichloromethane (3x 100 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure to give the product as off-white solid, 5g, mp 138°C.

**MS (ES):** 296.91 (M+1) for C_{17}H_{20}N_{4}O

^{1}H-NMR (DMSO-d_{6}) δ: 1.13 (m, 2H); 1.48 (m, 1H); 1.62 (m, 2H); 2.01 (t, 2H); 2.50 (m, 2H, under solvent peak); 2.86 (m, 2H); 4.35 (t, 2H); 6.76 (d, 1H); 7.63 (d, 1H); 7.90 (d, 1H); 7.98 (d, 1H); 8.07 (s, 1H).

Intermediate 15: tert-Butyl [1-{2-(7-cyano-2-oxoquinolin-1-(2H)-yl)ethyl]piperidin-4-yl}carbamate

A mixture of tert-butyl [1-{2-(7-bromo-2-oxoquinolin-1-(2H)-yl)ethyl]piperidin-4-yl}carbamate (Intermediate 16) (9.85 g, 21.9 mmol) and potassium cyanide (2.14 g, 32.8 mmol) in dry acetonitrile (60 mL) was degassed and flushed with nitrogen three times. Tributyltin chloride (0.039 mmol, 1.13 mL of a 51.6 mM solution in heptane) was added, followed by 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (63 mg, 0.11 mmol) and tris(dibenzylideneacetone)dipalladium (0) (100 mg, 0.11 mmol) and it was degassed and flushed with nitrogen like above. The mixture was stirred for 30 minutes at room temperature and then degassed and flushed with nitrogen again. It was heated at 85°C for 20 hours. The solvent was removed under reduced pressure and the residue was taken up in dichloromethane (500 mL) and washed with water (200 mL). The aqueous phase was back-extracted once with dichloromethane (200 mL) and combined organic phases were dried over sodium sulfate. Solvent was removed under reduced pressure and the residue was crystallized from acetonitrile (60 mL) to give the product as a colorless solid, 6.57g (76%), mp 202°C.

**MS (ES):** 397.21 (M+1) for C_{27}H_{30}N_{4}O_{3}
Intermediate 16: tert-Butyl (1-(2-((7-bromo-2-oxoquinolin-1(2H)-yl)ethylo)ringidin-4-yI)carbamate

7-Bromoquinolin-2(1H)-one (Intermediate 17) (7.4 g, 33 mmol) was deprotonated with sodium hydride (1.45 g, 60% in oil, 36 mmol) and alkylated with 2-[(tert-butoxycarbonylamino)piperidin-1-yl] ethyl methanesulfonate (Intermediate 6) (40 mmol) as described for Intermediate 2; Chromatography on silica gel with hexanes/acetone (5:2) gave 9.87 g (66%) of the product as a colorless solid, mp 155°C.

MS (ES): 450.452 (MH+) for C21H26BrN3O3;

1H-NMR (DMSO-d6): 8: 1.32 (m, 2H); 1.36 (s, 9H); 1.65 (m, 2H); 2.01 (t, 2H); 2.46 (m, 2H); 2.90 (m, 2H); 3.19 (m, 1H); 4.29 (t, 2H); 6.61 (d, 1H); 6.75 (d, 1H); 7.41 (d, 1H); 7.65 (d, 1H); 7.73 (brs, 1H); 7.89 (d, 1H).

Intermediate 17: 7-Bromoquinolin-2(1H)-one

(2E)-N-(3-bromophenyl)-3-phenylacrylamide (Intermediate 18) (16 g, 53 mmol) and aluminium trichloride (31.8 g, 238 mmol) were heated in chlorobenzene (100 mL) at 90°C for one hour. The reaction mixture was cooled to room temperature and poured onto ice. It was stirred until the ice was completely melted, the mixture was filtered and washed with ethyl acetate to give the crude product as light gold solid in a mixture with the minor product 5-bromoquinolin-2(1H)-one (3:2), 8.8 g (70%). This mixture could not be separated. The mixture was heated in phosphorus oxychloride (50 mL) at 65°C for one hour. The reaction mixture was cooled to room temperature and poured onto ice. It was carefully neutralized at 0°C with sodium carbonate, extracted into ethyl acetate (300 mL), washed with brine, dried over sodium sulfate and concentrated to give the crude mixture of 7-bromo-2-chloroquinoline and 5-bromo-2-chloroquinoline. The mixture was taken up in dichloromethane (100 mL), treated with silica gel (20 g), filtered and the filter cake was washed with dichloromethane. Filtrate and wash were combined and concentrated. The residue was crystallized from toluene/hexanes (70 mL, 1:1) to provide pure 7-bromo-2-chloroquinoline, 3.74 g as a colorless solid mp 113°C.

MS (ES): 242/244/246 (MH+) for C18H12BrCIN
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\(^1\text{H-NMR (DMSO-d6)}\): 7.63 (d, J 8.4 Hz, 1H); 7.81 (dd, J 8.4, 1.6 Hz, 1H); 8.03 (d, J 8.4 Hz, 1H); 8.18 (d, J 1.6 Hz, 1H); 8.48 (d, J 8.4 Hz, 1H).

7-Bromo-2-chloroquinoline was heated in 5M HCl (100 mL) and dioxane (10 mL) for 1 hour at reflux. The reaction mixture was cooled, filtered, and washed with water to give the title compound, 28.9 g, as a colorless solid, mp 295°C.

\textbf{MS (ES):} 224.13/226.13 (MH\(^+\)) for C\(_{14}\)H\(_{12}\)BrNO

\(^1\text{H-NMR (DMSO-d4)}\): 6.51 (d, J 9.6 Hz, 1H); 7.32 (dd, J 8.6, 1.6 Hz, 1H); 7.46 (d, J 1.6 Hz, 1H); 7.61 (d, J 8.6 Hz, 1H); 7.88 (d, J 9.6 Hz, 1H); 11.80 (brs, 1H).

\textbf{Intermediate 18: (2E)-N-(3-Bromophenyl)-2-phenylacrylamide}

To a solution of 3-bromoaaniline (13.1 mL, 120 mmol) in dichloromethane (100 mL) and 2,6-lutidine (21 mL, 180 mmol) at 0°C was added a solution of cinnamoyl chloride (20 g, 120 mmol) in dichloromethane (50 mL) dropwise. The reaction mixture was allowed to reach room temperature and was stirred for 2 hours. It was quenched with potassium phosphate buffer (100 mL, 1M, pH 7) and stirred for 15 minutes. Dichloromethane was removed under reduced pressure. The residue was extracted with ethyl acetate. The organic phase was washed with phosphate buffer (200 mL), dried over sodium sulfate and concentrated to dryness. The residue was crystallized from toluene/hexanes to give the product as colorless solid (33.4 g, 92%).

\textbf{MS (ES):} 302/304 (MH\(^+\)) for C\(_{15}\)H\(_{14}\)BrNO

\(^1\text{H-NMR (DMSO-d6)}\): 6.79 (d, 1H); 7.23-7.70 (m, 9H); 8.07 (s, 1H); 10.38 (s, 1H).

\textbf{Example 6}

2-Oxo-1-[2-(4-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl]methyl]amino]piperidin-1-yl)ethyl]-1,2-dihydroquinoline-7-carbonitrile

1-[2-(4-Amino-piperidin-1-yl)ethyl]-2-oxo-1,2-dihydroquinoline-7-carbonitrile (Intermediate 14, 70 mg, 0.24 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-carbaldehyde (WO 2004/058144) (42 mg, 0.24 mmol) and sodium triacetoxyborohydride (150 mg, 0.75 mmol) were reacted as described for \textbf{Example 5}. Chromatography on silica gel with dichloromethane/methanol (6:1) and crystallization from ethyl acetate/hexanes gave the product as a colorless solid, 73 mg (67%), mp 212°C.

\textbf{MS (ES):} 459.37 (MH\(^+\)) for C\(_{23}\)H\(_{24}\)N\(_{4}\)O\(_{4}\).
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\[ ^1H\text{-NMR (DMSO-}d_6\text{)} \delta: 1.19 (m, 2H); 1.74 (m, 2H); 2.01 (t, 2H); 2.35 (m, 1H); 2.51 (m, 2H, under solvent peak); 2.88 (m, 2H); 3.65 (s, 2H); 4.35 (t, 2H); 4.59 (s, 2H); 6.76 (d, 1H); 7.00 (d, 1H); 7.28 (d, 1H); 7.63 (dd, 1H); 7.89 (d, 1H); 7.99 (d, 1H); 8.06 (brs, 1H); 11.08 (brs, 1H). \]

Example 7

6-[(1-[2-(7,8-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-
yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

1-[2-(4-Aminopiperidin-1-yl)ethyl]-7,8-difluoroquinolin-2(1H)-one (Intermediate 19) (100 mg, 0.325 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/038144) (58 mg, 0.325 mmol) and sodium triacetoxy borohydride (207 mg, 0.98 mmol) were reacted as described for Example 1, but the aqueous workup was omitted, to give 107 mg of the mono acetate salt of the product after chromatography, as a colorless solid, mp 158-170°C.

**MS (ES):** 470.13 (MH+) for C_{36}H_{25}F_{2}N_{5}O_{3}

\[ ^1H\text{-NMR (DMSO-}d_6\text{)} \delta: 1.20 (m, 2H); 1.75 (m, 2H); 1.89 (s, 3H); 2.03 (t, 2H); 2.36 (m, 1H); 2.55 (m, 2H); 2.82 (m, 2H); 3.66 (s, 2H); 4.40 (m, 2H); 4.59 (s, 2H); 6.60 (d, 1H); 7.00 (d, 1H); 7.28 (d, 1H); 7.34 (m, 1H); 7.60 (d, 1H); 7.91 (d, 1H); 11.17 (brs, 1H). \]

**Intermediate 19:** 1-[2-(4-Aminopiperidin-1-yl)ethyl]-7,8-difluoroquinolin-2(1H)-one

The title compound was obtained from tert-butyl 1-[2-(7,8-difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl]carbamate (Intermediate 20) (412 mg, 1.01 mmol) by the procedure described for Intermediate 1, 316 mg (quantitative yield), as a colorless gum.

**MS (ES):** 308.29 (MH+) for C_{24}H_{29}F_{2}N_{3}O

\[ ^1H\text{-NMR (DMSO-}d_6\text{)} \delta: 1.15 (m, 2H); 1.46 (m, 1H); 1.62 (m, 2H); 2.03 (t, 2H); 2.53 (m, 2H, under solvent peak); 2.79 (m, 2H); 4.39 (m, 2H); 6.60 (d, 1H); 7.34 (m, 1H); 7.59 (m, 1H); 7.91 (d, 1H). \]

**Intermediate 20:** tert-Butyl 1-[2-(7,8-difluoro-2-oxoquinolin-1(2H)-
yl)ethyl]piperidin-4-yl]carbamate

7,8-Difluoroquinolin-2(1H)-one (Intermediate 21) (500 mg, 2.8 mmol) was deprotonated with sodium hydride (121 mg, 60% in oil, 3.64 mmol) and alkylated with 2-(4-
\[ ([\text{tert-butoxycarbonyl}][\text{amino}]piperidin-1-yl)]ethyl methanesulfonate (Intermediate 6) (3.3
mmol) as described for Intermediate 2. Chromatography on silica gel with hexanes/acetone 2:1 gave the product as a colorless solid, 414 mg (37%).

**MS (ES):** 408.30 (MH⁺) for C_{21}H_{25}F_{3}N_{5}O_{3}

**¹H-NMR (DMSO-d₆)** δ: 1.32 (m, 2H); 1.36 (s, 9H); 1.65 (m, 2H); 2.04 (t, 2H); 2.53 (m, 2H); 2.83 (m, 2H); 3.16 (m, 1H); 4.38 (m, 2H); 6.61 (d, 1H); 6.75 (d, 1H); 7.34 (m, 1H); 7.60 (m, 1H); 7.91 (m, 1H).

**Intermediate 21: 7,8-Difluoroquinolin-2(1H)-one**

The compound was prepared from (2E)-N-(2,3-difluorophenyl)-3-phenylacrylamide (Intermediate 22) (7.4 g, 28.5 mmol) and aluminium trichloride (19 g, 142 mmol) as described for Intermediate 17. The crude cyclization product was obtained as a single regioisomer, which was used without further purification, 2 g light brown solid (37%).

**MS (ES):** 182.04 (MH⁺) for C_{7}H_{11}F_{2}NO

**¹H-NMR (DMSO-d₆)** δ: 6.51 (d, 1H); 7.22 (m, 1H); 7.52 (m, 1H); 7.91 (m, 1H).

**Intermediate 22: (2E)-N-(2,3-Difluorophenyl)-3-phenylacrylamide**

The compound was prepared from 2,3-difluoroaniline (5 g, 38.7 mmol) and cinnamoyl chloride (6.45 g, 38.7 mmol) in the presence of 2,6-lutidine (6.8 mL, 58 mmol) as described for Intermediate 18 to give a colorless solid, 7.4 g (74%).

**MS (ES):** 260.08 (MH⁺) for C_{13}H_{11}F_{2}NO

**¹H-NMR (DMSO-d₆)** δ: 7.05 (d, 1H); 7.14-7.22 (m, 2H); 7.40-7.50 (m, 3H); 7.59-7.64 (m, 3H); 7.89 (t, 1H); 10.16 (brs, 1H).

**Example 8**

6-[[1-(2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl)piperidin-4-yl]amino]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

1-[2-(4-Aminopiperidin-1-yl)ethyl]-5,7-difluoroquinolin-2(1H)-one (Intermediate 23) (100 mg, 0.325 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazina-6-carbaldehyde (WO 2004/053144) (58 mg, 0.325 mmol) and sodium triacetox yborohydride (207 mg, 0.98 mmol) were reacted as described for Example 6, to give 114 mg of the mono acetate salt of the product as a colorless solid, mp 170-180°C.

**MS (ES):** 470.32 (MH⁺) for C_{22}H_{27}F_{3}N_{5}O_{3}
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\[^{1}\text{H-NMR (DMSO-d}_6\text{)}\] \(\delta\): 1.20 (m, 2H); 1.74 (m, 2H); 1.89 (s, 2H); 2.00 (t, 2H); 2.36 (m, 1H); 2.48 (m, 2H); 2.88 (m, 2H); 3.66 (s, 2H); 4.29 (t, 2H); 4.59 (s, 2H); 6.61 (d, 1H); 7.00 (d, 1H); 7.18-7.33 (m, 3H); 7.96 (d, 1H); 11.16 (brs, 1H).

**Intermediate 23: 1-[2-(4-Aminopiperidin-1-yl)ethyl]-5,7-difluoroquinolin-2(1H)-one**

The title compound was obtained from tert-butyl [1-[2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl] carbamate (Intermediate 24) (637 mg, 1.01 mmol) by the procedure described for Intermediate 1, 483 mg (quantitative), as a colorless solid.

**MS (ES):** 308.27 (MH\(^+\)) for C\(_{16}\)H\(_{19}\)F\(_2\)N\(_2\)O

\[^{1}\text{H-NMR (DMSO-d}_6\text{)}\] \(\delta\): 1.15 (m, 2H); 1.46-1.64 (m, 3H); 2.00 (t, 2H); 2.46 (m, 2H, under solvent peak); 2.85 (m, 2H); 4.28 (t, 2H); 6.61 (d, 1H); 7.21 (m, 1H); 7.30 (d, 1H); 7.95 (d, 1H).

**Intermediate 24: tert-Butyl [1-[2-(5,7-difluoro-2-oxoquinolin-1(2H)-
yl)ethyl]piperidin-4-yl] carbamate**

5,7-Difluoroquinolin-2(1H)-one (Intermediate 25) (500 mg, 2.8 mmol) was deprotonated with sodium hydride (121 mg, 60% in oil, 3.04 mmol) and alkylated with 2-[4-[[tert-butoxycarbonyl]amino]piperidin-1-yl]ethyl methanesulfonate (Intermediate 6) (3.3 mmol) as described for Intermediate 20. Colorless solid, 637 mg (57%).

**MS (ES):** 408.30 (MH\(^+\)) for C\(_{20}\)H\(_{23}\)F\(_2\)N\(_3\)O

\[^{1}\text{H-NMR (DMSO-d}_6\text{)}\] \(\delta\): 1.32 (m, 2H); 1.36 (s, 9H); 1.64 (m, 2H); 2.01 (t, 2H); 2.48 (m, 2H); 2.88 (m, 2H); 3.18 (m, 1H); 4.28 (m, 2H); 6.61 (d, 1H); 6.75 (d, 1H); 7.21 (m, 1H); 7.30 (d, 1H); 7.95 (m, 1H).

**Intermediate 25: 5,7-Difluoroquinolin-2(1H)-one**

The compound was prepared from (2E)-N-(3,5-difluorophenyl)-3-phenylacrylamide (Intermediate 26) (8.1 g, 31.2 mmol) and aluminum trichloride (21 g, 156 mmol) in a similar way as described for Intermediate 21. 3.47 g light brown solid (61%), mp 292-318°C.

**MS (ES):** 181.98 (MH\(^+\)) for C\(_8\)H\(_8\)F\(_2\)NO

\[^{1}\text{H-NMR (DMSO-d}_6\text{)}\] \(\delta\): 6.51 (d, 1H); 6.90 (m, 1H); 7.10 (ddd, 1H); 7.93 (d, 1H); 12.05 (brs, 1H).
Intermediate 26: \((2E)-N-(3,5\text{-dimethylphenyl})-3\text{-phenylacrylamide}\)

The compound was prepared from 3,5-dimethylaniline (5 g, 38.7 mmol) and cinnamoyl chloride (6.45 g, 38.7 mmol) in the presence of 2,6-lutidine (6.8 mL, 58 mmol) as described for Intermediate 18 to give a colorless solid, 8.1 g (81%).

\[\text{MS (ES)}: 260.10 (M^+)\text{ for }C_{15}H_{14}F_{2}NO\]

\[^1\text{H-NMR (DMSO-d$_6$)}\] $\delta$: 6.76 (d, 1H); 6.92 (m, 1H); 7.35-7.49 (m, 5H); 7.60-7.65 (m, 3H); 10.59 (s, 1H).

Example 9

6-[[\{1-\{2-(\text{3-Fluoro-2-oxoquinolin-1(2H)-yl})\text{ethyl}]\text{piperidin-4-yl} \text{amino}\}\text{methyl}]\text{-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one}}

1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-fluoroquinolin-2(1H)-one (Intermediate 27) (100 mg, 0.346 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-carbaldehyde (WO 2004/058144) (62 mg, 0.346 mmol) and sodium triacetoxy borohydride (220 mg, 1.04 mmol) were reacted as described for Example 7 to give 115 mg (74%) of the monoacetate salt of the product as a colorless solid, mp 150-155°C.

\[\text{MS (ES)}: 452.22 (M^+)\text{ for }C_{23}H_{26}FNO_3\]

\[^1\text{H-NMR (DMSO-d$_6$)}\] $\delta$: 1.22 (m, 2H); 1.75 (m, 2H); 1.89 (s, 3H); 2.01 (t, 2H); 2.37 (m, 1H); 2.48 (m, 2H); 2.89 (m, 2H); 3.67 (s, 2H); 4.29 (t, 2H); 4.59 (s, 2H); 6.55 (d, 1H); 7.00 (d, 1H); 7.12 (dd, 1H); 7.28 (d, 1H); 7.38 (dd, 1H); 7.78 (dd, 1H); 7.90 (d, 1H); 11.16 (brs, 1H).

Intermediate 27: 1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-fluoroquinolin-2(1H)-one

The title compound was obtained from tert-butyl \(\{2-(\text{3-fluoro-2-oxoquinolin-1(2H)-yl})\text{ethyl}]\text{piperidin-4-yl} \text{carbamate}\) (Intermediate 28) (565 mg, 1.45 mmol) by the procedure described for Intermediate 1, 425 mg (quantitative), as a colorless solid.

\[\text{MS (ES)}: 290.19 (M^+)\text{ for }C_{16}H_{20}FNO\]

\[^1\text{H-NMR (DMSO-d$_6$)}\] $\delta$: 1.16 (m, 2H); 1.62 (m, 2H); 2.00 (t, 2H); 2.46 (m, 2H, under solvent peak); 2.85 (m, 2H); 3.46 (m, 1H); 4.28 (t, 2H); 6.54 (d, 1H); 7.12 (dd, 1H); 7.36 (dd, 1H); 7.76 (dd, 1H); 7.89 (d, 1H).
Intermediate 29: tert-Butyl (1-f2-(7-fluoro-2-oxoquinolin-1(2H)-yl)ethyl)piperidin-4-yl)carbamate

7-Fluoroquinolin-2(1H)-one (Intermediate 29) (500 mg, 3.06 mmol) was deprotonated with sodium hydride (135 mg, 60% in oil, 3.37 mmol) and alkylated with 2-[(tert-butoxycarbonyl)amino]piperidin-1-yl)ethyl methanesulfonate (Intermediate 6) (3.7 mmol) as described for Intermediate 20. Colorless solid, 570 mg (48%).

MS (ES): 390.21 (MH+) for C_{21}H_{25}FN_{2}O_{3}

\[^{1}H\text{-NMR (DMSO-d6)}\]: 8: 1.32 (m, 2H); 1.36 (t, 9H); 1.64 (m, 2H); 2.02 (t, 2H); 2.48 (m, 2H); 2.90 (m, 2H); 3.19 (m, 1H); 4.28 (m, 2H); 6.54 (d, 1H); 6.75 (d, 1H); 7.12 (m, 1H); 7.38 (m, 1H); 7.78 (dd, 1H); 7.90 (d, 1H).

Intermediate 29: 7-Fluoroquinolin-2(1H)-one

The compound was prepared from (25)-N-(3-fluorophenyl)-3-phenylacrylamide (Intermediate 30) (13.8 g, 57.2 mmol) and aluminium trichloride (30.5 g, 229 mmol) in a similar way as described for Intermediate 21 to give a mixture of the title compound together with the corresponding 5-fluoro regioisomer in a ratio of 3:1. This mixture was vigorously stirred in dichloromethane (100 mL) for 3 hours at room temperature and then filtered. The solid obtained was resuspended in diethyl ether (200 mL) and stirred like above and filtered to give 3.63 g (34%) of the crude product containing 12% of the 5-fluoro regioisomer. This was used without further purification for the next step.

MS (ES): 164.02 (MH+) for C_{9}H_{8}FNO

\[^{1}H\text{-NMR (CDCl}_{3}/\text{MeOD)}\]: 8: 6.31 (d, 1H); 6.73 (dd); 6.79 (dd, 1H); 7.35 (dd, 1H); 7.60 (d, 1H).

Intermediate 30: (25)-N-(3-Fluorophenyl)-3-phenylacrylamide

The compound was prepared from 3-fluoroaniline (5.8 mL, 60 mmol) and cinnamoyl chloride (10 g, 60 mmol) in the presence of 2,6-lutidine (10.5 mL, 90 mmol) as described for Intermediate 18 to give a colorless solid, 13.9 g (96%), mp 110°C.

MS (ES): 242.20 (MH+) for C_{12}H_{12}FNO

\[^{1}H\text{-NMR (DMSO-d6)}\]: 8: 6.80 (d, 1H); 6.89 (m, 1H); 7.31-7.48 (m, 5H); 7.58-7.65 (m, 3H); 7.73 (m, 1H); 10.43 (s, 1H).
Example 10
1-(2-[2-(3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl)ethyl)-7-fluoroquinolin-2(1H)-one

5 (100 mg, 0.346 mmol), 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde (WO 2004/058144) (57 mg, 0.346 mmol) and sodium triacetoxyborohydride (220 mg, 1.04 mmol) were reacted as described for Example 7. The free base obtained after chromatography was dissolved in dichloromethane/ether (10 mL, 1:1) and HCl in ether (1M, 1 mL) was added under vigorous stirring. It was evaporated to dryness under reduced pressure and the residue was taken up as a suspension in dichloromethane/hexanes (10 mL, 1:1). It was filtered and dried to give 118 mg (78%) of the bis HCl salt of the product as a colorless solid, mp >275°C (decomposed).

MS (ES): 439.23 (M+H) for C_{24}H_{23}FN_{2}O_{4}

1H-NMR (DMSO-d<sub>6</sub>): δ: 2.10 (m, 2H); 2.37 (m, 2H); 3.10 (m, 2H); 3.20-3.38 (m, 3H);
15 3.78 (m, 2H); 4.27 (m, 2H); 4.37 (m, 2H); 4.43 (m, 2H); 4.62 (t, 2H); 6.60 (d, 1H); 7.19 (dd, 1H); 7.41 (s, 1H); 7.78 (dd, 1H); 7.84 (dd, 1H); 7.98 (d, 1H); 8.31 (s, 1H); 9.91 (brs, 2H); 11.04 (brs, 1H).

Example 11
6-[[1-(2-(7-Methoxy-2-oxo-3,4-dihydroquinolin-1(2H)-yl)ethyl)piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazine-3(4H)-one

1-(2-[4-Aminopiperidin-1-yl)ethyl]-7-methoxy-3,4-dihydroquinolin-2(1H)-one

(Intermediate 31) (110 mg, 0.36 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (65 mg, 0.325 mmol) and sodium triacetoxyborohydride (220 mg, 1.04 mmol) were reacted as described for Example 1, but the aqueous workup was omitted. Chromatography on a Phenomenex Synergy Polar-RP 4 μm column, eluent: 30-60% acetoniitrile, 10 mM ammonium acetate pH 8, followed by chromatography on silica gel with dichloromethane/methanol (7:1). The bis HCl salt of the product was prepared as described for Example 10 to give 46 mg (24%) as a colorless solid, mp >285°C (dec).

MS (ES): 466.21 (M+H) for C_{25}H_{21}N_{2}O_{4}

1H-NMR (DMSO-d<sub>6</sub>): δ: 2.10 (m, 2H); 2.36 (m, 2H); 2.53 (t, 2H); 2.86 (t, 2H); 3.10 (m, 2H); 3.16 (m, 2H); 3.36 (m, 1H); 3.70 (m, 2H); 3.73 (s, 3H); 4.16 (m, 2H); 4.25 (m, 2H);
4.70 (s, 2H); 6.80 (m, 1H); 6.86 (s, 1H); 7.23-7.28 (m, 2H); 7.45 (d, 1H); 9.70 (brs, 2H); 11.07 (brs, 1H); 11.37 (s, 1H).

**Intermediate 31:** 1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-methoxy-3,4-dihydroquinolin-2(1H)-one

The title compound was obtained from tert-butyl [1-[2-(7-methoxy-2-oxo-3,4-dihydroquinolin-1(2H)-yl)ethyl]piperidin-4-yl] carbamate (Intermediate 32) (550 mg, 1.36 mmol) by the procedure described for Intermediate 1, 338 mg (82%), as a colorless oil.

**MS (ES):** 304.23 (MH⁺) for C₁₇H₂₅N₃O₄

**¹H-NMR (DMSO-d₆):** 8: 1.19 (m, 2H); 1.62 (m, 2H); 1.96 (t, 2H); 2.36 (t, 2H); 2.46 (m, 2H); 2.73-2.80 (m, 5H); 3.71 (s, 3H); 3.91 (m, 2H); 6.77-6.84 (m, 2H); 7.04 (m, 1H).

**Intermediate 32:** tert-Butyl [1-[2-(7-methoxy-2-oxo-3,4-dihydroquinolin-1(2H)-yl)ethyl]piperidin-4-yl] carbamate

7-Methoxy-3,4-dihydroquinolin-2(1H)-one (Intermediate 33) (300 mg, 1.78 mmol) was deprotonated with sodium hydride (75 mg, 60% in oil, 1.85 mmol) and alkylated with 2-[[tert-butoxycarbonyl]amino]piperidin-1-yl)ethyl methanesulfonate (Intermediate 6) (2.03 mmol) as described for Intermediate 2. Chromatography on silica gel eluting with ethyl acetate and then acetone/ dichloromethane (4:1) gave the product as a colorless oil, 559 mg (82%).

**MS (ES):** 404.21 (MH⁺) for C₂₂H₂₃N₃O₄

**¹H-NMR (DMSO-d₆):** 8: 1.32 (m, 2H); 1.36 (s, 9H); 1.64 (m, 2H); 1.93-2.00 (m, 4H); 2.37 (m, 2H); 2.47 (m, 2H); 2.78 (m, 2H); 3.16 (m, 1H); 3.71 (s, 3H); 3.91 (t, 2H); 6.72-6.82 (m, 3H); 7.05 (d, 1H).

**Intermediate 33:** 7-Methoxy-3,4-dihydroquinolin-2(1H)-one

A mixture of 7-hydroxy-3,4-dihydroquinolin-2(1H)-one (3.0 g, 17 mmol) and triethyl amine (3.14 mL, 22 mmol) in dichloromethane/ methanol/ acetonitrile (10:1:10, 168 mL) was treated with (trimethylsilyl) diazomethane (2M solution in hexanes, 10.25 mL, 20.5 mmol). It was stirred overnight at room temperature, the solvent was removed under reduced pressure and chromatography on silica gel with hexanes/ acetone (1:1) gave 2.2 g (67%) of the product as a colorless solid.

**MS (ES):** 178.16 (MH⁺) for C₁₄H₁₄NO₂
\textbf{Example 12}

\((3S,4R)-1-[2-(5,7\text{-difluoro-2-oxoquinolin-1(2H)-yl})\text{ethyl}]\text{-4-[(2,3-dihydro[1,4]dioxin-2,3-c-pyridin-7-ylmethyl)amino]piperidine-3-carboxylic acid}

A solution of methyl \((3S,4R)-1-[2-(5,7\text{-difluoro-2-oxoquinolin-1(2H)-yl})\text{ethyl}]\text{-4-[(2,3-dihydro[1,4]dioxin-2,3-c-pyridin-7-ylmethyl)amino]piperidine-3-carboxylate}

(Example 13) (120 mg, 0.233 mmol) in tetrahydrofuran/ water (1:1, 10 mL) was treated with sodium hydroxide (15\% aqueous, 0.2 mL) at room temperature for 3 hours. It was quenched with glacial acetic acid (1 mL) and concentrated to dryness under reduced pressure.

Chromatography on a C18 cartridge (RediSep, ISCO) with 0-25 \% acetonitrile in water, containing 0.1\% acetic acid and treatment with HCl as described for Example 10 gave 113 mg (90\%) of the mono hydrochloride salt of the product as a colorless solid, mp 100-180°C.

\textbf{MS (ES)}: 501.03 (MH\textsuperscript{+}) for \(\text{C}_{13}\text{H}_{13}\text{F}_{3}\text{N}_{4}\text{O}_{3}\)

\textbf{\textsuperscript{1}H-NMR (DMSO-d_6)} \(\delta\) 2.02 (m, 2H); 2.60 (m, 2H); 3.15-3.51 (m, 8H); 4.18 (m, 2H); 4.33 (m, 2H); 4.37 (m, 2H); 4.50 (m, 1H); 6.62 (d, 1H); 7.12 (s, 1H); 7.24 (m, 1H); 7.41 (m, 1H); 7.98 (d, 1H); 8.15 (s, 1H).

\textbf{Example 13}

\((3S,4R)-1-[2-(5,7\text{-difluoro-2-oxoquinolin-1(2H)-yl})\text{ethyl}]\text{-4-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]amino]piperidine-3-carboxylic acid}

Methyl \((3S,4R)-1-[2-(5,7\text{-difluoro-2-oxoquinolin-1(2H)-yl})\text{ethyl}]\text{-4-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]amino]piperidine-3-carboxylate}

(Example 15) (80 mg, 0.155 mmol) was treated with sodium hydroxide as described for Example 12 to give 51 mg (61\%) of the mono hydrochloride salt of the product as a colorless solid, mp 150-180°C.

\textbf{MS (ES)}: 504.19 (MH\textsuperscript{+}) for \(\text{C}_{33}\text{H}_{32}\text{F}_{2}\text{N}_{4}\text{O}_{3}\)

\textbf{\textsuperscript{1}H-NMR (DMSO-d_6)} \(\delta\) 2.10 (m, 2H); 2.75-3.75 (m, 8H); 3.86 (m, 2H); 4.33 (m, 1H); 4.54 (m, 1H); 6.50 (m, 1H); 6.64 (d, 1H); 6.91 (d, 1H); 7.19-7.34 (m, 3H); 7.48 (m, 2H); 8.00 (s, 1H); 9.19 (brs, 1H).
Example 14
Methyl (3S,4R)-1-[2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl]-4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino)piperidine-3-carboxylate

Methyl (3S,4R)-4-amino-1-[2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidine-3-carboxylate (Intermediate 34) (120 mg, 0.328 mmol), 2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-carbaldehyde (WO 2004/058144) (54 mg, 0.328 mmol) and sodium triacetoxyborohydride (209 mg, 0.98 mmol) were reacted as described for Example 6. Chromatography on silica gel with dichloromethane/methanol (20:1) gave 130 mg (77%) of product as a colorless hard foam.

MS (ES): 515.03 (MH+) for C26H22F2N2O5

1H-NMR (DMSO-d6) δ: 1.52 (m, 1H); 1.75 (m, 1H); 2.43 (m, 1H); 2.50 (m, 1H); 2.54 (m, 2H); 2.60-2.73 (m, 3H); 2.87 (m, 1H); 3.51 (s, 3H); 3.53 (d, 1H); 3.69 (d, 1H); 4.22-4.34 (m, 6H); 6.61 (d, 1H); 6.86 (s, 1H); 7.21 (m, 1H); 7.30 (m, 1H); 7.95 (d, 1H); 7.97 (s, 1H).

Example 15
Methyl (3S,4R)-1-[2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl]-4-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]amino)piperidine-3-carboxylate

Methyl (3S,4R)-4-amino-1-[2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidine-3-carboxylate (Intermediate 34) (120 mg, 0.328 mmol), (2E)-3-(2,5-difluorophenyl)acrylaldehyde (FR 2872164) (54 mg, 0.328 mmol) and sodium triacetoxyborohydride (209 mg, 0.98 mmol) were reacted as described for Example 6. Chromatography on silica gel with dichloromethane/N,N-dimethylformamide (30:1) gave 83 mg (49%) of product as a colorless hard foam.

MS (ES): 518.10 (MH+) for C23H22F2N4O3

1H-NMR (DMSO-d6) δ: 1.56 (m, 1H); 1.75 (m, 1H); 1.90 (m, 1H); 2.41 (m, 1H); 2.51-2.72 (m, 5H); 2.90 (m, 1H); 3.25 (dd, 1H); 3.39 (dd, 1H); 3.51 (s, 3H); 4.29 (m, 2H); 6.42 (m, 1H); 6.57 (d, 1H); 6.61 (d, 1H); 7.09 (m, 1H); 7.17-7.24 (m, 2H); 7.30 (m, 1H); 7.43 (m, 1H); 7.95 (d, 1H).

Intermediate 34: Methyl (3S,4R)-4-amino-1-[2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidine-3-carboxylate

A solution of methyl (3S,4R)-4-[(benzzyloxy)carbonyl]amino]-1-[2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidine-3-carboxylate (Intermediate 35) (595 mg, 1.19 mmol)
in methanol (10 mL) was hydrogenated over palladium on carbon (10%, wet) at normal
pressure and room temperature for 30 minutes. It was filtered through a 0.45 µm membrane,
washed with methanol and the wash and filtrate were concentrated under reduced pressure to
give 395 mg (91%) of the product as a colorless hard foam.

**Intermediate 35**: Methyl (3S,4R)-4-[[benzyloxy]carbonyl]amino]-1-(2,5,7-
difluoro-2-oxoquinolin-1-(2H)-yl)ethyl piperidine-3-carboxylate

5.7-Difluoroquinolin-2-(1H)-one (Intermediate 25) (350 mg, 1.93 mmol) was
deprotonated with sodium hydride (85 mg, 60% in oil, 2.13 mmol) and alkylated with methyl
(3S,4R)-4-[[benzyloxy]carbonyl]amino]-1-(2-chloroethyl)piperidine-3-carboxylate
(Intermediate 36) (1.93 mmol) as described for Intermediate 20. Colorless hard foam, 604
mg (63%).

**Intermediate 35**: Methyl (3S,4R)-4-[[benzyloxy]carbonyl]amino]-1-(2-
chboroethyl)piperidine-3-carboxylate

Methyl (3S,4R)-4-[[benzyloxy]carbonyl]amino]-1-(2-hydroxyethyl)piperidine-3-
carboxylate (Intermediate 37) (650 mg, 1.93 mmol) was reacted with methanesulfonyle
chloride (0.18 mL, 2.32 mmol) in the presence of triethylamine (0.38 mL, 2.7 mmol) as
described for Intermediate 6. The crude chloride was used without delay for the next step.

**Intermediate 37**: Methyl (3S,4R)-4-[[benzyloxy]carbonyl]amino]-1-(2-
hydroxyethyl)piperidine-3-carboxylate

A mixture of methyl (3S,4R)-4-[[benzyloxy]carbonyl]amino]piperidine-3-
carboxylate (WO 2005/066176) (2.29 g, 7.83 mmol), N,N-diisopropylethylamine (2.05 mL,
11.75 mmol and 2-bromoethanol (0.722 mL, 10.18 mmol) in dry acetonitrile (17 mL) was
heated in the microwave at 70°C for 4.5 hours. The solvent was removed under reduced pressure and the residue taken up in ethyl acetate (200 mL) and washed with saturated aqueous sodium hydrogen carbonate solution (100 mL). The aqueous phase was back extracted once with ethyl acetate (100 mL) and the combined organic phases were dried over sodium sulfate. Chromatography on silica gel with dichloromethane/methanol (12:1) gave 2.0 g (76%), mp 73°C.

**MS (ES):** 337.16 (MH+) for C17H24N2O5

**1H-NMR (DMSO-d6) δ:** 1.66 (m, 2H); 2.34-2.55 (m, 5H); 2.67-2.79 (m, 2H); 3.44 (dt, 2H); 3.51 (s, 3H); 3.95 (m, 1H); 4.31 (s, 1H); 4.97 (d, 1H); 5.02 (d, 1H); 7.21 (d, 1H); 7.25-7.38 (m, 5H).

**Example 16**

(3R,4R)-1-[[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]-4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino]piperidine-3-carboxylic acid

Methyl (3R,4R)-1-[[2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl]-4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino]piperidine-3-carboxylate (Example 18) (201 mg, 0.4 mmol) was saponified and converted into the bis hydrochloride salt as described for Example 12, 194 mg (87%), colorless solid, mp > 190°C.

**MS (ES):** 501.22 (MH+) for C25H28F7N3O5

**1H-NMR (DMSO-d6) δ:** 2.24 (m, 1H); 2.46 (m, 1H); 3.12 (m, 1H); 3.34 (m, 4H); 3.58 (m, 1H); 3.83 (m, 1H); 3.93 (m, 1H); 4.24 (d, 1H); 4.31-4.44 (m, 5H); 4.63 (m, 2H); 6.66 (d, 1H); 7.26-7.31 (m, 2H); 7.69 (d, 1H); 8.02 (d, 1H); 8.25 (s, 1H); 11.51 (bs, 1H).

**Example 17**

(3R,4R)-1-[[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]-4-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]amino]piperidine-3-carboxylic acid

Methyl (3R,4R)-1-[[2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl]-4-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]amino]piperidine-3-carboxylate (Example 19) (166 mg, 0.2 mmol) was treated with sodium hydroxide as described for Example 12 to give 82 mg (69%) of the bis hydrochloride salt of the product as a colorless solid, mp > 205°C.

**MS (ES):** 504.23 (MH+) for C26H23F6N3O5
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\[ ^1H\text{-NMR (DMSO-}d_6 \text{)} \delta: 2.15 (m, 1H); 2.40 (m, 1H); 3.01-3.98 (m, 10H); 4.60 (m, 2H); 6.50 (m, 1H); 6.67 (d, 1H); 6.95 (d, 1H); 7.20-7.35 (m, 3H); 7.47 (m, 1H); 7.62 (m, 1H); 8.02 (d, 1H). \]

**Example 18**

Methyl (3\text{R},4\text{R})-1-[2-(5,7-difluoro-2-oxoquinolin-1(2\text{H})-yl)ethyl]-4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methylamino]piperidine-3-carboxylate

Methyl (3\text{R},4\text{R})-4-amino-1-[2-(5,7-difluoro-2-oxoquinolin-1(2\text{H})-yl)ethyl]piperidine-3-carboxylate (Intermediate 38) (195 mg, 0.53 mmol), 2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-carbaldehyde (WO 2004/058144) (88 mg, 0.53 mmol) and sodium trimethoxyborohydride (339 mg, 1.6 mmol) were reacted as described for Example 14 to give 216 mg (79%) of product as a colorless hard foam.

MS (ES): 515.23 (M\text{H}^+ \text{)} for C\text{_{28}}H\text{_{28}}F\text{_{2}}N\text{\textsubscript{3}}O\text{\textsubscript{5}}

\[ ^1H\text{-NMR (DMSO-}d_6 \text{)} \delta: 1.18 (m, 1H); 1.92 (m, 1H); 2.05 (ddd, 1H); 2.14 (dd, 1H); 2.34 (ddd, 1H); 2.52 (t, 2H); 2.57 (m, 1H); 2.88 (m, 1H); 3.03 (m, 1H); 3.57 (d, 1H); 3.58 (s, 3H); 3.69 (d, 1H); 4.24-4.33 (m, 6H); 6.61 (d, 1H); 6.87 (s, 1H); 7.21 (ddd, 1H); 7.33 (m, 1H); 7.93-7.96 (m, 2H).

**Example 19**

Methyl (3\text{R},4\text{R})-1-[2-(5,7-difluoro-2-oxoquinolin-1(2\text{H})-yl)ethyl]-4-[(2\text{E})-3-(2,5-difluorophenyl)prop-2-en-1-ylamino]piperidine-3-carboxylate

Methyl (3\text{R},4\text{R})-4-amino-1-[2-(5,7-difluoro-2-oxoquinolin-1(2\text{H})-yl)ethyl]piperidine-3-carboxylate (Intermediate 38) (195 mg, 0.53 mmol), (2\text{E})-3-(2,5-difluorophenyl)acrylaldehyde (FR 2872164) (50 mg, 0.53 mmol) and sodium trimethoxyborohydride (339 mg, 1.6 mmol) were reacted as described for Example 6. Chromatography on silica gel with dichloromethane/N,N-dimethylformamide (25:1 to 15:1) gave 119 mg (43%) of product as a colorless oil.

MS (ES): 518.25 (M\text{H}^+ \text{)} for C\text{_{27}}H\text{_{27}}F\text{_{2}}N\text{\textsubscript{3}}O\text{\textsubscript{5}}

\[ ^1H\text{-NMR (DMSO-}d_6 \text{)} \delta: 1.20 (m, 1H); 1.94 (m, 1H); 2.08 (ddd, 1H); 2.16 (dd, 1H); 2.34 (ddd, 1H); 2.53 (t, 2H); 2.61 (ddd, 1H); 2.90 (m, 1H); 3.04 (m, 1H); 3.24 (dd, 1H); 3.39 (dd, 1H); 3.58 (s, 3H); 4.28 (m, 2H); 6.40 (m, 1H); 6.55-6.62 (m, 2H); 7.05-7.25 (m, 3H); 7.32 (d, 1H); 7.42 (m, 1H); 7.95 (d, 1H).
Intermediate 38: Methyl (3R,4R)-4-amino-1-[2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidine-3-carboxylate

Methyl (3R,4R)-4-[[benzoyloxy]carbonylamino]-1-[2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidine-3-carboxylate (Intermediate 39) (535 mg, 1.07 mmol) was hydrogenated as described for Intermediate 34 to give 391 mg (quantitative) of the product as a colorless hard foam.

**MS (ES):** 366 (M+H) for C_{16}H_{21}F_{2}N_{3}O_{3}

Intermediate 39: Methyl (3R,4R)-4-[[benzoyloxy]carbonylamino]-1-[2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidine-3-carboxylate

5,7-Difluoroquinolin-2(1H)-one (Intermediate 25) (350 mg, 1.93 mmol) was deprotonated with sodium hydride (85 mg, 60% in oil, 2.13 mmol) and alkylated with methyl (3R,4R)-4-[[benzoyloxy]carbonylamino]-1-{[2-[(methylsulfonyl)oxy]ethyl]piperidine-3-carboxylate (Intermediate 40) (1.93 mmol) as described for Intermediate 20 to give the product as a colorless hard foam, 538 mg (56%).

**MS (ES):** 500.38 (M+H) for C_{20}H_{27}F_{3}N_{3}O_{3}

^1H-NMR (600 MHz, DMSO-d_6) δ: 1.40 (ddddd, 1H); 1.70 (m, 1H); 2.10-1.45 (m, 2H); 2.44 (dd, 1H); 2.54 (t, 2H); 2.89 (m, 1H); 3.07 (m, 1H); 3.49 (t, 3H); 3.54 (m, 1H); 4.28 (m, 2H); 4.95 (d, 1H); 4.99 (d, 1H); 6.61 (d, 1H); 7.11 (ddd, 1H); 7.29-7.37 (m, 7H); 7.95 (d, 1H).

Intermediate 40: Methyl (3R,4R)-4-[[benzoyloxy]carbonylamino]-1-[2-[(methylsulfonyl)oxy]ethyl]piperidine-3-carboxylate

Methyl (3R,4R)-4-[[benzoyloxy]carbonylamino]-1-{[2-hydroxyethyl]piperidine-3-carboxylate (Intermediate 41) (650 mg, 1.93 mmol) was reacted with methanesulfonyl chloride (0.18 mL, 2.32 mmol) in the presence of triethylamine (0.38 mL, 2.7 mmol) as described for Intermediate 6. The crude product was used without delay for the next step.

**MS (ES):** 415.3 (M+H) for C_{16}H_{26}N_{3}O_{7}S

Intermediate 41: Methyl (3R,4R)-4-[[benzoyloxy]carbonylamino]-1-{[2-hydroxyethyl]piperidine-3-carboxylate

Methyl (3R,4R)-4-[[benzoyloxy]carbonylamino]piperidine-3-carboxylate (WO 2005/066176) (2.0 g, 6.84 mmol), N,N-diisopropylethylamine (1.8 mL, 10.26 mmol) and 2-
bromoethanol (0.63 mL, 8.9 mmol) were reacted as described for Intermediate 37 to give 1.38 g (60%) of the product as a colorless oil.

**MS (ES):** 337.36 (M+H) for C_{17}H_{26}N_{2}O_{3}

**{H-NMR (DMSO-d_{6})}**: 8: 1.43 (dddd, 1H); 1.70 (m, 1H); 1.97-2.14 (m, 2H); 2.37 (t, 2H); 2.49 (m, 1H); 2.80 (m, 1H); 2.94 (m, 1H); 3.44 (dt, 2H); 3.50 (s, 3H); 3.54 (m, 1H); 4.39 (t, 1H); 4.95 (d, 1H); 5.00 (d, 1H); 7.27-7.38 (m, 6H).

**Example 20**

Cis(+)-[(-)-2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)(ethyl)-3-hydroxypiperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

Cis(±)-[2-(4-amino-3-hydroxypiperidin-1-yl)ethyl]-5,7-difluoroquinolin-2(1H)-one (175 mg, 0.54 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazino-6-carbaldehyde (WO 2004/058144) (96 mg, 0.54 mmol) and sodium triacetoxy borohydride (344 mg, 1.6 mmol) were reacted as described for Example 1 to give 186 mg (71%) of the free base of the product as a colorless oil.

**MS (ES):** 486.22 (M+H) for C_{26}H_{33}F_{13}N_{5}O_{5}

**{H-NMR (MeOD)}**: 8: 1.67-1.78 (m, 2H); 2.22 (m, 1H); 2.33 (d, 1H); 2.55-2.69 (m, 3H); 2.90 (m, 1H); 3.06 (m, 1H); 3.75 (d, 1H); 3.79 (d, 1H); 3.91 (m, 1H); 4.30-4.46 (m, 2H); 4.59 (s, 2H); 6.61 (d, 1H); 6.93 (dd, 1H); 6.95 (d, 1H); 7.21 (d, 1H); 7.27 (m, 1H); 7.96 (d, 1H).

**Intermediate 42**: Cis(±)-[2-(4-amino-3-hydroxypiperidin-1-yl)ethyl]-5,7-difluoroquinolin-2(1H)-one

Cis(+)-[2-(4-azido-3-hydroxypiperidin-1-yl)ethyl]-5,7-difluoroquinolin-2(1H)-one (Intermediate 43) (190 mg, 0.54 mmol) was hydrogenated as described for Intermediate 34, for 3 hours, to give the product as a colorless oil, 175 mg (quantitative).

**MS (ES):** 324.02 (M+H) for C_{16}H_{19}F_{2}N_{3}O_{2}

**{H-NMR (CDCl_3)}**: 8: 1.82 (m, 2H); 2.25 (ddd, 1H); 2.39 (d, 1H); 2.62-2.73 (m, 3H); 2.90 (m, 1H); 2.98 (m, 1H); 3.13 (m, 1H); 3.92 (m, 1H); 4.23 (ddd, 1H); 4.44 (ddd, 1H); 6.63 (d, 1H); 6.70 (dd, 1H); 6.91 (d, 1H); 7.85 (d, 1H).
Intermediate 43: Cis(±)-1-[(2-[4-azido-3-hydroxypiperidin-1-yl]ethyl)-5,7-difluorocinnolin-2(1H)-one

5,7-Difluorocinnolin-2(1H)-one (Intermediate 25) (389 mg, 2.15 mmol) was deprotonated with sodium hydride (95 mg, 60% in oil, 2.36 mmol) and alkylated with cis(±)
2-(4-azido-3-hydroxypiperidin-1-yl)ethyl methanesulfonate (Intermediate 44) (2.15 mmol) as described for Intermediate 20, except after 24 hours, potassium carbonate (100 mg, 0.72 mmol) was added and the resulting mixture was stirred for another 24 hours at room temperature to give the product as a colorless hard foam, 195 mg (26%).

MS (ES): 350.15 (MH+) for C_{19}H_{17}F_{2}N_{4}O_{2}

^{1}H NMR (DMSO-d_{6}) δ: 1.56 (m, 1H); 1.71 (m, 1H); 2.32 (m, 1H); 2.40 (m, 1H); 2.48 (m, 1H); 2.53 (dd, 2H); 2.59 (m, 1H); 3.61-3.71 (m, 2H); 4.29 (dd, 2H); 5.05 (d, 1H); 6.61 (d, 1H); 7.21 (ddd, 1H); 7.32 (d, 1H); 7.95 (d, 1H).

Intermediate 44: Cis(±)-2-(4-azido-3-hydroxypiperidin-1-yl)ethyl methanesulfonate

A solution of cis(±)4-azido-1-(2-hydroxyethyl)piperidin-3-ol (Intermediate 45) (0.4 g, 2.15 mmol) in dry dichloromethane (15 mL) and 2,6-lutidine (0.325 mL, 2.8 mmol) was treated at -20°C dropwise with a solution of methanesulfonyl chloride (0.175 mL, 2.26 mmol) in dichloromethane (5 mL). The temperature was allowed to reach 0°C and kept at 0°C for 10 hours. The resulting reaction mixture was diluted with dichloromethane (50 mL) and washed with saturated aqueous sodium hydrogen carbonate solution (10 mL). The aqueous phase was back extracted with dichloromethane (20 mL) and the combined organic phases were dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was codistilled with dry DMF (10 mL) without heating. This crude preparation of the mesylate was used without further purification directly for the next step.

MS (ES): 265.02 (MH+) for C_{19}H_{16}N_{4}O_{2}S

Intermediate 45: Cis(±)-4-azido-1-(2-hydroxyethyl)piperidin-3-ol

Cis(±)4-azidopiperidin-3-ol (prepared following the procedure described in WO 2003/066176 for the chiral material) (0.945 g, 6.65 mmol), N,N-diisopropylethylamine (1.7 mL, 10 mmol) and 2-bromoethanol (0.61 mL, 3.64 mmol) were reacted as described for Intermediate 37, except heating for one hour. The solvent was removed under reduced pressure. The residue was taken up in dichloromethane (100 mL), washed with 1M sodium hydroxide solution (30 mL) and the aqueous phase was back extracted five times with
dichloromethane (5 x 100 mL). The combined organic phases were dried over sodium sulfate. Chromatography on silica gel with dichloromethane/methanol 3:1 gave 1.15 g (93%) of the product as a colorless oil.

**MS (ES):** 187.24 (MH⁺) for C₇H₁₆N₄O₂

**¹H-NMR (DMSO-d₆)** δ: 1.61 (m, 1H); 1.72 (m, 1H); 2.28-2.38 (m, 5H); 2.45 (m, 1H); 3.43 (ddd, 2H); 3.57 (m, 1H); 3.73 (m, 1H); 4.33 (dd, 1H); 5.01 (d, 1H).

**Example 21**

4-(2-[4-(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino)piperidin-1-yl)ethyl]-6-methoxy-2H-1,4-benzoxazin-3(4H)-one

A mixture of 4-[2-{4-aminopiperidin-1-yl}ethyl]-6-methoxy-2H-1,4-benzoxazin-3(4H)-one trifluoroacetate (Intermediate 46) (0.4 mmol), N,N-diisopropylethylamine (1 mL) and 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carboxaldehyde (WO 2004/0581144) (74 mg, 0.45 mmol) in dichloromethane/methanol (1:1, 10 mL) was reacted and reduced with sodium cyanoborohydride (50 mg, 0.74 mmol) as described for Example 4. Reverse phase chromatography with water/acetonitrile/trifluoroacetic acid gave the product as the trifluoroacetic acid salt. The salt was dissolved in water and chloroform and basified with saturated sodium carbonate. The layers were separated and the aqueous was extracted with chloroform. The organic extracts were dried over magnesium sulfate and evaporated to dryness to give the free base of the title compound as a gum, 54 mg (32%).

**MS (ES):** 455.33 (MH⁺) for C₂₅H₂₀N₄O₅

**¹H-NMR (CDCl₃-d₆)** δ: 1.46 (m, 2H); 1.88 (m, 2H); 2.14 (m, 2H); 2.54 (m, 1H); 2.58 (t, J = 7.3 Hz, 2H); 2.95 (m, 2H); 3.78 (s, 3H); 3.79 (s, 2H); 4.01 (t, J = 7.4 Hz, 2H); 4.29 (m, 4H); 4.52 (s, 2H); 6.50 (dd, J = 6.2, 2.7 Hz, 1H); 6.67 (d, J = 2.7 Hz, 1H); 6.81 (s, 1H); 6.89 (d, J = 8.7 Hz, 1H); 8.03 (s, 1H).

**Intermediate 46:** 4-[2-{4-Aminopiperidin-1-yl}ethyl]-6-methoxy-2H-1,4-benzoxazin-3(4H)-one

tert-Butyl (1-[2-(6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidino-4-yl)carbamate (Intermediate 47) (510 mg, 1.26 mmol) was reacted as described for Intermediate 14. The crude trifluoroacetate of the title compound was used without further purification for the next step (quantitative yield).

**MS (ES):** 306 (MH⁺) for C₁₅H₂₁N₄O₅
Intermediate 47: tert-Butyl (1-[2-(6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoazinin-4-yl)ethyl]piperidine-4-yl)carbonate

6-Methoxy-2H-1,4-benzoazinin-3(4H)-one (Intermediate 48) (380 mg, 2.1 mmol) was deprotonated with sodium hydride (100 mg, 60% in oil, 2.5 mmol) and alkylated with 2-{(tert-butoxycarbonylamino)piperidin-1-yl}ethyl methanesulfonate (Intermediate 6) (2.3 mmol) as described for Intermediate 2. Chromatography on silica gel with hexanes/ethyl acetate (1:1) afforded 510 mg (60%) of the product.

MS (ES): 466.49 (MH⁺) for C₂₄H₂₆N₂O₅

¹H-NMR (CDCl₃-d) δ: 1.34 (m, 2H); 1.36 (m, 2H); 1.62 (m, 2H); 1.98 (m, 2H); 2.43 (m, 2H); 2.84 (m, 2H); 3.20 (m, 1H); 3.73 (s, 3H); 3.96 (m, 2H); 4.53 (s, 2H); 6.56 (m, 1H); 6.76 (m, 1H); 6.92 (m, 1H).

Intermediate 48: 6-Methoxy-2H-1,4-benzoazinin-3(4H)-one

To a solution of ethyl (4-methoxy-2-nitrophenoxy)acetate (Intermediate 49) (1.8 g, 7.1 mmol) in acetic acid (20 mL) was added iron powder (1.1 g, 19.9 mmol). The reaction was heated at 90°C for 3 hours. It was cooled to room temperature, diluted with ethyl acetate, filtered through celite, and concentrated to dryness under reduced pressure. Silica gel chromatography with hexanes/ethyl acetate (7:3) afforded product, 1 g (79%).

MS (ES): 180.15 (MH⁺) for C₇H₆NO₃

¹H-NMR (CDCl₃-d) δ: 3.75 (s, 3H); 4.55 (s, 2H); 6.40 (d, 1H); 6.50 (dd, 1H); 6.89 (d, 1H); 8.85 (bs, 1H).

Intermediate 49: Ethyl (4-methoxy-2-nitrophenoxy)acetate

A mixture of 4-methoxy-2-nitrophenol (2 g, 11.8 mmol), caesium carbonate (7.7 g, 23.6 mmol) and 2-bromo ethyl acetate (1.31 mL, 11.8 mmol) in acetone (50 mL) was heated at 50°C overnight. The mixture was heated at 55°C for an additional 1 hour, then filtered and concentrated to dryness under reduced pressure. Silica gel chromatography with hexanes/ethyl acetate (4:1) afforded product, 1.8 g (60%).

MS (ES): 256.26 (MH⁺) for C₁₁H₁₃NO₆

¹H-NMR (CDCl₃-d) δ: 1.28 (t, 3H); 3.81 (s, 3H); 4.25 (q, 2H); 4.70 (s, 2H); 7.04 (m, 2H); 7.39 (d, 1H).
Example 22

6-{[(1-{[2-(6-Methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoazain-4-yl)ethyl]piperidin-4-yl}amino)methyl]-2H-pyridin[3,2-b][1,4]oxazin-3(4H)-one}

4-{(4-aminopiperidin-1-yl)ethyl}-6-methoxy-2H-1,4-benzoazain-3(4H)-one

trifluoroacette (Intermediate 46) (0.4 mmol), 3-oxo-3,4-dihydro-2H-pyridin[3,2-b][1,4]oxazin-6-carbaldehyde (WO 2004/058144) (80 mg, 0.44 mmol) and sodium cyanoborohydride were reacted as described under Example 21, but, the reaction was stirred at room temperature overnight after sodium cyanoborohydride addition to give the title compound as a free base, 30 mg (17%).

MS (ES): 468.27 (MH+) for C24H26N4O5,

1H-NMR (CDCl3-d) δ: 1.56 (m, 2H); 1.96 (m, 2H); 2.18 (m, 3H); 2.62 (m, 3H); 3.91 (m, 2H); 3.79 (s, 3H); 3.84 (s, 2H); 4.06 (m, 2H); 4.51 (s, 2H); 6.51 (1H); 6.67 (s, 1H); 6.89 (1H); 6.95 (1H); 7.20 (1H).

Example 23

6-{[(1-{[2-(6-Methoxy-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl)ethyl]piperidin-4-yl}amino)methyl]-2H-pyridin[3,2-b][1,4]oxazin-3(4H)-one}

4-{(4-aminopiperidin-1-yl)ethyl}-6-methoxy-2H-1,4-benzothiazin-3(4H)-one

(Intermediate 50) (0.9 mmol), 3-oxo-3,4-dihydro-2H-pyridin[3,2-b][1,4]oxazin-6-carbaldehyde (WO 2004/058144) (190 mg, 1.1 mmol) and sodium cyanoborohydride (110 mg, 1.77 mmol) were reacted as described under Example 21, with stirring for 2.5 hours at room temperature after sodium cyanoborohydride addition. The title compound was obtained as a solid, 52 mg (13%).

MS (ES): 454.26 (MH+) for C24H25N4O5S

1H-NMR (CDCl3-d) δ: 1.49 (m, 2H); 1.91 (m, 3H); 2.16 (m, 2H); 2.54 (m, 1H); 2.61 (m, 2H); 2.96 (m, 2H); 3.33 (s, 2H); 3.81 (s, 5H); 4.09 (m, 2H); 4.63 (s, 2H); 6.58 (dd, 1H); 6.87 (d, 1H); 6.93 (d, 1H); 7.20 (d, 1H); 7.24 (d, 1H).

Intermediate 50: 4-{(4-aminopiperidin-1-yl)ethyl}-6-methoxy-2H-1,4-benzothiazin-3(4H)-one

tert-Butyl {1-{[2-(6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl)ethyl]piperidin-4-yl}carbonate (Intermediate 51) (750 mg, 1.78 mmol) was reacted as
described for Intermediate 14. The crude trifluoroacetate of the title compound was used without further purification for the next step (quantitative yield).

**MS (ES):** 322 (M+H) for C_{16}H_{13}N_{2}O_{3}S

**Intermediate 51: tert-Butyl [1,2-(4-methoxy-2-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl)ethyl]piperezin-4-yl]carbonate**

6-Methoxy-2H-1,4-benzothiazin-3(4H)-one (Intermediate 52) (410 mg, 2.1 mmol) was deprotonated with sodium hydride (100 mg, 60% in oil, 2.5 mmol) and alkylated with 2-{4-[( tert-butoxycarbonylamino)piperezin-1-yl]ethyl} methanesulfonate (Intermediate 6) (2.3 mmol) as described for Intermediate 2. Chromatography on silica gel with hexanes/ethyl acetate (1:3) afforded 750 mg (85%) of the product.

**MS (ES):** 422.24 (M+H) for C_{21}H_{31}N_{2}O_{4}S

**{H-NMR (CDCl_{3-}) δ:}** 1.40 (m, 2H); 1.45 (s, 9H); 1.92 (m, 2H); 2.22 (m, 2H); 2.62 (t, 2H); 2.88 (m, 2H); 3.35 (s, 2H); 3.49 (m, 1H); 3.82 (s, 3H); 4.08 (t, 2H); 4.43 (m, 1H); 6.61 (dd, 1H); 6.86 (d, 1H); 7.28 (s, 1H).

**Intermediate 52: 6-Methoxy-2H-1,4-benzothiazin-3(4H)-one**

Prepared from ethyl [(4-methoxy-2-nitrophenyl)thio]acetate (Intermediate 53, 3 g, 11 mmol) according to procedure described for preparation of Intermediate 48. Silica gel chromatography with hexanes/ethyl acetate (3:2) afforded desired product, 2 g (93%).

**MS (ES):** 196.12 (M+H) for C_{9}H_{10}NO_{3}S

**{H-NMR (CDCl_{3-}) δ:}** 3.39 (s, 2H); 3.78 (s, 2H); 6.44 (d, 1H); 6.59 (dd, 1H); 7.30 (d, 1H); 8.63 (bs, 1H).

**Intermediate 53: Ethyl [(4-methoxy-2-nitrophenyl)thio]acetate**

Ethyl mercaptoacetate (2.3 mL, 21.5 mmol) was dissolved in DMF (20 mL) and cooled to 0°C. Sodium hydride (1 g, 60% in oil, 25.8 mmol) was added and the reaction was stirred for 1 hour. Then a solution of 1-bromo-4-methoxy-2-nitrobenzene (5 g, 21.5 mmol) in DMF (20 mL) was added at 0°C. The reaction mixture was allowed to warm to room temperature and stirred overnight. It was diluted with ethyl acetate, washed with water (four times) and with brine and then dried over magnesium sulfate. Silica gel chromatography with hexanes/ethyl acetate (4:1) afforded the product, 3 g (52%).

**MS (ES):** 272.14 (M+H) for C_{11}H_{11}NO_{3}S
$^1$H-NMR (CDCl$_3$-d): 6: 1.24 (t, 3H); 3.68 (s, 2H); 3.85 (s, 3H); 4.18 (q, 2H); 7.15 (dd, 1H); 7.47 (d, 1H); 7.65 (d, 1H).

Example 24

4-(2-{4-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino)piperidin-1-yl}ethyl)-6-methoxy-2H-1,4-benzothiazin-3(4H)-one

4-[2-{4-Aminopiperidin-1-yl}ethyl]-6-methoxy-2H-1,4-benzothiazin-3(4H)-one

(Intermediate 50) (0.9 mmol), 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde (WO 2004/058144) (130 mg, 1.1 mmol), and sodium cyanoborohydride (110 mg, 1.76 mmol) were reacted as described under Example 21 to give 55 mg (13%) product as a dry film.

MS (ES): 471.26 (MH$^+$) for C$_{24}$H$_{30}$N$_2$O$_6$S

$^1$H-NMR (CDCl$_3$-d): 6: 1.47 (m, 2H); 1.91 (m, 2H); 2.15 (m, 2H); 2.54 (m, 1H); 2.60 (t, J = 6.4 Hz, 2H); 2.94 (m, 2H); 3.33 (s, 2H); 3.47 (s, 2H); 3.80 (s, 5H); 4.08 (t, 2H); 4.29 (m, 4H); 6.58 (dd, 1H); 6.80 (s, 1H); 6.88 (d, 1H); 7.23 (d, 1H); 8.08 (s, 1H).

Example 25

6-[(1-{2-[(6-Fluoro-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)methyl]piperidin-1-yl}amino)methyl]-2H-pyrido[3,2-b]1,4]oxazin-3(4H)-one

4-[2-{4-Aminopiperidin-1-yl}ethyl]-6-fluoro-2H-1,4-benzoxazin-3(4H)-one

(Intermediate 54), (0.7 mmol), 3-oxo,3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (150 mg, 0.84 mmol) and sodium cyanoborohydride (90 mg, 1.4 mmol) were reacted as described under Example 21 to give 51 mg (16%) product as a solid.

MS (ES): 456.24 (MH$^+$) for C$_{21}$H$_{26}$FN$_4$O$_4$

$^1$H-NMR (CDCl$_3$-d): 6: 1.52 (m, 2H); 1.94 (m, 2H); 2.15 (m, 2H); 2.57 (m, 1H); 2.59 (t, J = 7.1 Hz, 2H); 2.97 (m, 2H); 3.84 (s, 2H); 4.01 (t, J = 7.1 Hz, 2H); 4.54 (s, 2H); 4.62 (s, 2H); 6.68 (m, 1H); 6.86 (m, 1H); 6.89 (m, 1H); 6.95 (d, J = 8.1 Hz, 1H); 7.20 (d, J = 8.1 Hz, 1H).

Intermediate 54: 4-(2-{4-Aminopiperidin-1-yl}ethyl)-6-fluoro-2H-1,4-benzoxazin-3(4H)-one

$t$-Butyl {1-{2-[(6-fluoro-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)methyl]piperidin-4-yl} carbamate (Intermediate 55) (640 mg, 1.56 mmol) was reacted as described for
Intermediate 14. The crude trifluoro acetate of the title compound was used without further purification for the next step (quantitative yield).

\[ \text{MS (ES): 294 (M\text{H}^+ \text{ for C}_{13}\text{H}_{20}\text{FN}_5\text{O}_2} \]

5

**Intermediate 55: tert-Butyl \((\text{1-[2-[6-fluoro-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl]ethyl)piperidin-4-yl}))/carbamate**

Commercially available 6-fluoro-2H-1,4-benzoxazin-3(4H)-one (350 mg, 2.1 mmol) was deprotonated with sodium hydride and alkylated with 2-\{4-\[(\text{tert-butoxycarbonyl} \text{amino})\text{piperidin-1-yl})\}ethyl methanesulfonate (Intermediate 6) (2.3 mmol) as described for Intermediate 2. Chromatography on silica gel with hexanes/ethyl acetate (1:1) gave 550 mg (67%) product.

\[ \text{MS (ES): 394.26 (M\text{H}^+) \text{ for C}_{23}\text{H}_{22}\text{FN}_4\text{O}_4} \]

\[ ^1\text{H-NMR (CDCl}_3\text{)}: 5 \text{: 1.39 (m, 2H); 1.43 (s, 9H); 1.92 (m, 2H); 2.20 (m, 2H); 2.58 (t, 2H); 2.88 (m, 2H); 3.45 (m, 1H); 3.98 (t, 2H); 4.14 (m, 1H); 4.55 (s, 2H); 6.68 (m, 1H); 6.85 (m, 1H); 6.91 (m, 1H).} \]

Example 26

4-(2-\{4-\[(2,3-Dihydro1,4)dioxino[2,3-c\text{]pyridin-7-yl}methyl)amino\text{piperidin-1-yl}\}ethyl)-6-fluoro-2H-1,4-benzoxazin-3(4H)-one

4-[2-(4-Aminopiperidin-1-yl)ethyl]-6-fluoro-2H-1,4-benzoxazin-3(4H)-one

(Intermediate 54) (0.7 mmol), 2,3-dihydro[1,4]dioxino[2,3-c\text{]pyridine-7-carbaldehyde (WO 2004/058144) (140 mg, 0.84 mmol), and sodium cyanoborohydride (90 mg, 1.4 mmol) were reacted as described under Example 21 to give 100 mg (32%) product.

\[ \text{MS (ES): 443.24 (M\text{H}^+) \text{ for C}_{23}\text{H}_{22}\text{FN}_4\text{O}_4} \]

\[ ^1\text{H-NMR (CDCl}_3\text{)}: 5 \text{: 1.46 (m, 2H); 1.90 (m, 2H); 2.13 (m, 2H); 2.53 (m, 1H); 2.57 (t, 2H); 2.93 (m, 2H); 3.80 (s, 2H); 3.99 (t, 2H); 4.29 (m, 4H); 4.54 (s, 2H); 6.67 (td, 1H); 6.81 (s, 1H); 6.96 (dd, 1H); 7.16 (dd, 1H); 8.00 (s, 1H).} \]

Example 27

6-[(1-[2-(6-Chloro-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl)piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

4-[2-(4-Aminopiperidin-1-yl)ethyl]-6-chloro-2H-1,4-benzoxazin-3(4H)-one

(Intermediate 56) (0.8 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-
carbaldhyde (WO 2004/058144) (150 mg, 0.84 mmol) and sodium cyanoborohydride (90 mg, 1.4 mmol) were reacted as described under Example 21 to give 78 mg (21%) product as a solid.

MS (ES): 472.24 (MH⁺) for C_{23}H_{25}ClN_{3}O_{4}

¹H-NMR (CDCl₃-d) δ: 1.50 (m, 2H); 1.93 (m, 3H); 2.15 (m, 2H); 2.56 (m, 1H); 2.59 (1, 2H); 2.96 (m, 2H); 3.82 (s, 2H); 4.01 (t, 2H); 4.56 (s, 2H); 4.63 (s, 2H); 6.92 (m, 3H); 7.12 (d, 1H); 7.20 (d, 1H).

Intermediate 56: 4-[2-(4-Aminopiperidin-1-yl)ethyl]-6-chloro-2H-1,4-benzoxazin-3(4H)-one

tert-Butyl [1-[2-(6-chloro-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl] carbamate (Intermediate 57) (640 mg, 1.56 mmol) was reacted as described for Intermediate 14. The crude trifluoro acetate of the title compound was used without further purification for the next step (quantitative yield).

MS (ES): 310 (MH⁺) for C_{13}H_{16}ClN_{2}O_{2}

Intermediate 57: tert-Butyl [1-[2-(6-chloro-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl] carbamate

Commercially available 6-chloro-2H-1,4-benzoxazin-3(4H)-one (380 mg, 2.1 mmol) was deprotonated with sodium hydride and alkylation with 2-[4-[(tert-butoxycarbonyl)amino]piperidin-1-yl] ethyl methanesulfonate (Intermediate 6) (2.3 mmol) as described for Intermediate 2. Chromatography on silica gel with hexanes/ethyl acetate (1:1) gave 640 mg (74%) product.

MS (ES): 410.22 (MH⁺) for C_{23}H_{25}ClN_{3}O_{4}

¹H-NMR (CDCl₃-d) δ: 1.43 (m, 2H); 1.43 (s, 9H); 1.92 (m, 2H); 2.21 (m, 2H); 2.58 (m, 2H); 2.88 (m, 2H); 3.45 (m, 1H); 3.99 (m, 2H); 4.41 (m, 1H); 4.56 (s, 2H); 6.91 (m, 2H); 7.13 (s, 1H).

Example 28

6-\{(1-[2-(6-Methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl)amino\}methyl\}2H-pyrido[3,2-b][1,4]thiazin-3(4H)-one

4-[2-(4-Aminopiperidin-1-yl)ethyl]-5-methoxy-2H-1,4-benzoxazin-3(4H)-one (Intermediate 46) (0.2 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-
carbaldehyde (WO 2004/058144) (4.2 mg, 0.22 mmol) and sodium cyanoborohydride (23 mg, 0.36 mmol) were reacted as described under Example 21 to give 28 mg (32%) of product as a dry film.

\[
\text{MS (ES)}: 484.27 (M^+ \text{ for } C_{26}H_{39}N_3O_2S}
\]

\[
{^1}H\text{-NMR (CDCl}_3\text{-d)} \delta: 1.50 (m, 2H); 1.92 (m, 2H); 2.17 (m, 3H); 2.55 (m, 1H); 2.61 (m, 2H); 2.98 (m, 2H); 3.46 (s, 2H); 3.78 (s, 3H); 3.84 (s, 2H); 4.04 (m, 2H); 4.51 (s, 2H); 6.50 (dd, 1H); 6.67 (d, 1H); 6.89 (d, 1H); 6.98 (d, 1H); 7.57 (d, 1H).
\]

**Example 29**

3-Oxo-4-[2-(4-[[3-oxo-3,4-dihydro-2H-pyrido][3,2-b][1,4]oxazin-6-yl)methyl]amino]piperidin-1-yl]ethyl]3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile

4-[2-[4-aminopiperidin-1-yl]ethyl]3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile (Intermediate 58) (0.8 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-carbaldehyde (WO 2004/058144) (140 mg, 0.79 mmol) and sodium cyanoborohydride (83 mg, 1.32 mmol) were reacted as described under Example 21 to give 60 mg (19%) product as a solid.

\[
\text{MS (ES)}: 463.32 (M^+ \text{ for } C_{19}H_{26}N_4O_4}
\]

\[
{^1}H\text{-NMR (CDCl}_3\text{-d)} \delta: 1.49 (m, 2H); 1.94 (m, 2H); 2.14 (m, 2H); 2.56 (m, 1H); 2.59 (t, J = 6.7 Hz, 2H); 2.94 (m, 2H); 3.84 (s, 2H); 4.03 (t, 2H); 4.62 (s, 2H); 4.67 (s, 2H); 6.94 (d, 1H); 7.03 (d, 1H); 7.19 (d, 1H); 7.30 (dd, 1H); 7.46 (d, 1H).
\]

**Intermediate 58**: 4-[2-(4-Aminopiperidin-1-yl)ethyl]3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile trifluoroacetate

tert-Butyl [1-(2-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl]carbamate (Intermediate 59) (610 mg, 1.52 mmol) was reacted as described for Intermediate 14. The crude trifluoroacetate of the title compound was used without further purification for the next step (quantitative yield).

\[
\text{MS (ES)}: 301 (M^+ \text{ for } C_{10}H_{26}N_4O_2}
\]

**Intermediate 59**: tert-Butyl [1-(2-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl]carbamate

3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile (Intermediate 60) (350 mg, 2.0 mmol) was deprotonated with sodium hydride and acylated with 2-[(tert-
butoxycarbonylamino[piperidin-1-yl]ethyl methanesulfonate (Intermediate 6) (2.2 mmol) as described for Intermediate 2. Chromatography on silica gel with hexanes/ethyl acetate (1:3) afforded 610 mg (75%) of the product.

\[ \text{MS (ES)}: 401.27 (M+H\textsuperscript{+}) \text{ for C}_{21}H_{29}N_4O_5 \]

\[ ^{1}H\text{-NMR (CDCl}_3\text{-d)} \delta: 1.41 (m, 2H); 1.42 (s, 9H); 1.93 (m, 2H); 2.21 (m, 2H); 2.58 (m, 2H); 2.87 (m, 2H); 3.45 (m, 1H); 4.02 (m, 2H); 4.43 (m, 1H); 4.67 (s, 2H); 7.03 (d, 1H); 7.30 (m, 1H); 7.47 (s, 1H). \]

**Intermediate 6b: 3-Oxo-3,4-dihydro-2H-[1,4]-benzoxazine-6-carbonitrile**

The title compound was prepared similarly to literature procedure (Calicchio, G. et al., *Bioorg. Med. Chem. Lett.*, 2002, 12, 2663), but in one step. Commercially available 3-amino-4-hydroxybenzonitrile (2.5 g, 18.6 mmol) was dissolved in chloroform (300 mL) and saturated sodium bicarbonate (90 mL). The biphasic reaction mixture was cooled to 0°C and bromoacetyl bromide (2.4 mL, 28 mmol) was added dropwise. The reaction was stirred overnight at room temperature. The layers were separated and the aqueous layer was filtered to yield the desired product as a tan solid, 2.3 g (69%).

\[ \text{MS (ES)}: 175.11 (M+H\textsuperscript{+}) \text{ for C}_{5}H_{12}N_2O_2 \]

\[ ^{1}H\text{-NMR (DMSO-d}_6\text{-d)} \delta: 4.70 (s, 2H); 7.11 (d, 1H); 7.19 (d, 1H); 7.40 (m, 1H); 10.98 (bs, 1H). \]

**Example 30**

6-[(1-(2-[3-Oxo-6-(trifluoromethyl)-2,3-dihydro-4H-1,4-benzoxazin-4-yl]ethyl)piperidin-1-yl)amino[methyl]-2H-pyrido[3,2-b]1,4]oxazine-3(4H)-one (Intermediate 61) (0.55 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (120 mg, 0.66 mmol) and sodium cyanoborohydride (69 mg, 1.1 mmol) were reacted as described under Example 21 to give 44 mg (15%) product as a solid.

\[ \text{MS (ES)}: 522.25 (M+H\textsuperscript{+}) \text{ for C}_{24}H_{29}F_2N_3O_5 \]

\[ ^{1}H\text{-NMR (CDCl}_3\text{-d)} \delta: 1.53 (m, 2H); 1.95 (m, 2H); 2.14 (m, 2H); 2.59 (t, 2H); 2.59 (m, 1H); 2.96 (m, 2H); 3.85 (s, 2H); 4.02 (t, 2H); 4.59 (s, 2H); 4.63 (s, 2H); 6.35 (d, 1H); 6.96 (d, 3H); 6.97 (d, 1H); 7.20 (d, 1H). \]
Intermediate 61: 4-[2-(4-Aminopiperidin-1-yl)ethyl]-6-(trifluoromethoxy)-2H-1,4-benzoazin-3(4H)-one

tert-Butyl (1·2-[3-oxo-6-(trifluoromethoxy)-2,3-dihydro-4H-1,4-benzoazin-4-yl]piperidin-4-yl)carbonate (Intermediate 62) (790 mg, 1.72 mmol) was reacted as described for Intermediate 14. The crude trifluoroacetate of the title compound was used without further purification for the next step (quantitative yield).

MS (ES): 360 (MH+) for C_{19}H_{29}F_{3}N_{3}O_{5}

Intermediate 62: tert-Butyl (1·2-[3-oxo-6-(trifluoromethoxy)-2,3-dihydro-4H-1,4-benzoazin-4-yl]piperidin-4-yl)carbonate

6-(Trifluoromethoxy)-2H-1,4-benzoazin-3(4H)-one (Intermediate 63) (490 mg, 2.0 mmol) was deprotonated with sodium hydride and alkylated with 2-[4-[(tert-butoxycarbonylamino)piperidin-1-yl]ethyl methanesulfonate (Intermediate 6) (2.2 mmol) as described for Intermediate 2. Chromatography on silica gel with hexanes/ethyl acetate (2:3) afforded 790 mg (86%) of the product.

MS (ES): 460.26 (MH+) for C_{21}H_{29}F_{3}N_{3}O_{5}

{^1}H-NMR (CDCl_{3}) δ: 1.38 (m, 2H); 1.43 (s, 9H); 1.92 (m, 2H); 2.20 (m, 2H); 2.57 (m, 2H); 2.87 (m, 2H); 3.45 (m, 1H); 4.00 (m, 2H); 4.41 (m, 1H); 4.58 (s, 2H); 6.85 (m, 1H); 6.95 (s, 1H); 6.99 (m, 1H).

Intermediate 63: 6-(Trifluoromethoxy)-2H-1,4-benzoazin-3(4H)-one

Ethyl [2-nitro-4-(trifluoromethoxy)phenoxy]acetate (Intermediate 64) (1.14 g, 3.7 mmol) and iron powder (510 mg, 9.2 mmol) were reacted according to procedure for Intermediate 48, but heating for only one hour. Silica gel chromatography with hexanes/ethyl acetate (4:1) afforded product, 770 mg (90%).

MS (ES): 234.16 (MH+) for C_{9}H_{8}F_{3}NO_{3}

{^1}H-NMR (CDCl_{3}) δ: 4.63 (s, 2H); 6.73 (m, 1H); 6.84 (m, 1H); 6.97 (m, 1H); 8.93 (bs, 1H).

Intermediate 64: Ethyl [2-nitro-4-(trifluoromethoxy)phenoxy]acetate

Prepared from 2-nitro-4-(trifluoromethoxy)phenol (2 g, 8.9 mmol) according to procedure for Intermediate 49. Silica gel chromatography with hexanes/ethyl acetate (4:1) afforded product, 1.14 g (41%).
Example 31

6-[[1-2-[6-Fluoro-3-oxo-2,3-dihydro-4H-1,4-benzoazin-4-yl)ethyl]piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]thiazin-3(4H)-one

Example 32

4-[2-(4-Aminopiperidin-1-yl)ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoazin-6-carbonitrile

(Intermediate 58) (2.8 mmol), 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde (WO 2004/058144) (550 mg, 3.36 mmol), and sodium cyanoborohydride (350 mg, 5.6 mmol) were reacted as described under Example 21 to give the crude free base. The product was precipitated from chloroform by addition of 2M HCl in ether. The precipitate was collected by filtration to give title compound as the bis HCl salt, 420 mg.
Example 33

\[
\begin{align*}
6-[(1-[2-\text{(6-Bromo-3-oxo-2,3-dihydro-4H-1,4-benzoazizin-4-yl)ethyl]piperidin-4-yl}amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one \\
4-\text{[2-(4-Aminopiperidin-1-yl)ethyl]-6-bromo-2H-1,4-benzoazizin-3(4H)-one}
\end{align*}
\]

(Intermediate 65) (0.57 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (120 mg, 0.67 mmol) and sodium cyanoborohydride (72 mg, 1.14 mmol) were reacted as described under Example 21 to give 65 mg (22%) product as a solid.

\[
\text{MS (ES): 516.22 (M+)} \text{ for C}_{28}\text{H}_{28}\text{BrN}_{3}\text{O}_{4}
\]

\[
\text{H-NMR (CDCl}_{3}\text{):}$
\begin{align*}
5.15 (s, 2H); 1.93 (m, 2H); 2.14 (m, 2H); 2.57 (m, 1H); 2.59 (t, 2H); 2.96 (m, 2H); 3.83 (s, 2H); 4.00 (t, 2H); 4.56 (s, 2H); 4.63 (s, 2H); 6.84 (d, 1H); 6.95 (d, 1H); 7.08 (dd, 1H); 7.20 (d, 1H); 7.27 (d, 1H).
\end{align*}
\]

(Intermediate 65: 4-[[2-(4-Aminopiperidin-1-yl)ethyl]-6-bromo-2H-1,4-benzoazizin-3(4H)-one]

\[
\text{tert-Butyl } \text{[1-[2-\text{(6-bromo-3-oxo-2,3-dihydro-4H-1,4-benzoazizin-4-yl)ethyl]piperidin-4-yl}] carbamate (Intermediate 66) (261 mg, 0.57 mmol) was reacted as described for Intermediate 14. The crude trifluoro acetate of the title compound was used without further purification for the next step (quantitative, yield)}.
\]

\[
\text{MS (ES): 354 (M+)} \text{ for C}_{35}\text{H}_{27}\text{BrN}_{3}\text{O}_{2}
\]

(Intermediate 66: tert-Butyl [1-[2-(6-bromo-3-oxo-2,3-dihydro-4H-1,4-benzoazizin-4-yl)ethyl]piperidin-4-yl] carbamate

\[
\text{6-Bromo-2H-1,4-benzoazizin-3(4H)-one (Intermediate 67) (200 mg, 0.37 mmol) was}
\]

deprotonated with sodium hydride and alkylated with 2-\text{[4-\text{[(tert-butoxycarbonyl)amino]piperidin-1-yl}]ethyl methanesulfonate (Intermediate 6) (0.96 mmol) as described for Intermediate 2. Chromatography on silica gel with hexanes/ethyl acetate (1:3) afforded 261 mg (67%) product.

(Intermediate 67: 6-Bromo-2H-1,4-benzoazizin-3(4H)-one

\[
\text{2-Amino-4-bromophenol (2.1 g, 11 mmol) and bromo acetyl bromide (1.4 mL, 16.5 mmol) were reacted according to the procedure for Intermediate 60 to afford product as a solid, 2.1 g (85%).}
\]


Example 34

6-[(1-[2-(6-Hydroxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

A solution of 6-[(1-[2-(6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one (Example 22) (100 mg, 0.21 mmol) in dichloromethane was cooled to -78°C and treated with 1M boron tribromide (0.63 mL, 0.63 mmol) dropwise. The reaction mixture was stirred at room temperature overnight. The reaction mixture was cooled to -78°C and an additional 1 equivalent of 1M boron tribromide was added. The reaction was stirred for 4 hours at room temperature, and then quenched with saturated sodium bicarbonate. The organic layer was separated and the aqueous phase was extracted three times with dichloromethane. The combined organic extracts were dried over magnesium sulfate and concentrated to dryness under reduced pressure to afford crude product, 11 mg (11%), as a solid.

MS (ES): 454.35 (MH⁺) for C₂₃H₂₇N₃O₃

¹H-NMR (DMSO-d₆) δ: 1.47 (m, 2H); 1.98 (m, 4H); 2.94 (m, 3H); 3.94 (m, 4H); 4.49 (s, 2H); 4.66 (s, 2H); 6.38 (dd, J = 6.0, 2.5 Hz, 1H); 6.60 (d, J = 2.2 Hz, 1H); 6.80 (d, J = 8.7 Hz, 1H); 7.12 (d, J = 8.1 Hz, 1H); 7.40 (d, J = 8.3 Hz, 1H); 9.33 (s, 1H); 11.29 (s, 1H).

Example 35

4-[(2-Difluorophenyl)cyclopropyl](methyl)amino)piperidin-1-yl)ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-carbonitrile

4-[2-(4-Aminopiperidin-1-yl)ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-carbonitrile (Intermediate 58) (1 mmol), 2-(2,5-difluorophenyl)cyclopropanocarbaldehyde (Intermediate 68) (200 mg, 1.1 mmol) and sodium cyanohydride (125 mg, 2 mmol) were reacted as described under Example 21 to give 196 mg (42%) product as a gum.

MS (ES): 506.35 (MH⁺) for C₂₆H₂₅F₂N₄O₂

¹H-NMR (CDCl₃-d) δ: 0.94 (m, 2H); 1.31 (m, 1H); 1.41 (m, 2H); 1.89 (m, 3H); 2.13 (m, 2H); 2.55 (m, 1H); 2.57 (t, 2H); 2.70 (d, 2H); 2.92 (m, 2H); 4.03 (t, 2H); 4.67 (s, 2H); 6.55 (m, 1H); 6.77 (m, 1H); 6.93 (m, 1H); 7.03 (d, 1H); 7.30 (dd, 1H); 7.38 (d, 1H).
Intermediate 68: 2-(2,5-Difluorophenyl)cyclopropane-carboxaldehyde

To a solution of oxalyl chloride (1.2 mL, 13.5 mmol) in dichloromethane at -78°C was added dimethyl sulfoxide (1.9 mL, 27 mmol) dropwise and it was stirred at -78°C for 30 minutes. A solution of [2-(2,5-difluorophenyl)cyclopropyl]methanol (Intermediate 69) (830 mg, 4.5 mmol) in dichloromethane was added dropwise. The reaction mixture was stirred at -78°C for 30 minutes. Triethylamine (6.3 mL, 45 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure. Silica gel chromatography with hexanes/ethyl acetate (9:1) afforded the desired product, 546 mg (66%).

GC/MS: 182 (M+) for C\textsubscript{10}H\textsubscript{4}F\textsubscript{2}O

\textsuperscript{1}H-NMR (CDCl\textsubscript{3}-d): 1.52 (m, 1H); 1.73 (m, 1H); 2.17 (m, 1H); 2.73 (m, 1H); 6.65 (m, 1H); 6.87 (m, 1H); 6.98 (m, 1H); 9.36 (d, 1H).

Intermediate 69: [2-(2,5-Difluorophenyl)cyclopropyl]methanol

To a solution of (2E)-3-(2,5-difluorophenyl)prop-2-en-1-ol (Intermediate 70) (2.12 g, 12.5 mmol) in dichloromethane at -10°C was added dropwise diethyl zinc (1M, 75 mL, 75 mmol) over 20 minutes. Diodomethane (6 mL, 75 mmol) was added and the reaction mixture was stirred at room temperature overnight. Saturated ammonium chloride was added carefully to quench the reaction. The reaction mixture was diluted with diethyl ether and the layers were separated. The organic phase was washed with 10% aqueous hydrochloric acid, saturated sodium bicarbonate and brine, then dried over magnesium sulfate and concentrated to dryness under reduced pressure. Silica gel chromatography with hexanes/ethyl acetate (4:1) afforded the product, 940 mg (41%).

GC/MS: 184 (M+) for C\textsubscript{10}H\textsubscript{16}F\textsubscript{2}O

\textsuperscript{1}H-NMR (DMSO-d\textsubscript{6})\: δ: 0.92 (m, 2H); 1.36 (m, 1H); 1.91 (m, 1H); 3.43 (m, 2H); 4.64 (t, 1H); 6.82 (m, 1H); 6.97 (m, 1H); 7.15 (m, 1H).

Intermediate 70: (2E)-3-(2,5-Difluorophenyl)acryl acid

A mixture of (2E)-3-(2,5-difluorophenyl)acrylic acid (1 g, 5.43 mmol) and N,N-diisopropylethylamine (1.7 mL, 9.8 mmol) in tetrahydrofuran (THF) was treated with isobutyl chloroformate (1.4 mL, 10.8 mmol) at room temperature. The reaction mixture was stirred for 30 minutes, and then filtered. The filtrate was cooled to 0°C and 2M lithium borohydride (4.1 mL, 8.2 mmol) was added dropwise. The reaction mixture was stirred at 0°C for 30 minutes.
then at room temperature for 30 minutes. Ice and 1N hydrochloric acid were added to the reaction mixture to adjust the pH to 7. The aqueous layer was extracted with ethyl acetate twice. The combined organic extracts were dried over sodium sulfate and concentrated to dryness under reduced pressure. Silica gel chromatography with hexanes/ethyl acetate (3:2) afforded desired product, 750 mg (82%).

**GC/MS:** 170 (M⁺) for C₉H₁₅F₂O

**¹H-NMR (DMSO-d₆)**: δ: 4.15 (t, 2H); 5.01 (t, 1H); 6.61 (m, 2H); 7.10 (m, 1H); 7.23 (m, 1H); 7.48 (m, 1H).

**Example 36**

6-[(1-[2-(6,8-difluoro-3-oxo-2,3-dihydro-4H-1,4-benzoazoxin-4-yl)ethyl]piperidin-4-y]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazine-3(4H)-one

4-[2-(4-Aminopiperidin-1-yl)ethyl]-6,8-difluoro-2H-1,4-benzoazoxin-3(4H)-one

(Intermediate 71) (1 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (220 mg, 1.24 mmol) and sodium cyanoborohydride (130 mg, 2.1 mmol) were reacted as described for Example 21 to give 41 mg (8%) product as a dry film.

**MS (ES):** 474.26 (M⁻) for C₂₃H₂₁F₂N₅O₄

**¹H-NMR (DMSO-d₆):** δ: 1.19 (m, 2H); 1.74 (m, 2H); 1.96 (m, 3H); 3.34 (m, 1H); 2.42 (m, 2H); 2.82 (m, 2H); 3.65 (s, 2H); 3.97 (m, 2H); 4.59 (s, 2H); 4.70 (s, 2H); 7.06 (d, 1H); 7.09 (m, 2H); 7.23 (d, 1H); 11.16 (s, 1H).

**Intermediate 71:** 4-[2-(4-Aminopiperidin-1-yl)ethyl]-6,8-difluoro-2H-1,4-benzoazoxin-3(4H)-one

tert-Butyl {1-[2-(6,8-difluoro-3-oxo-2,3-dihydro-4H-1,4-benzoazoxin-4-yl)ethyl]piperidin-4-yl} carbamate (Intermediate 72) (423 mg, 1 mmol) was reacted as described for Intermediate 14. The crude trifluoro acetate of the title compound was used without further purification for the next step (quantitative yield).

**MS (ES):** 312.2 (M⁻) for C₁₃H₁₉F₂N₅O₂
Intermediate 72: tert-Butyl (E)-2-(6,8-difluoro-3-oxo-2,3-dihydro-4H-1,4-benzoazin-4-yl)ethyl)piperidin-4-yl)carbamate

6,8-difluoro-2H-1,4-benzoazin-3(4H)-one (Intermediate 73) (205 mg, 1.11 mmol) was deprotonated with sodium hydride and alkylated with 2-(4-[[tert-
butyloxycarbonyl]amino]piperidin-1-yl)ethyl methanesulfonate (Intermediate 6) (1.2 mmol) as described for Intermediate 2. Chromatography on silica gel with hexanes/ethyl acetate (1:3) afforded 423 mg (92%) product.

**MS (ES):** 412.36 (MH+) for C_{29}H_{27}F_{2}N_{5}O_{4}

Intermediate 73: 6,8-Difluoro-2H-1,4-benzoazin-3(4H)-one

Commercially available 2-amino-4,6-difluorophenol (1 g, 6.9 mmol) and bromo acetyl bromide (0.9 mL, 10.3 mmol) were reacted according to the procedure for Intermediate 60 to afford the product as a solid, 208 mg (16%).

**MS (ES):** 184.34 (M-H) for C_{8}H_{5}F_{2}NO_{2}

**{H-NMR (DMSO-d_{6}):** 5: 4.64 (s, 2H); 6.55 (m, 1H); 6.94 (m, 1H): 10.99 (s, 1H).

Example 37

4-[2-(4-[[{2E}-3-(2,5-Difluorophenyl)prop-2-en-1-yl]amino]piperidin-1-yl)ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoazin-6-carbonitrile

**MS (ES):** 453 (MH+) for C_{33}H_{28}N_{4}O_{2}

**{H-NMR (CDCl_{3}):** 5: 1.43 (q, 2H); 1.93 (d, 2H); 2.15 (t, 2H); 2.58 (t, 3H); 2.93 (d, 2H); 3.48 (d, 2H); 4.03 (t, 2H); 4.67 (s, 2H); 6.35 (dt, 1H); 6.65 (d, 1H); 6.88 (m, 1H); 6.96 (m, 1H); 7.03 (d, 1H); 7.12 (m, 1H); 7.30 (dd, 1H); 7.40 (d, 1H).
Example 38

6-[[trans-4-[2-(6-Methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]cyclohexyl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

4-[2-(trans-4-amino)cyclohexyl]ethyl]-6-methoxy-2H-1,4-benzoxazin-3(4H)-one

(Intermediate 74) (310 mg, 1.73 mmol) 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (1.73 mmol) and sodium cyanoborohydride were reacted as described under Example 21 to give 110 mg (24%) product.

MS (ES): 467 (MH+) for C_{23}H_{29}N_2O_3

^1H-NMR (CDCl_3) δ: 1.05 (q, 2H); 1.19 (d, 2H); 1.35 (m, 1H); 1.53 (q, 2H); 1.86 (d, 2H); 2.00 (d, 2H); 2.47 (m, 1H); 3.77 (s, 3H); 3.84-3.91 (m, 4H); 4.50 (s, 2H); 4.61 (s, 2H); 6.47 (m, 2H); 6.90 (t, 2H); 7.18 (d, 2H).

Intermediate 74: 4-[2-(trans-4-Aminocyclohexyl)ethyl]-6-methoxy-2H-1,4-benzoxazin-3(4H)-one

tert-Butyl (trans-4-[2-(6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]cyclohexyl) carbamate (Intermediate 75) was reacted as described for Intermediate 14. The crude trifluoroacetate of the title compound was used without further purification for the next step (quantitative yield).

MS (ES): 305 (MH+) for C_{17}H_{23}N_2O_3

Intermediate 75: tert-Butyl (trans-4-[2-(6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]cyclohexyl) carbamate

6-Methoxy-2H-1,4-benzoxazin-3(4H)-one (Intermediate 48) (310 mg, 1.73 mmol) was deprotonated with sodium hydride and alkylated with 2-(trans-4-[[tert

butoxycarbonylamino)cyclohexyl]ethyl methanesulfonate (Intermediate 76) (2 mmol) as described for Intermediate 2. Chromatography on silica gel with dichloromethane/methanol (20:1) afforded the product as a solid (58%).

MS (ES): 405 (MH+) for C_{22}H_{29}N_2O_5
**Intermediate 76:** 2-{(trans-4-[(tert-Butoxycarbonyl)amino)cyclohexyl]ethyl) methanesulfonate

Commercially available tert-butyl [trans-4-(2-hydroxyethyl)cyclohexyl]carbamate (500mg, 2.05 mmol) was reacted according to the procedure described for Intermediate 6 to give the product as a white solid (yield 92%).

^1H-NMR (CDCl₃) δ: 1.07 (m, 4H); 1.42 (m, 9H); 1.62 (m, 3H); 1.79 (m, 3H); 1.98 (m, 1H); 2.90 (s, 3H); 3.05 (s, br, 1H); 4.24 (t, 2H); 4.35 (s, 1H).

**Example 39**

3-Oxo-4-{2-(trans-4-{[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino)cyclohexyl}ethyl]-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile

4-{2-[(trans-4-amino)cyclohexyl]ethyl}-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile (Intermediate 77), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carboxaldehyde (WO 2004/058144) (1.73 mmol) and sodium cyanoborohydride were reacted following the procedure described for Example 21 to give the product in 7% yield, as an off-white solid.

**MS (ES):** 462 (MH⁺) for C₂₅H₂₃N₅O₄

^1H-NMR (CDCl₃) δ: 1.05 (q, 2H); 1.45 (m, 5H); 1.88 (d, 2H); 2.07 (d, 2H); 2.65 (t, 1H); 3.90 (m, 2H); 3.95 (s, 2H); 4.61 (s, 2H); 4.66 (s, 2H); 6.97 (d, 1H); 7.04 (d, 1H); 7.17 (d, 1H); 7.20 (d, 1H); 7.31 (dd, 1H).

**Intermediate 77:** 4-{2-(trans-4-Aminocyclohexyl)ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile

**Intermediate 78:** tert-Butyl (trans-4-[2-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]cyclohexyl]carbamate (Intermediate 78) was reacted as described for Intermediate 14. The crude trifluoro acetate of the title compound was used without further purification for the next step (quantitative yield).

**MS (ES):** 300 (MH⁺) for C₁₇H₁₅N₃O₃

**Intermediate 78:** tert-Butyl (trans-4-[2-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]cyclohexyl]carbamate

3-Oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile (Intermediate 60) (350 mg, 2.0 mmol) was deprotonated with sodium hydride and alkylated with 2-{(trans-4-{(tert
butoxy)carbonyl]amino[cyclohexyl]ethyl methanesulphonate (Intermediate 76) as described for Intermediate 2. Chromatography on silica gel with dichloromethane/ methanol (20:1) afforded the product as a solid (50%).

MS (ES) 400 (MH⁺) for C_{29}H_{36}N_{5}O_{4}

**Example 40**

6-Bromo-4-[[2-4-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino][piperidin-1-yl]ethyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

4-[[2-(4-Aminopiperidin-1-yl)ethyl]-6-bromo-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one (Intermediate 79), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-3-6-carbaldehyde (WO 2004/058144) and sodium cyanoborohydride were reacted as described under Example 21 to give the product as an off-white solid in 64% yield.

MS (ES): 517, 519(MH⁺) for C_{32}H_{37}BrN_{10}O_{4}

^{1}H-NMR (DMSO-d_{6}) 8: 1.25 (q, 2H); 1.81 (d, 5H); 1.98 (t, 2H); 2.6 (s, 2H); 2.89 (t, 2H); 3.15 (s, 1H); 3.83 (s, 2H); 4.05 (t, 2H); 4.62 (s, 2H); 4.76 (s, 2H); 6.97 (d, 1H); 7.04 (d, 1H); 7.25 (d, 1H); 7.34 (dd, 2H); 11.23 (s, br, 1H)

**Intermediate 79**: 4-[[2-(4-Aminopiperidin-1-yl)ethyl]-6-bromo-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

**Intermediate 80**: tert-Butyl (1-[[2-(6-bromo-3-oxo-2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazin-4-yl)ethyl][piperidin-4-yl]carbonate was reacted as described for Intermediate 14. The crude trifluoroacetate of the title compound was used without further purification for the next step (quantitative yield).

MS (ES): 355/ 357 (MH⁺) for C_{14}H_{19}BrN_{10}O_{3}

**Intermediate 80**: tert-Butyl (1-[[2-(6-bromo-3-oxo-2,3-dihydro-4H-pyrido[3,2-b][1,4]oxazin-4-yl)ethyl][piperidin-4-yl]carbonate

6-Bromo-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one (WO 2004/058144) (935 mg, 4.08 mmol) was deprotonated with sodium hydride and alkylation with 2-(4-[[tert-butoxycarbonyl]amino][piperidin-1-yl]ethyl methanesulphonate (Intermediate 6) (5.6 mmol) as described for Intermediate 2, but chromatography was omitted, to give the product as a solid in 92% yield.

MS (ES): 455, 457 (MH⁺) for C_{26}H_{27}BrN_{10}O_{4}
Example 41

6-[(1-[2-(6-Nitro-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

4-[2-(4-Aminopiperidin-1-yl)ethyl]-6-nitro-2H-1,4-benzoxazin-3(4H)-one

(Intermediate 81), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) and sodium cyanoborohydride were reacted as described under Example 21 to give the product as an off-white solid in 7% yield.

MS (ES): 483 (M+H) for C23H20N6O6

1H-NMR (CDCl3) δ: 1.55 (q, 2H); 1.92 (d, 2H); 2.15 (t, 2H); 2.64 (t, 3H); 2.95 (d, 2H); 3.86 (s, 2H); 4.08 (t, 2H); 4.62 (s, 2H); 4.71 (s, 2H); 5.93 (d, 1H); 7.03 (d, 1H); 7.17 (d, 1H); 7.90 (dd, 1H); 8.13 (d, 1H).

Intermediate 81: 4-[2-(4-Aminopiperidin-1-yl)ethyl]-6-nitro-2H-1,4-benzoxazin-3(4H)-one

tert-Butyl (1-[2-(6-nitro-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl) carbamate (Intermediate 82) was reacted as described for Intermediate 14. The crude trifluoroacetate of the title compound was used without further purification for the next step (quantitative yield).

MS (ES): 321 (M+H) for C12H20N4O4

Intermediate 82: tert-Butyl (1-[2-(6-nitro-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl) carbamate

6-Nitro-2H-1,4-benzoxazin-3(4H)-one (Intermediate 83) (776 mg, 4 mmol) was deprotonated with sodium hydride and alkylated with 2-[4-[(tert-butoxycarbonylamino)piperidin-1-yl]ethyl methanesulfonate (Intermediate 6) (5.6 mmol) as described for Intermediate 2. The product precipitated upon quenching of the reaction mixture with water and was isolated by filtration in 98% yield, yellow solid.

MS (ES): 421 (M+H) for C26H22N4O6.

Intermediate 83: 6-Nitro-2H-1,4-benzoxazin-3(4H)-one

The title compound was prepared according to the procedure described for Intermediate 60, in 28% yield, yellow solid.

MS (ES): 195 (M+H) for C6H6N2O4.
$^1$H-NMR (DMSO-d$_6$) δ: 4.80 (s, 2H); 7.18 (d, 1H); 7.75 (s, 1H); 7.85 (d, 1H); 11.10 (s, 1H)

**Example 42**

3-Oxo-4-[2-(4-[[3-oxo-3,4-dihydro-2H-pyrind[3,2-b][1,4]oxazin-6-yI)methyl]amino]piperidin-1-yl]ethyl]-3,4-dihydro-2H-pyrind[3,2-b][1,4]oxazine-6-carbonitrile

and

**Example 43**

3-Oxo-4-[2-(4-[[3-oxo-3,4-dihydro-2H-pyrind[3,2-b][1,4]oxazin-6-yI)methyl]amino]piperidin-1-yl]ethyl]-3,4-dihydro-2H-pyrind[3,2-b][1,4]oxazine-6-carboxamide

A mixture of 6-bromo-4-[2-(4-[[3-oxo-3,4-dihydro-2H-pyrind[3,2-b][1,4]oxazin-6-yI)methyl]amino]piperidin-1-yl]ethyl]-2H-pyrind[3,2-b][1,4]oxazin-3(4H)-one (Example 40) (200 mg, 0.387 mmol), zinc cyanide (135 mg, 1.14 mmol) and tetrakis(triphenylphosphine)palladium(0) (50 mg, 0.043 mmol) in anhydrous DMF (3 mL) over molecular sieves 3 A was vortexed and then heated in the microwave at 200 °C for one hour. Reverse phase chromatography and generation of the free base as described for Example 21 gave 27 mg (15%) of Example 42 and 23 mg (12%) of Example 43, both off-white solids.

**Example 42:**

MS (ES): 464(MH$^+$) for C$_{23}$H$_{28}$N$_7$O$_4$

$^1$H-NMR (DMSO-d$_6$) δ: 1.17 (q, 2H); 1.77 (d, 2H); 20.1 (t, 2H); 2.86 (d, 2H); 3.75 (s, 2H); 4.09 (t, 2H); 4.61 (s, 2H); 4.88 (s, 2H); 7.00 (d, 1H); 7.30 (d, 1H); 7.53 (d, 1H); 7.69 (d, 1H); 11.20 (s, br, 1H).

**Example 43:**

MS (ES): 482(MH$^+$) for C$_{23}$H$_{28}$N$_7$O$_4$

$^1$H-NMR (DMSO-d$_6$) δ: 1.09 (q, 2H); 1.66 (d, 2H); 1.91 (t, 2H); 2.31 (m, 1H); 2.43 (m, 2H); 2.83 (d, 2H); 3.04 (s, 2H); 3.63 (s, 2H) 4.28 (t, 2H); 4.59 (s, 2H); 4.80 (s, 2H); 6.96 (d, 1H); 7.26 (d, 1H); 7.45 (d, 1H); 7.57 (s, 1H); 7.64 (d, 1H); 7.90 (s, 1H); 11.30 (s, br, 1H).
Example 44

Methyl 3-oxo-4-[(2-((3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl)amino)piperidin-1-yl)ethyl]-3,4-dihydro-2H-1,4-benzoazaine-6-carboxylate

Methyl 4-[(2-(4-aminopiperidin-1-yl)ethyl)-3-oxo-3,4-dihydro-2H-1,4-benzoazaine-6-carboxylate (Intermediate 84), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-carboxaldehyde (WO 2004/058144) and sodium cyanoborohydride were reacted as described under Example 21 to give the product as an off-white solid in 13% yield.

MS (ES): 496(MH⁺) for C₂₅H₂₉N₆O₆

¹H-NMR (CDCl₃) δ: 1.53 (m, 3H); 2.16 (m, 3H); 2.49 (m, 2H); 2.62 (m, 3H); 3.00 (d, 2H); 3.87 (s, 2H); 3.90 (s, 3H); 4.09 (t, 2H); 4.62 (s, 2H); 4.64 (s, 2H); 6.95 (d, 1H); 6.98 (d, 1H); 7.19 (d, 1H); 7.19 (d, 1H); 7.69 (d, 1H); 7.78 (d, 1H).

Intermediate 84: Methyl 4-[(2-(4-aminopiperidin-1-yl)ethyl)-3-oxo-3,4-dihydro-2H-1,4-benzoazaine-6-carboxylate

Methyl 4-[(2-((tert-butoxycarbonyl)amino)piperidin-1-yl)ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoazaine-6-carboxylate (Intermediate 85) was reacted as described for Intermediate 14. The crude trifluoro acetate of the title compound was used without further purification for the next step (quantitative yield).

MS (ES): 334(MH⁺) for C₁₇H₂₁N₅O₄

Intermediate 85: Methyl 4-[(2-(4-((tert-butoxycarbonyl)amino)piperidin-1-yl)ethyl)-3-oxo-3,4-dihydro-2H-1,4-benzoazaine-6-carboxylate

Methyl 3-oxo-3,4-dihydro-2H-1,4-benzoazaine-6-carboxylate (Intermediate 86) (330 mg, 1.59 mmol) was deprotonated with sodium hydride and alkylated with 2-[(4-(tert-butoxycarbonyl)amino)piperidin-1-yl)ethyl methanethiolate (Intermediate 6) (5.6 mmol) as described for Intermediate 2. Chromatography on silica gel with dichloromethane/methanol (20:1) gave the product in 85% yield as a yellow solid.

MS (ES): 434(MH⁺) for C₂₇H₂₉N₅O₆

Intermediate 86: Methyl 3-oxo-3,4-dihydro-2H-1,4-benzoazaine-6-carboxylate

3-Oxo-3,4-dihydro-2H-1,4-benzoazaine-6-carbonitrile (Intermediate 60) was heated with chlorotrimethylsilane in methanol according to literature procedure (Fen-tair Lu et al. Tetrahedron Letters, 39, 1998, page 9455-9456). After removal of volatiles, the product was
purified by chromatography on silica gel with methanol/dichloromethane (1:20) and obtained as off white solid, 40% yield.

**MS (ES):** 208 (MH⁺) for C_{10}H_{12}NO_{4}

^{1}H-NMR (DMSO-d_{6}) δ: 3.80 (s, 3H); 4.67 (s, 2H); 7.03 (d, 1H); 7.50 (d, 1H); 7.55 (d, 1H); 10.99 (s, 1H).

**Example 45**

6-[(1-{1-2-(6-Acetyl-3-oxo-2,3-dihydro-4H-1,4-benzoazin-4-yl)ethyl]piperidin-4-yl}amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

6-Acetyl-4-[2-(4-aminopiperidin-1-yl)ethyl]-2H-1,4-benzoazin-3(4H)-one (Intermediate 87), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) and sodium cyanoborohydride were reacted as described under Example 21 to give the product as an off-white solid in 7% yield.

**MS (ES):** 480(MH⁺) for C_{23}H_{25}N_{4}O_{5}

^{1}H-NMR (CDCl_{3}) δ: 1.49 (m, 2H); 1.98 (d, 2H); 2.13 (t, 2H); 2.57 (s, 4H); 2.60 (m, 3H); 2.94 (d, 2H); 2.99 (s, 2H); 4.09 (t, 2H); 4.60 (s, 2H); 4.64 (s, 2H); 6.59 (d, 1H); 6.70 (d, 1H); 7.16 (d, 1H); 7.58 (d, 1H); 7.74 (s, 1H).

**Intermediate 87: 6-Acetyl-4-[2-(4-aminopiperidin-1-yl)ethyl]-2H-1,4-benzoazin-3(4H)-one**

3(4H)-one

tert-Butyl 1-{1-2-(6-acetyl-3-oxo-2,3-dihydro-4H-1,4-benzoazin-4-yl)ethyl]piperidin-4-yl}carbamate (Intermediate 88) was reacted as described for Intermediate 14. The crude trifluoro acetate of the title compound was obtained as a colorless solid and used without further purification for the next step (quantitative yield).

**MS (ES):** 318 (MH⁺) for C_{17}H_{25}N_{3}O_{3}

**Intermediate 88: (tert-Butyl) 1-{1-2-(6-acetyl-3-oxo-2,3-dihydro-4H-1,4-benzoazin-4-yl)ethyl]piperidin-4-yl}carbamate**

6-Acetyl-2H-1,4-benzoazin-3(4H)-one (Intermediate 89) (382 mg, 2.0 mmol) was deprotonated with sodium hydride and alkylated with 2-{4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}ethyl methanesulfonate (Intermediate 6) (2.2 mmol) as described for Intermediate 2. Chromatography on silica gel with hexanes/ethyl acetate (1:1) gave the product in 94% yield as a colorless solid.
Intermediate 89: 6-Acetyl-2H-1,4-benzoxazin-3(4H)-one

Ethyl (4-acetyl-2-nitrophenoxy)acetate (Intermediate 90) was reacted with iron in acetic acid as described for Intermediate 48. The crude product was obtained as an off white solid after work up. Recrystallization with ethyl acetate / methanol afforded the product as a colorless solid in 51% yield.

**MS (ES):** 192 (MH⁺) for C₁₆H₅NO₅

**¹H-NMR (DMSO-d₆):** 6: 2.50 (s, 3H); 4.68 (s, 2H); 7.06 (d, 1H); 7.47 (d, 1H); 7.60 (dd, 1H); 10.88 (s, 1H).

Intermediate 90: Ethyl (4-acetyl-2-nitrophenoxy)acetate

1-(4-hydroxy-3-nitrophenyl)ethanone was reacted with cesium carbonate and 2-bromoethyl acetate as described for Intermediate 49. Chromatography on silica gel with hexanes/ethyl acetate (1:1) gave the product in 69% yield as a pink solid.

**MS (ES):** 268 (MH⁺) for C₁₂H₁₃NO₅

**¹H-NMR (CDCl₃):** 6: 1.30 (t, 3H); 2.60 (s, 3H); 4.30 (q, 2H); 4.86 (s, 2H); 7.00 (d, 1H); 8.20 (d, 1H); 8.50 (s, 1H).

Example 46

6-Acetyl-4-(2-[4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl]ethyl)-2H-1,4-benzoxazin-3(4H)-one

6-Acetyl-4-[2-(4-aminopiperidin-1-yl)ethyl]-2H-1,4-benzoxazin-3(4H)-one (Intermediate 87), 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde (WO 2004/055144) and sodium cyanoborohydride were reacted as described for Example 21. The reaction was converted to the free base was treated with HCl in dioxane (2M, excess) and the excess HCl and dioxane were removed under reduced pressure to give the bis hydrochloride salt of the product, 25 mg (9%), as an off-white solid.

**MS (ES):** 467 (MH⁺) for C₂₂H₁₇N₃O₇

**¹H-NMR (DMSO-d₆):** 6: 2.10 (m, 2H); 2.32 (d, 1H); 2.65 (s, 3H); 3.07 (m, 2H); 3.27 (s, 3H) 3.57 (s, 1H); 3.77 (d, 2H); 4.19 (s, 2H); 4.35 (dd, 4H); 4.46 (t, 2H); 4.81 (s, 2H); 7.12 (d, 1H); 7.24 (s, 1H); 7.66 (d, 1H); 7.76 (s, 1H); 8.18 (s, 1H); 9.73 (bs, 2H); 11.06 (bs, 1H).
Example 47

4-[(2-[2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yilmethyl]amino)piperidin-1-yl]ethyl]-6-methyl-2H-1,4-benzoazin-3(4H)-one

4-[(2-[4-Aminopiperidin-1-yl]ethyl]-6-methyl-2H-1,4-benzoazin-3(4H)-one

(Intermediate 91), 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde (WO 2004/058144) and sodium cyanoborohydride were reacted as described for Example 21 to give the product as an oil, 4.7 mg (2%).

**MS (ES):** 439 (M+H) for C_{21}H_{29}N_{4}O_{4}

**1H-NMR (CDCl3)**: δ: 2.13 (m, 2H); 2.25 (s, 2H); 2.31 (s, 3H); 2.61 (s, 2H); 3.06 (m, 2H); 3.33 (m, 1H); 3.51 (m, 2H); 4.14 (s, 2H); 4.20-4.40 (m, 6H); 4.53 (s, 2H); 6.70-6.95 (m, 4H); 8.09 (s, 1H).

**Intermediate 91; 4-[2-(4-Aminopiperidin-1-yl)ethyl]-6-methyl-2H-1,4-benzoazin-3(4H)-one**

tert-Butyl (1-[2-(6-methyl-3-oxo-2,3-dihydro-4H-1,4-benzoazin-4-yl)ethyl]piperidin-4-yl) carbamate (Intermediate 92) was reacted as described for Intermediate 14. The crude trifluoro acetate of the title compound was obtained as a colorless solid and used without further purification for the next step (quantitative yield).

**MS (ES):** 290 (M+H) for C_{16}H_{23}N_{3}O_{2}

**Intermediate 92; tert-Butyl (1-[2-(6-methyl-3-oxo-2,3-dihydro-4H-1,4-benzoazin-4-yl)ethyl]piperidin-4-yl) carbamate**

Commercially available 6-methyl-2H-1,4-benzoazin-3(4H)-one (326mg, 2.0 mmol) was deprotonated with sodium hydride and alkylated with 2-(4-{(tert-butoxycarbonyl)amino}piperidin-1-yl)ethyl methanesulfonate (Intermediate 6) (2.2 mmol) as described for Intermediate 2. Chromatography on silica gel with dichloromethane/methanol (20:1) gave the product in 66% yield as a colorless solid.

**MS (ES):** 390 (M+H) for C_{21}H_{21}N_{3}O_{4}
Example 48

3-Oxo-4-[2-(6-{[3-oxo-3,4-dihydro-2H-pyrido][3,2-b][1,4]oxazin-6-yl]methyl}amino]-3-azabicyclo[3.1.0]hex-3-yl)ethyl]-3,4-dihydro-2H-1,4-benzoazaine-6-carbonitrile

4-[2-(6-Amino-3-azabicyclo[3.1.0]hex-3-yl)ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoazaine-6-carbonitrile (Intermediate 93), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-carboxaldehyde (WO 2004/058144) and sodium cyanoborohydride were reacted as described under Example 21 to give the product as an off-white solid in 6% yield.

MS (ES): 461 (MH⁺) for C₂₄H₂₄N₆O₄

H-NMR (CDCl₃) δ: 2.46 (m, 4H); 2.66 (t, 2H); 3.01 (d, 2H); 3.83 (s, 2H); 3.98 (m, 3H) 4.63 (s, 2H); 4.64 (s, 2H); 6.89 (d, 1H); 7.02 (d, 1H); 7.18 (d, 1H); 7.31 (m, 2H).

Intermediate 93: 4-[2-(6-Amino-3-azabicyclo[3.1.0]hex-3-yl)ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoazaine-6-carbonitrile

terr-Butyl (3-[2-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoazaine-4-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl) carbamate (Intermediate 94) was reacted as described for Intermediate 14. The crude trifluoro acetate of the title compound was obtained as a colorless solid and used without further purification for the next step (quantitative yield).

MS (ES): 299 (MH⁺) for C₁₆H₁₈N₄O₂.

Intermediate 94: terr-Butyl (3-[2-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoazaine-4-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl) carbamate

3-Oxo-3,4-dihydro-2H-1,4-benzoazaine-6-carbonitrile (Intermediate 60) (231 mg, 1.5 mmol) was deprotonated with sodium hydride and alkylation with 2-[6-[(tert-butoxy carbonyl)amino]-3-azabicyclo[3.1.0]hex-3-yl] ethyl methanesulfonate (Intermediate 95) (1.55 mmol) as described for Intermediate 2. Chromatography on silica gel with dichloromethane/ methanol (20:1) gave 442 mg (94%) product as a yellow gum.

MS (ES): 399 (MH⁺) for C₂₁H₂₆N₄O₄

Intermediate 95: 2-[6-[(tert-Butoxy carbonyl)amino]-3-azabicyclo[3.1.0]hex-3-yl] ethyl methanesulfonate

To a mixture of tert-butyl (3-[2-hydroxyethyl]-3-azabicyclo[3.1.0]hex-6-yl) carbamate (Intermediate 96) (376 mg, 1.55 mmol) and triethyl amine (0.283 mL, 3 mmol) in anhydrous
chloroform (15 mL) was added at 0°C methanesulfonyl chloride (228 mg, 3 mmol) via syringe. The reaction was allowed to warm to room temperature over 1 hr and worked up as described for Intermediate 6. The crude mesylate was used for the next step without delay.

**Intermediate 96: tert-Butyl [3-(2-hydroxyethyl)-3-azabicyclo[3.1.0]hex-6-yl]carbamate**

A mixture of tert-butyl 3-azabicyclo[3.1.0]hex-6-ylcarbamate (T. P. Braithwaite et al. Synlett, 1996, page 1100 and T. Norris et al. J. Chem. Soc. Perkin I, 2000, page 1615-1622), 2-bromoethanol (669 mg, 3.36 mmol) and N,N-ethyldiisopropyl amine (0.087 mL) in acetonitrile (9 mL) was heated in the microwave at 70°C for 30 minutes. Chromatography on silica gel with chloroform/methanol (20:1) gave 376 mg (46%) of the product.

MS(ES) 242 for C_{12}H_{22}N_{2}O_{3}

**Example 49**

4-(2-{4-[2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl]amino[piperidin-1-yl]ethyl}-2H-1,4-benzoxazin-3(4H)-one

4-{2-(4-Aminopiperidin-1-yl)ethyl}-2H-1,4-benzoxazin-3(4H)-one (Intermediate 97), 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde (WO 2004/058144) and sodium cyanoborohydride were reacted as described for Example 21 to give the product as a off-white solid, 81 mg (16%).

MS(ES): 425(MH^+) for C_{23}H_{28}N_{4}O_{4}2HCl

^1H-NMR (DMSO-d_6) \delta: 2.2-3.8 (m, 14H); 3.87 (s, 1H); 4.42 (m, 4H); 4.75 (s, 2H); 7.11 (m, 3H); 7.40-7.60 (m, 2H); 8.29 (s, 1H); 10.01 (s, 2H); 10.01 (s, 2H); 11.35 (brs, 1H).

**Intermediate 97: 4-{2-(4-Aminopiperidin-1-yl)ethyl}-2H-1,4-benzoxazin-3(4H)-one**

tert-Butyl {1-[2-(3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl}carbamate (Intermediate 98) was reacted as described for Intermediate 14. The crude trifluoro acetate of the title compound was obtained as a colorless solid and used without further purification for the next step (quantitative yield).

MS (ES): 276 (MH^+) for C_{15}H_{11}N_{2}O_{2}
Intermediate 28: tert-Butyl (1-[(2-f3-o xo-2,3-dihydro-4H-1,4-benzoxazin-4-
eyl)ethyl]piperidin-4-yl) carbamate

2H-1,4-Benzoxazin-3(4H)-one (298 mg, 2.0 mmol) was deprotonated with sodium hydride and alkylated with 2-(4-[(tert-butoxycarbonyl)amino]piperidin-1-yl)ethyl methanesulfonate (Intermediate 6) (2.0 mmol) as described for Intermediate 2. Chromatography on silica gel with dichloromethane/ methanol (20:1) gave the product in 63% yield as a yellow gum.

**MS (ES):** 376 (MH⁺) for C₇₃H₇₉N₉O₄

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**Example 50**

6-[(1-(2-(6-Hydroxyethyl)-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-
eyl)ethyl]piperidin-4-yl)amino][methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

6-[(1-(2-(6-Acetyl-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-
eyl)amino][methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one (Example 45) (309 mg, 0.645 mmol) was reduced with sodium borohydride (47 mg, 2 equivalents) in methanol (12 mL) at 0 °C. After quenching the reaction with water, the reaction mixture was concentrated under reduced pressure and extracted with chloroform. The chloroform layer was washed with brine and dried over magnesium sulfate and concentrated to dryness to give the as an off-white solid, 202 mg (95%).

**MS (ES):** 482 (MH⁺) for C₃₃H₃₉N₉O₃

**H-NMR (CDCl₃) δ:** 1.47 (d, 3H); 1.50 (q, 2H); 1.89 (d, 2H); 2.18 (m, 2H); 2.62 (m, 1H) 2.65 (t, 2H); 3.00 (d, 2H); 3.82 (s, 2H); 4.09 (t, 2H); 4.55 (s, 2H); 4.61 (s, 2H); 4.86 (q, 1H) 6.91 (m, 3H); 7.18 (d, 1H); 7.26 (s, 1H).

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**Example 51**

Ethyl N-[1-[(2-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-
eyl)ethyl]piperidin-4-yl)]-N-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]glycinate

To a mixture of 4-(2-(4-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl)amino]piperidin-1-yl)ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-carbonitrile (Example 37) (120 mg, 0.265 mmol) and ethyl diazoacetate (0.09 mL) in dichloromethane (5 mL) was added rhodium(II) acetate (4 mg, 0.009 mmol) at room temperature. After 72 hrs, the product was concentrated and purified by preparative TLC to give 6.7 mg of product (5%).

**MS (ES):** 539 (MH⁺) for C₆₉H₇₇N₉O₄
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\[ ^1H \text{NMR (CDCl}_3 \text{)} \delta: 1.22 (t, 3H); 1.25 (m, 2H); 1.52 (m, 4H); 1.84 (d, 2H); 2.16 (bs, 2H) 2.60 (m, 2H); 2.70 (m, 1H); 3.03 (m, 2H); 3.37 (s, 2H); 3.45 (d, 2H); 4.07 (m, 2H); 4.11 (q, 2H); 4.68 (s, 2H); 6.32 (dt, 1H); 6.67 (d, 1H); 6.86 (m, 1H); 6.97 (dm, 1H); 7.02 (d, 1H); 7.13 (m, 1H); 7.30 (dd, 1H); 7.45 (s, 1H).\]

**Example 52**

6-[[1-[(2-[6-(Methylsulfonyl)-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl]amino]methyl]-2H-pyrido[3,2-d][1,4]oxazin-3(4H)-one

4-[[2-(4-Aminopiperidin-1-yl)ethyl]-6-(methylsulfonyl)-2H-1,4-benzoxazin-3(4H)-one

(Intermediate 99), 3-oxo-2,3-dihydro-2H-pyrido[3,2-d][1,4]oxazine-6-carboxaldehyde (WO 2004/058144) and sodium cyanoborohydride were reacted as described under Example 21 to give the product as an off-white solid in 8% yield.

**MS (ES):** 516 (MH\(^{+}\)) for C\(_{24}\)H\(_{23}\)N\(_{5}\)O\(_{4}\)S

**Intermediate 99:** 4-[[2-(4-Aminopiperidin-1-yl)ethyl]-6-(methylsulfonyl)-2H-1,4-benzoxazin-3(4H)-one

**Intermediate 100:** tert-Butyl (1-[(6-((methylsulfonyl)-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl)piperidin-4-yl)carbonate (Intermediate 100) was reacted as described for Intermediate 14. The crude trifluoro acetate of the title compound was obtained as a colorless solid and used without further purification for the next step (quantitative yield).

**MS (ES):** 353 (MH\(^{+}\)) for C\(_{16}\)H\(_{23}\)N\(_{4}\)O\(_{4}\)S

**Intermediate 101:** tert-Butyl (1-[(6-((methylsulfonyl)-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl)piperidin-4-yl)carbonate

6-(Methylsulfonyl)-2H-1,4-benzoxazin-3(4H)-one (Intermediate 101) (280 mg, 1.23 mmol) was deprotonated with sodium hydride and alkylated with 2-[[tetra-butoxy carbonyl]amino]piperidin-1-yl]ethyl methanesulfonate (Intermediate 6) (1.62 mmol) as described for Intermediate 2. Chromatography on silica gel with dichloromethane/methanol (20:1) gave the product in 66% yield as a yellow gum.

**MS (ES):** 454 (MH\(^{+}\)) for C\(_{31}\)H\(_{31}\)N\(_{5}\)O\(_{4}\)S
Intermediate 101: 6-(Methylsulfonyl)-2H-1,4-benzoxazin-3(4H)-one

4-Methylsulfonyl-2-aminophenol (Intermediate 102) (690 mg, 3.68 mmol) was dissolved in chloroform (30 mL) and saturated sodium bicarbonate (20 mL). The biphasic reaction mixture was cooled to 0°C and bromoacetyl bromide (889 mg, 4.42 mmol) was added dropwise. The reaction was stirred overnight at room temperature. The layers were separated and the aqueous layer was filtered to yield the desired product as a solid, 280 mg (33%).

MS (ES): 223(MH⁺) for C₇H₅NO₃S

¹H-NMR (DMSO-d₆) δ: 3.16 (s, 3H); 4.73 (s, 2H); 7.15 (d, 1H); 7.41 (s, 1H); 7.50 (d, 1H); 11.05 (s, 1H).

Intermediate 102 4-Methylsulfonyl-2-aminophenol

The title compound was prepared by reacting 2-methoxy-5-methylsulfonyl aniline (5.0 g, 24.8 mmol) with boron tribromide (26 mmol, 26 mL, 1M in dichloromethane) in chloroform (30 mL) at 0°C. After 20 minutes, the reaction was quenched with sodium bicarbonate and the pH of the aqueous phase was adjusted to pH 7 and extracted with ethyl acetate. Concentration under reduced pressure gave 690 mg of product as an orange solid (15%).

MS (ES): 188(MH⁺) for C₁₀H₉NO₃S

Example 53

6-[(1-[2-[(6-Ethylsulfonyl)-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-y1][ethyl]piperidin-4-yl]amino[methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one]

4-[2-(4-Aminopiperidin-1-yl)ethyl]-6-(methylsulfonyl)-2H-1,4-benzoxazin-3(4H)-one

(Intermediate 103), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-carbaldehyde (WO 2004/058144) and sodium cyanoborohydride were reacted as described under Example 21 to give the product as an off-white solid in 19% yield.

MS (ES): 530(MH⁺) for C₂₅H₂₃N₅O₆S

¹H-NMR (DMSO-d₆) δ: 1.11 (t, 3H); 1.30 (q, 2H); 1.74 (d, 2H); 2.00 (t, 2H); 2.40 (m, 3H); 2.82 (d, 2H); 3.32 (m, 4H); 3.67 (s, 2H); 4.05 (t, 2H); 4.60 (s, 2H); 4.78 (s, 2H); 7.01 (d, 1H); 7.28 (d, 1H); 7.30 (d, 1H); 7.50 (d, 1H); 7.68 (s, 1H); 11.18 (brs, 1H).
Intermediate 103: 4-[2-(4-Aminopiperidin-1-yl)ethyl]-6-(methylsulfonfonyl)-2H-1,4-benzoxazin-3(4H)-one

*tert*-Butyl (1-[2-{6-(ethylsulfonfonyl)-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl}ethyl]piperidin-4-yl)carbonate (Intermediate 104) was reacted as described for Intermediate 14. The crude trifluoro acetate of the title compound was obtained as a colorless solid and used without further purification for the next step (quantitative yield).

**MS (ES):** 363 (MH⁺) for C₁₇H₂₅N₃O₄S

Intermediate 104: *tert*-Butyl (1-{2-[6-(ethylsulfonfonyl)-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl]ethyl}piperidin-4-yl)carbonate

6-(Ethylsulfonfonyl)-2H-1,4-benzoxazin-3(4H)-one (Intermediate 105) (482 mg, 2 mmol) was deprotonated with sodium hydride and alkylated with 2-4-[(tert-butoxycarbonyl)amino]piperidin-1-yl)ethyl methanesulfonate (Intermediate 6) (2.2 mmol) as described for Intermediate 2. Chromatography on silica gel with hexanes/ethyl acetate gave the product in 81% yield as a yellow gum.

**MS (ES):** 468 (MH⁺) for C₂₂H₃₅N₅O₆S

Intermediate 105: 6-(Ethylsulfonyl)-2H-1,4-benzoxazin-3(4H)-one

Commercially available 4-ethylsulfonyl-2-aminophenol (4.02 g, 20 mmol) was dissolved in DMF (30 mL) and mixed with cesium carbonate (6.5 g, 20 mmol). The reaction mixture was cooled to 0°C and bromoacetyl bromide (4.0 g, 20 mmol) in DMF (5 mL) was added dropwise. The reaction was stirred overnight at room temperature. After aqueous work up, the product was purified by silica gel chromatography with methanol/dichloromethane to give the product as an orange solid, 1.7 g (35%).

**MS (ES):** 242 (MH⁺) for C₁₀H₁₁NO₄S

¹H NMR (DMSO-d₆) δ: 1.09 (t, 3H); 3.24 (q, 2H); 4.72 (s, 2H); 7.16 (d, 1H); 7.37 (s, 1H); 7.41 (d, 1H); 11.00 (s, 1H).

Example 54


1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-methoxy-1,4-dihydro-2H-3,1-benzoxazin-2-one trifluoro acetate (Intermediate 106) (324 mg, 0.78 mmol) was converted to the free base
using N,N-disopropylethylamine for 30 minutes and reacted with 3-oxo-3,4-dihydro-2H-pyrrole[3,2-b][1,4]oxazine-6-carboxaldehyde (WO 2004/058144) (153 mg, 0.86 mmol) and sodium cyanoborohydride (98 mg, 1.56 mmol) as described under Example 21. The reaction mixture was filtered through a 0.45 µm membrane and concentrated to dryness under reduced pressure. Chromatography on silica gel with dichloromethane/ methanol (9:1) gave the free base of the title compound as a colorless foam. The free base was taken up in 1,4 dioxane (2 mL), followed by addition of 4M HCl in 1,4-dioxane (0.30 mL). The resulting precipitate was collected by filtration and gave 75 mg (48%) of the bis-hydrochloride salt of the product.

**MS (ES)**: 468.17 (M+H)\(^+\) for C\(_{24}\)H\(_{27}\)N\(_5\)O\(_3\)

**\(^1\)H NMR (DMSO-d\(_6\))**: 5.269 (m, 2H); 2.31 - 2.44 (m, 2H); 3.00 - 3.15 (m, 2H); 3.66 - 3.78 (m, 2H); 3.82 (s, 3H); 4.13 - 4.22 (m, 2H); 4.22 - 4.35 (m, 2H); 4.69 (s, 2H); 5.25 (s, 2H); 6.70 (d, 1H); 6.85 (s, 1H); 7.20 (dd, 2H); 7.45 (d, 1H); 9.56 - 9.71 (m, 2H); 11.05 - 11.19 (m, 1H); 11.37 (s, 1H).

**Intermediate 106**: 1-{2-(4-Aminopiperidin-1-yl)ethyl}-7-methoxy-1,4-dihydro-2H-3,1-benzoxazin-2-one

A solution of tert-butyl \{1-{2-(7-methoxy-2-oxo-2H-3,1-benzoxazin-1(4H)- yl)ethyl}piperidin-4-yl\} carbamate (Intermediate 107) (319 mg, 0.78 mmol) in dichloromethane (8 mL) was treated at room temperature under vigorous stirring with trifluoroacetic acid (0.75 mL, 10 mmol). After 2 hours, the reaction mixture was concentrated under reduced pressure to give 324 mg (quantitative) of product as a brown oil.

**MS (ES)**: 302.24 (M+H)\(^+\) for C\(_{16}\)H\(_{22}\)N\(_3\)O\(_2\)

**Intermediate 107**: tert-Butyl \{1-{2-(7-methoxy-2-oxo-2H-3,1-benzoxazin-1(4H)- yl)ethyl}piperidin-4-yl\} carbamate

A solution of 7-methoxyquinolin-2(1H)-one (Intermediate 108, 310 mg, 1.8 mmol) in dry N,N-dimethylformamide (5 mL) was treated at 0°C under stirring with lithium bis(trimethylsilyl)amide (1 M in tetrahydrofuran, 1.9 mL, 1.9 mmol). The mixture was then stirred for 30 minutes at room temperature and alkylated with 2-{4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}ethyl methanesulfonate (Intermediate 6, 2.03 mmol) as described for Intermediate 2. Chromatography on silica gel with dichloromethane/ methanol (95:5) gave 333 mg (47%) of the product as a colorless solid.

**MS (ES)**: 406 (M+H)\(^+\) for C\(_{21}\)H\(_{25}\)N\(_3\)O\(_5\)
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$^1$H-NMR (CDCl$_3$) 5: 1.34-1.46 (m, 1H); 1.86 (d, 2H); 2.12-2.25 (m, 2H); 2.60-2.64 (m, 2H); 2.60-2.64 (m, 2H); 2.81-2.90 (m, 2H); 3.33-3.45 (m, 1H); 3.76 (s, 3H); 3.97 - 3.91 (m, 2H); 4.32- 4.42 (m, 1H); 5.05 (s, 2H); 6.49-6.56 (m, 2H); 6.94 (d, 1H).

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**Intermediate 108: 7-Methoxyquinolin-2(1H)-one**

A solution of (2-amino-4-methoxyphenyl) methanol (**Intermediate 109**, 744 mg, 4.85 mmol) in toluene (25 mL) was treated with triethylamine (1.36 mL, 9.7 mmol) and triphosgene (1.58 g, 5.34 mL). The reaction was stirred at room temperature for 1.5 hours and then was heated to 110 °C for an additional 2 hours. The reaction was cooled to room temperature, diluted with water (25 mL), filtered, extracted aqueous layer with toluene (3 x 30 mL) and ethyl acetate (2x 20 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. Chromatography on silica gel with hexanes/ethyl acetate (3:2) gave 314 mg (36%) of the product as a colorless solid.

$^1$H-NMR (DMSO-d$_6$) 8: 3.78 (s, 3H); 5.26 (s, 2H); 6.38 (d, 1H); 6.59 (d, 1H); 6.98 (d, 1H); 8.36 (brs, 1H).

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**Intermediate 109: (2-Amino-4-methoxyphenyl)methanol**

To a solution of commercially available 4-methoxy-2-nitrobenzoic acid (4.0 g, 20.66 mmol) in tetrahydrofuran (20 mL) at -15 °C under nitrogen was added N-methylmorphorine (2.2 ml, 20 mmol) followed by isobutyl chloroformate (2.6 mL, 20 mmol) in portions. After 5 min, the reaction was filtered and the solid was rinsed with tetrahydrofuran (20 mL). The filtrate was cooled to -15 °C and a solution of sodium borohydride in water (3 M, 10 mL) was added to the filtrate. The reaction was stirred for 5 min. The reaction mixture was partitioned between water and dichloromethane, and extracted aqueous layer with dichloromethane (3 x 100 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was redissolved in tetrahydrofuran (35 mL) and added palladium (10% on carbon, 400 mg) and stirred under hydrogen gas for 18 hours. The reaction mixture was then filtered through celite and concentrated under reduced pressure. The residue was chromatographed on silica gel with hexanes/ethyl acetate (3:2) gave 744 mg (24% yield) of product as a yellow solid.

$^1$H-NMR (DMSO-d$_6$) 8: 3.63 (s, 3H); 4.30 (s, 2H); 4.84 - 4.96 (m, 2H); 6.08 (dd, 1H); 6.20 (d, 1H); 6.90 (d, 1H).
Example 55

7-Methoxy-3-methyl-1-[2-(4-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino]piperidin-1-yl]ethyl]quinazoline-2,4(1H,3H)-dione

1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-methoxyquinazoline-2,4(1H,3H)-dione

(Intermediate 110, crude, 153 mg, 0.46 mmol) was converted to the free base with N,N-dilisopropylethylamine for 30 min and reacted with 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-carboxaldehyde (WO 2004/058144) (90 mg, 0.51 mmol) as described under Example 21. The reaction mixture was cooled to 0°C, and sodium triacetoxyborohydride (194 mg, 0.92 mmol) was added. The resulting reaction mixture was stirred at room temperature for 18 hours and then worked up as described for Example 54 to give the bis-hydrochloride salt of the product, 12.3 mg (25%), as a colorless solid.

**MS (ES):** 495 (MH⁺) for C₂₅H₃₀N₆O₄

**¹H NMR (DMSO-δ₆)** 8 1.85-2.32 (m, 1H); 3.68-3.88 (m, 3H); 3.89-4.08 (m, 3H); 4.10-4.43 (m, 5H); 4.50-4.78 (m, 6H); 6.91-7.44 (m, 5H); 7.99 (bs, 1H); 9.74 (br s, 2H);

11.16-11.38 (m, 2H).

**Intermediate 110:** 1-[2-(4-Amino-2-oxopiperidin-1-yl)ethyl]-7-methoxy-3-methylquinazoline-2,4(1H,3H)-dione

**tert-Butyl 1-[2-(7-methoxy-3-methyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)ethyl]piperidin-4-yl] carbamate (Intermediate 111, 350 mg, 0.83 mmol) was reacted as described for Intermediate 106. The crude trifluoroacetate of the title compound was obtained as a black oil, 395 mg (quantitative), and used without further purification for the next step.

**MS (ES):** 319 (MH⁺) for C₇₁H₇₅N₁₆O₃

**Intermediate 111:** tert-Butyl 1-[2-(7-methoxy-3-methyl)-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)ethyl]piperidin-4-yl] carbamate

7-Methoxy-3-methylquinazoline-2,4(1H,3H)-dione (Intermediate 112, 523 mg, 2.5 mmol) was deprotonated with lithium bis(trimethylsilyl)amide (1M in tetrahydrofuran, 1.9 mL, 1.9 mmol) and alkylated with 2-[4-[[tert-butoxy carbonyl]amino]piperidin-1-yl]ethyl methanesulfonate (Intermediate 6, 3.4 mmol) as described for Intermediate 2. Chromatography on silica gel with dichloromethane/methanol (95:5) gave 200 mg (18%) of the product as a colorless solid.
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**MS (ES):** 433 (M+H) for C_{25}H_{35}N_4O_5.

**^1H NMR** (CDCl₃) δ 1.16-1.28 (m, 1H); 1.14-1.43 (m, 1H); 1.89-2.04 (m, 3H); 2.25-2.47 (m, 2H); 2.80 (d, 3H); 2.94-3.14 (m, 2H); 3.77 (s, 3H); 4.22-4.36 (m, 1H); 4.40-4.56 (m, 1H); 4.99-5.09 (m, 1H); 7.02-7.03 (m, 1H); 7.31-7.47 (m, 2H).

**Intermediate 112: 7-Methoxy-3-methylquinazoline-2,4(1H,3H)-dione**

2-Amino-4-methoxybenzoic acid (**Intermediate 113**, 950 mg, 6.2 mmol) and 1,3-dimethyl urea (5.4 g, 62 mmol) were heated at 150 °C for 16 hours. The reaction was cooled to 100 °C and diluted with water. The mixture was partitioned between ethyl acetate and water, the aqueous phase extracted with ethyl acetate (3 x 20 mL) and then chloroform/2-propanol (3:1, 2x 20 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. Chromatography on silica gel with hexanes/ethyl acetate (1:2) to give a 350 mg (27%) product as an orange oil.

**MS (ES):** 205 (M+H) for C_{16}H_{18}N_4O_3.

**^1H NMR** (DMSO-d₆) δ: 2.60 (d, 3H); 3.68 (s, 3H); 5.95 (d, 1H); 6.45 (dd, 1H); 6.86 (dd, 1H); 8.47 (s, 1H).

**Intermediate 113: 2-Amino-4-methoxybenzoic acid**

4-Methoxy-2-nitrobenzoic acid (3 g, 16.4 mmol) was hydrogenated over palladium on carbon (10%, 300 mg) in methanol (30 mL) at room temperature and normal pressure for 18 hours. The reaction mixture was filtered through celite and concentrated to dryness under reduce pressure to give 2.50 g (100%) of the product as a colorless solid.

**^1H NMR** (DMSO-d₆) δ: 3.70 (s, 3H); 6.09 (dd, 1H); 6.23 (d, 1H); 7.59 (d, 1H).

**Example 56**

4-(2-{4-[2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl]methylamino}-2-oxopiperidin-1-yl)ethyl)-6-methoxy-2H-1,4-benzoxazin-3(4H)-one

4-(2-{4-Amino-2-oxopiperidin-1-yl)ethyl}-6-methoxy-2H-1,4-benzoxazin-3(4H)-one trifluoroacetate (**Intermediate 114**, crude, 390 mg, 0.83 mmol) was converted to the free base with N,N-diisopropylethylamine and reacted with 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde (WO 2004/058144) (150 mg, 0.91 mmol) and sodium triacetoxymethylhydride (360 mg, 1.7 mmol) as described for Example 55 to give the bis hydrochloride salt of the product as a colorless solid, 89 mg (63%).

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**MS (ES)**: 469.19 (MH+) for C_{28}H_{27}N_{6}O_{4}

**1H NMR (DMSO-d_{6})**: 8 1.84 (dd, 1H); 2.26 (d, 1H); 2.37 - 2.46 (m, 1H); 2.68 - 2.77 (m, 1H); 3.29 - 3.49 (m, 5H); 3.75 (s, 3H); 4.32-4.42 (m, 4H); 4.52 (s, 2H); 6.56 (dd, 1H); 6.91-6.98 (m, 2H); 7.22 (s, 1H); 8.23 (s, 1H); 9.52 (bs, 2H).

**Intermediate 114**: 4-[2-(4-Amino-2-oxopiperidin-1-yl)ethyl]-6-methoxy-2H-1,4-benzoxazin-3(4H)-one

tert-Butyl [1-[2-(6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]-2-oxopiperidin-4-yl] carbamate (**Intermediate 115**, 350 mg, 0.83 mmol) was reacted as described for **Intermediate 106**. The crude trifluoro acetate of the title compound was obtained as a black oil, 395 mg (quantitative), and used without further purification for the next step.

**MS (ES)**: 320 (MH+) for C_{19}H_{17}N_{3}O_{4}

**Intermediate 115**: tert-Butyl [1-[2-(6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]-2-oxopiperidin-4-yl] carbamate

A mixture of tert-butyl [1-[2-(6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl] carbamate (**Intermediate 47**, 1.39 g, 3.4 mmol) in water/ethyl acetate (40 mL, 4:1) was treated with sodium periodate (2.8 g, 21.4 mmol) and ruthenium (IV) oxide hydrate (50 mg, 0.34 mmol) at room temperature. After 53 hours, the reaction was diluted with ethyl acetate, the aqueous phase was extracted with ethyl acetate (6 x 25 mL), and the combined organic layers were washed with 2-propanol (20 mL) and stirred for 2 hours at room temperature. The reaction mixture was then filtered through celite, dried over sodium sulfate, and concentrated in vacuo. Chromatography on silica gel with dichloromethane/methanol (95:5) gave 350 mg (25%) of the product as a colorless solid.

**MS (ES)**: 415 (MH+) for C_{29}H_{24}N_{6}O_{4}

**1H NMR (DMSO-d_{6})**: 8 1.37 (s, 9H); 1.51-1.56 (m, 1H); 1.81-1.94 (m, 1H); 2.02 - 2.11 (m, 1H); 2.33-2.41 (dd, 1H); 3.06 - 3.12 (m, 1H); 3.27 - 3.31 (m, 2H); 3.40 - 3.45 (m, 2H); 3.55-3.65 (m, 1H); 3.75 (s, 3H); 3.99 (t, 2H); 4.52 (s, 2H); 6.57 (dd, 1H); 6.90-6.98 (m, 3H).
Example 57

6-[(1R,2R-[5-Methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoazaxin-4-yl]ethyl]-2-oxopiperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

4-[2-(4-amino-2-oxopiperidin-1-yl)ethyl]-6-methoxy-2H-1,4-benzoazaxin-3(4H)-one trifluoroacetate (Intermediate 114, crude, 335 mg, 1.05 mmol) was converted to the free base with N,N-diisopropylethylamine and reacted with 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (205 mg, 1.15 mmol) and sodium triacetoxy borohydride (132 mg, 2.10 mmol) as described for Example 55 to give the bis hydrochloride salt of the product as a colorless solid, 36 mg (46%).

MS (ES): 482.15 (M+H) for C_{24}H_{27}N_{2}O_{4}

^1H NMR (DMSO-d6) δ: 1.75-1.95 (m, 1H); 2.20-2.41 (m, 1H); 2.74 (dd, 1H); 3.76 (s, 3H); 3.92-4.07 (m, 2H); 4.12-4.23 (m, 1H); 4.53-4.62 (m, 2H); 4.69 (s, 2H); 6.57 (dd, 2.26, 1H); 6.90-6.99 (m, 2H); 7.20 (d, 1H); 7.43 (d, 1H); 9.39 (bs, 1H); 11.35 (s, 1H).

Example 58

3-Oxo-4-[2-(2-oxo-4-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl]methyl]amino)piperidin-1-yl)ethyl]-3,4-dihydro-2H-1,4-benzoazaxine-6-carbonitrile

4-[2-(4-Amino-2-oxopiperidin-1-yl)ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoazaxin-6-carbonitrile trifluoroacetate (Intermediate 116, crude, 232 mg, 0.54 mmol) was converted to the free base with N,N-diisopropylethylamine and reacted with 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (110 mg, 0.60 mmol) and sodium triacetoxy borohydride (240 mg, 1.10 mmol) as described for Example 55 to give the bis hydrochloride salt of the product as a colorless solid, 65 mg (49%).

MS (ES): 477.35 (M+H) for C_{24}H_{24}N_{2}O_{3}

^1H NMR (DMSO-d6) δ: 1.79-1.84 (m, 1H); 2.28-2.42 (m, 2H); 2.70-2.77 (m, 1H); 3.51-3.56 (m, 2H); 4.08-4.16 (m, 4H); 4.68 (s, 3H); 4.73 (s, 3H); 7.14-7.22 (m, 2H); 7.43-7.52 (m, 2H); 9.46 (bs, 1H); 11.35 (s, 1H).

Intermediate 116: 4-[2-(4-Amino-2-oxopiperidin-1-yl)ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoazaxine-6-carbonitrile

tert-Butyl {1-[2-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoazaxin-4-yl)ethyl]-2-oxopiperidin-4-yl}carbamate (Intermediate 117, 225 mg, 0.54 mmol) was reacted as described for Intermediate 106. The crude trifluoroacetate of the title compound was
obtained as a red oil, 232 mg (quantitative), and used without further purification for the next step.

**MS (ES):** 315 (MH⁺) for C_{17}H_{18}N_{4}O_{2}

**Intermediate 117:** tert-Butyl (1-[2-(6-cyano-3-oxo-2,3-dihydro-4'H-1,4-benzoxazin-4-yl)ethyl]-2-oxopiperidin-4-yl)carbamate

tert-Butyl (1-[2-(6-cyano-3-oxo-2,3-dihydro-4'H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl)carbamate (Intermediate 59, 835 mg, 2.1 mmol) was reacted with sodium periodate (2.8 g, 13.1 mmol) and ruthenium (IV) oxide hydrate (30 mg, .21 mmol) as described for

**Intermediate 115** for 16 hours, except, chloroform was used for aqueous workup. The product was obtained as a colorless solid, 250 mg (27%).

**MS (ES):** 415 (MH⁺) for C_{21}H_{26}N_{4}O_{5}

**¹H NMR (DMSO-d₆)δ:** 1.36 (s, 9H); 1.42 - 1.57 (m, 2H); 1.87 (d, 1H); 2.00 (dd, 1H); 2.32 (dd, 1H); 3.38 - 3.48 (m, 2H); 3.51 - 3.63 (m, 1H); 4.07 (t, 2H); 4.72 (s, 2H); 6.94 (d, 1H); 7.14 (d, 1H); 7.48 (dd, 1H); 7.84 (d, 1H).

**Example 59**


7-Methoxy-1-(3-piperazin-1-ylpropyl)-1,4-dihydro-2H-3,1-benzoxazin-2-one trifluoroacetate (Intermediate 113, crude, 886 mg, 1.66 mmol) was converted to the free base with NaN,N-diisopropylethylamine and reacted with 3-oxo-3,4-dihydro-2H-pyrrole[3,2-b][1,4]oxazine-6-carboxaldehyde (WO 2004/058144) (220 mg, 1.23 mmol) and sodium tris(ethoxy)borohydride (521 mg, 2.46 mmol) as described for Example 55 to give the free base of the product as a pink foam after chromatography on silica gel with dichloromethane/methanol (93:7), 86 mg (21%).

**MS (ES):** 468.19 (MH⁺) for C_{24}H_{29}N_{5}O_{2}

**¹H NMR (DMSO-d₆)δ:** 1.60-1.75 (m, 2H); 2.19 - 2.44 (m, 9H); 3.37-3.43 (m, 2H); 3.72 (s, 2H); 3.83-3.96 (m, 2H); 4.53 (s, 2H); 4.60 (s, 2H); 6.56 (d, 1H); 6.78 (d, 1H); 6.88 - 7.02 (m, 2H); 7.29 (d, 1H); 11.22 (s, 1H).
Intermediate 118: 6-Methoxy-4-(3-piperazin-1-ylpropyl)-2H-1,4-benzoxazin-3(4H)-one

tert-Butyl (1-[2-(7-methoxy-2-oxoquinolin-1(2H)-yl)propyl)piperidin-4-yl] carbonate (Intermediate 119, 500 mg, 1.23 mmol) was reacted as described for Intermediate 106. The crude trifluoroacetate of the title compound was obtained as a yellow oil, 866 mg (quantitative), and used without further purification for the next step.

MS (ES): 306 (M+H) for C_{16}H_{23}N_{3}O_{3}

Intermediate 119: tert-Butyl 4-[2-(6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propyl]piperazine-1-carboxylate

6-Methoxy-2H-1,4-benzoxazin-3(4H)-one (Intermediate 48, 440 mg, 2.5 mmol) was deprotonated with sodium hydride (125 mg, 60% in oil, 3.2 mmol) and allylated with tert-butyl 4-[3-[(methylsulfonyl)oxy]propyl]piperazine-1-carboxylate (Intermediate 120, 2.5 mmol) as described for Intermediate 2. Chromatography on silica gel with dichloromethane/2-propanol (95:5) gave 1.25 g (quantitative) of the product as a yellow oil.

MS (ES): 406 (M+H) for C_{20}H_{21}N_{3}O_{3}

{\textsuperscript{1}H-NMR (CDCl}_{3}: 8: 1.45 (s, 9H); 1.78 - 1.90 (m, 2H) 2.36 - 2.40 (m, 6H); 3.43 (m, 4H); 3.77 (s, 3H); 3.95 (t, 2H); 4.52 (s, 2H); 6.49 (dd, 1H); 6.67 (d, 1H); 6.89 (d, 1H).

Intermediate 120: tert-Butyl 4-[3-[(methylsulfonyl)oxy]propyl]piperazine-1-carboxylate

tert-Butyl 4-(3-hydroxypropyl)piperazine-1-carboxylate (Intermediate 121, 2.38 g, 9.8 mmol) was reacted with methanesulfonyl chloride (0.91 mL, 11.7 mmol) in the presence of triethylamine (1.9 mL, 13.7 mmol) as described for Intermediate 6. The crude product was used without further purification for the next step.

{\textsuperscript{1}H-NMR (CDCl}_{3}: 8: 1.44 (s, 9H); 1.94 - 2.04 (m, 2H); 2.43 - 2.51 (m, 6H); 3.01 (s, 3H); 3.50-3.40 (m, 4H); 4.28-4.33 (m, 2H).

Intermediate 121: tert-Butyl 4-(3-hydroxypropyl)piperazine-1-carboxylate

A mixture of tert-butyl piperazine-1-carboxylate (2.75 g, 14.8 mmol), 1-bromo-3-propanol (1.43 mL, 16.2 mmol) and potassium carbonate (2.25 mL, 27.5 mmol) in acetonitrile (75 mL) was heated at 95°C for 4 hours. The solvent was removed under reduced pressure, and the residue was taken up in dichloromethane (300 mL) and washed with water, brine,
dried over sodium sulfate and concentrated under reduced pressure. Chromatography on silica gel with methanol in dichloromethane (0-10%) gave a tan solid 2.88 g (80% yield).

**MS (ES):** 245 (MH⁺) for C₁₁H₂₅N₂O₂.

**¹H NMR (CDCl₃):** 8: 1.44 (m, 9H); 1.70-1.82 (m, 2H); 2.40-2.53 (m, 2H); 2.62-2.65 (m, 2H); 3.43-3.50 (m, 4H); 2.77 (m, 2H); 3.73-3.82 (m, 2H).

**Example 60**

4-{3-[4-(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)piperazin-1-yl]propyl}-6-methoxy-2H-1,4-benzoazoxin-3(4H)-one

7-Methoxy-1-(3-piperazin-1-ylpropyl)-1,4-dihydro-2H-3,1-benzoazoxin-2-one trifluoroacetate (Intermediate 118, crude, 963 mg, 1.81 mmol) was converted to the free base with N₂N-diisopropylethylamine and reacted with 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde (WO 2004/058144) (203 mg, 123 mmol) and sodium triacetoxy borohydride (240 mg, 1.10 mmol) as described for Example 55 to give the free base of the product as an oil after chromatography on silica gel with dichloromethane/ methanol (93:7), 125 mg (22%).

**MS (ES):** 455.15 (MH⁺) for C₂₄H₃₈N₂O₅.

**¹H NMR (DMSO-D₆):** 8: 1.67 (s, 2H); 2.26-2.41 (m, 8H); 3.41 (s, 2H); 3.72 (s, 3H); 3.88 (s, 2H); 4.29 (d, 4H); 4.52 (s, 2H); 6.56 (d, 1H); 6.78 (s, 1H); 6.83-6.99 (m, 3H); 7.99 (s, 1H).

**Example 61**

4-{2-[1-{(2E)-3-(2,5-Difluorophenyl)prop-2-en-1-yl]piperidin-4-yl}amino}ethyl]-6-methoxy-2H-1,4-benzoazoxin-3(4H)-one

1-{(2E)-3-(2,5-Difluoropheny)prop-2-en-1-yl]piperidin-4-yl}methyl trifluoroacetate

(Intermediate 122, 430 mg, 0.85 mmol) was converted to the free base with N₂N-diisopropylethylamine and reacted with (6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoazoxin-4-yl)acetalddehyde (Intermediate 125, 197 mg, 0.90 mmol) and sodium triacetoxy borohydride (132 mg, 2.10 mmol) as described for Example 55 and purified by Reverse Phase Chromatography with 20 to 75% acetonitrile/water containing 0.1% TFA to give the trifluoroacetic acid salt of the product, 31 mg.

**MS (ES):** 458.27 (MH⁺) for C₂₇H₂₉F₂N₄O₅.
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**Intermediate 122:** 1-[(2E)-3-(2,5-Difluorophenyl)prop-2-en-1-yl]piperidin-4-amine
tert-Butyl (1-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]piperidin-4-yl) carbamate

(Intermediate 123, 299 mg, 0.85 mmol) was reacted as described for Intermediate 106. The crude trifluoroacetate of the title compound was obtained as an oil, 430 mg (quantitative), and used without further purification for the next step.

**Intermediate 123:** tert-Butyl 1-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]piperidin-4-yl) carbamate

A mixture of tert-butyl piperidin-4-yl carbamate (248 mg, 1.2 mmol), potassium carbonate (188 mg, 1.4 mmol) and 2-[(1E)-3-chloro-1-prop-1-en-1-yl]-1,4-difluorobenzene (Intermediate 124, 257 mg, 1.4 mmol) in ethanol (7 mL) was heated to 80 °C for 18 hours. The mixture was concentrated under reduced pressure, the residue taken up in dichloromethane (20 mL) and water (20 mL), the aqueous phase was back extracted with dichloromethane (2 x 20 mL) and the combined organic phases were dried over sodium sulfate. Chromatography on silica gel with dichloromethane/methanol (95:5) gave 300 mg (69%) of product as a brown foam.

**MS (ES):** 253 (M+H) for C_{14}H_{13}F_{2}N_{2}O.

**Intermediate 124:** 2-[(1E)-3-Chloro-1-prop-1-en-1-yl]-1,4-difluorobenzene

A mixture of (2E)-3-(2,5-difluorophenyl)prop-2-en-1-ol (Intermediate 70, 700 mg, 4.12 mmol), 1,4-dioxane (5 mL), and hydrochloric acid (12.1 M, 1 mL) was heated in the microwave at 100 °C for 3 hours. It was concentrated to dryness under reduced pressure, the residue taken up in ethyl acetate (10 mL), washed with water (1 x 10 mL), saturated sodium bicarbonate solution, brine and dried over sodium sulfate. The solvent was removed under reduced pressure to give 698 mg (89% yield) of product as a yellow oil.
\textit{**119**}

$^1\text{H NMR (CDCl}_3\text{)} \delta$ 4.24 (dd, 2H); 5.38 (dt, 1H); 6.75 (d, 1H); 6.88 - 7.04 (m, 2H); 7.13 (ddd, 1H).

\textbf{Intermediate 125:} (6-Methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)acetaldehyde

To a solution of oxalyl chloride (0.26 mL, 3.0 mmol) in dichloromethane (10 mL) at $-70^\circ\text{C}$ was added a solution of dimethyl sulfoxide (DMSO, 0.426 mL, 6.0 mmol) in dichloromethane (10 mL). After thirty minutes a solution of 4-(2-hydroxyethyl)-6-methoxy-2H-1,4-benzoxazin-3(4H)-one (Intermediate 126, 550 mg, 2.5 mmol) in dichloromethane (3.5 mL) was added dropwise and it was stirred for 90 minutes. Triethyl amine (1.74 mL, 12.5 mmol) was added it was stirred at $-70^\circ\text{C}$ for another 45 minutes. The reaction was quenched with water and warmed to 0°C. It was diluted with dichloromethane, the aqueous phase was extracted with dichloromethane (3 x 25 mL) and the combined organic phases were washed with 1N HCl (2 X 25 mL), water (25 mL), 1M sodium carbonate solution (2 X 25 mL), water, brine, dried over magnesium sulfate and concentrated at reduced pressure. Chromatography on silica gel with dichloromethane/methanol (96:4) gave the product as a yellow oil, 292 mg (53%).

$^1\text{H NMR (CDCl}_3\text{)} \delta$ 3.71-3.78 (m, 3H); 4.63 (s, 2H); 4.69 (s, 2H); 6.22 (d, 1H); 6.53 (dd, 1H); 6.95 (d, 1H); 9.67 (s, 1H).

\textbf{Intermediate 126:} 4-(2-Hydroxyethyl)-6-methoxy-2H-1,4-benzoxazin-3(4H)-one

To a solution of 4-(2-\{[(tert-butyldimethyl)silyl]oxy\}ethyl)-6-methoxy-2H-1,4-benzoxazin-3(4H)-one (Intermediate 127, 1.38 g, 4.1 mmol) in tetrahydrofuran (40 mL) was added tetrabutyl ammonium fluoride (1M in tetrahydrofuran (THF), 4.1 mL, 4.1 mmol). The reaction was stirred at room temperature for two hours. The solvent was removed under reduced pressure and the residue was taken up in dichloromethane, washed with water and dried over magnesium sulfate. Chromatography on silica gel using dichloromethane/methanol (95:5) gave the title compound as a yellow oil (570 mg, 62%).

$^1\text{H NMR (CDCl}_3\text{)} \delta$ ppm. 3.77 (s, 3H); 3.92 (s, 2H); 4.08 (t, 2H); 4.55 (s, 2H); 6.52 (dd, 1H); 6.68 (d, 1H); 6.90 (d, 1H).
Intermediate 127: 4-(2-((tert-Butyl)(dimethyl)silyl)oxy)ethyl)-6-methoxy-2H-1,4-
benzoxazin-3(4H)-one

To a solution of 6-methoxy-2H-1,4-benzoxazin-3(4H)-one (Intermediate 4B) (800
mg, 4.5 mmol) in DMF (16 mL) was added sodium hydride (60% in mineral oil, 260 mg, 6.5
mmol). After 20 minutes, (2-bromoethoxy)(tert-butyl)dimethylsilane (1.4 mL, 6.5 mmol) was
added and it was heated to 70°C in the microwave for 40 minutes. The reaction mixture was
partitioned between water (100 mL) and ethyl acetate (100 mL). The aqueous phase was
extracted with ethyl acetate (4 x 50 mL). The combined organic phases were washed with
water (6 x 250 mL), dried over magnesium sulfate and concentrated at reduced pressure to
afford the product as a yellow oil which was used without further purification. (1.38 g, 91%).

\[^{1}H\text{ NMR (CDCl}_3\text{)}\text{ δ: -0.02 (s, 6H); 0.83 (s, 9H); 3.77 (s, 3H); 3.84 - 3.91 (m, 2H); 4.01}
(t, 2H); 4.52 (s, 2H); 6.50 (dd, 1H); 6.82 (d, 1H); 6.87 (d, 1H).]

Example 62

4-(3-(4-(2-E)-3-(2,5-Difluorophenyl)prop-2-en-1-yl)piperezin-1-yl)propyl)-6-
methoxy-2H-1,4-benzoxazin-3(4H)-one

A solution of 6-methoxy-4-(3-piperazin-1-ylpropyl)-2H-1,4-benzoxazin-3(4H)-one
trifluoroacetate (Intermediate 118, 985 mg, 1.52 mmol) in dry ethanol (10 mL) was
converted to the free base with N,N-diisopropylethylamine for 30 min and then was added 2-
[(1E)-4-chloroprop-1-en-1-yl]-1,4-difluorobenzene (Intermediate 124, 315 mg, 1.67 mmol),
and potassium carbonate (230 mg, 1.67 mmol). The mixture was heated at 80°C for 18 hours,
cooled to room temperature and then concentrated to dryness under reduced pressure. The
residue was partitioned between water (50 mL) and dichloromethane (100 mL). The organic
phase was dried over sodium sulfate and concentrated under reduced pressure.

Chromatography on silica gel with dichloromethane/methanol (95:5) gave the free base of the
title compound as a yellow foam. The free base was taken up in dichloromethane (14 mL),
followed by the addition of 2M HCl in ether (0.41 mL). The precipitate was collected by
filtration and to give the bis hydrochloride salt of the product as a colorless solid, 171 mg
(79%).

\[^{1}H\text{ NMR (DMSO-D}_{6}\text{)}\text{ δ 1.90-2.04 (bs, 2H); 3.15-3.30 (m, 6H); 3.75 (s, 3H); 3.95 (m, 3H);}
4.57 (s, 2H); 6.45-6.54 (m, 1H); 6.57-6.61 (m, 1H); 6.81 (d, 1H); 6.93 (d, J = 9Hz, 1H);
7.26-7.33 (m, 2H); 7.56 (m, 1H).]

\[^{13}C\text{ NMR (DMSO-D}_{6}\text{)}\text{ δ 20.0 (CH); 32.6 (CH); 49.1 (NCH); 118.5 (CH); 119.2 (C=O);}
124.7 (CH); 129.7 (CH); 132.4 (CH); 137.8 (CH); 141.5 (CH); 148.6 (CH); 151.8 (C=O);}
164.2 (C=O).}

M S (ES): 458.30 (M\text{H}^+)\text{ for C}_{29}H_{29}F_{2}N_{3}O_{3}
Example 63

6-[[1-[(2-(6-Methoxy-2-oxo-1,7-naphthyridin-1(2H)-yl)ethyl)piperidin-4-yl]amino]methyl]-2H-pyrrolo[3,2-b][1,4]oxazin-3(4H)-one

A solution of 1-[(2-(4-aminopiperidin-1-yl)ethyl]-6-methoxy-1,7-naphthyridin-2(1H)-one (Intermediate 128, crude, 116 mg, 0.38 mmol) and 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde [WO2004/058144] (32 mg, 0.46 mmol) in chloroform/methanol (6 mL, 10:1) was heated over 3 Å molecular sieves at 70°C for 18 hours. The reaction mixture was cooled to 0°C, and sodium triacetoxylborohydride (160 mg, 0.84 mmol) was added. The resulting reaction mixture was allowed to warm to room temperature and stirred for 18 hours. The reaction was diluted with dichloromethane (50 mL) and water (10 mL). The aqueous phase was separated and evaporated to give a solid. The solid was suspended in methanol and filtered. The resultant solid was dissolved in dichloromethane : methanol (1:1) and treated with 2N HCl in ether to obtain the dihydrochloride salt. The colorless precipitate was collected by filtration and gave 28 mg (14%) of the bis-
hydrochloride salt of the product.

**MS:** 465 (MH)<sup>+</sup> for C<sub>30</sub>H<sub>28</sub>N<sub>6</sub>O<sub>4</sub>

**1H NMR:** (DMSO-D<sub>6</sub>) δ ppm: 2.04-2.19 (m, 2H); 2.19-2.31 (m, 1H); 2.32-2.45 (m, 3H); 3.05-3.21 (m, 4H) 3.69-3.84 (m, 2H); 3.89 (s, 3H); 4.05-4.20 (m, 2H); 4.62-4.75 (m, 4H); 6.83 (d, 1H); 7.20 (s, 1H); 7.30 (d, 1H); 7.42 (d, 1H); 7.92 (d, 1H); 8.78 (s, 1H); 9.94 (s, 1H); 11.39 (s, 2H).

Intermediate 128: 1,12-(4-Aminopiperidin-1-yl)ethyl]-6-methoxy-1,7-naphthyridin-2(1H)-one

A solution of tert-butyl (1-[(2-(6-chloro-2-oxo-1,7-naphthyridin-1(2H)-yl)ethyl)piperidin-4-yl]carbamate (Intermediate 129, 335 mg, 0.83 mmol) was treated with a solution of sodium methoxide in methanol (0.5 M, 4 mL). The reaction was sealed in a tube and heated at 150°C for 4 hours using microwave irradiation. The reaction was diluted with water and ethyl acetate. The layers were separated. The aqueous phase was washed with ethyl acetate twice. The organic extracts were combined, dried over magnesium sulfate and evaporated at reduced pressure to give 116 mg (64%) of the crude product as a yellow oil.

**MS:** 303 (MH<sup>+</sup>) for C<sub>14</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub>
Intermediate 129. tert-Butyl [1-(2-(7-methoxy-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl]carbonate

6-Chloro-1,7-naphthyridin-2(1H)-one (J. Org. Chem. 1990, 55, 4744-4750) (360 mg, 2.0 mmol) was deprotonated with sodium hydride (100 mg, 60% in oil, 2.4 mmol) and alkylated with 2-(4-((tert-butoxycarbonyl)amino)piperidin-1-yl)ethyl methanesulfonate (Intermediate 6) 2.75 mmol as described for Intermediate 2. Chromatography on silica gel with methanol in dichloromethane (0-10%) gave 334 mg (20%) of the product as a colorless solid.

MS (ES): 407 (MH+) for C_{28}H_{37}ClN_{4}O_{3} (350)

1H NMR (DMSO-d_6) δ 1.19-1.32 (m, 1H); 1.36 (s, 9H); 1.56-1.70 (m, 2H); 2.01 (s, 2H); 2.51-2.57 (m, 2H); 2.64-2.75 (m, 1H); 2.82-2.93 (m, 2H); 3.10-3.25 (m, 2H); 3.29-3.31 (m, 1H); 4.30-4.40 (m, 2H); 6.71-6.80 (m, 1H); 6.91 (d, 1H); 7.87 (s, 1H); 7.91 (d, 1H); 8.74 (s, 1H).

Example 64

Methyl 1-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]-4-[3-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propyl]piperidin-3-carboxylate

A solution of methyl 4-[(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propyl]piperidin-3-carboxylate trifluoroacetate (Intermediate 130, crude, 171, 0.48 mmol), (2E)-3-(2,5-difluorophenyl)acrylaldehyde [FR 2872164] (31 mg, 0.48 mmol), and triethylamine (0.13 mL, 0.96 mmol) in chloroform/methanol (6 mL, 10:1) was heated over 3 Å molecular sieves at 70°C for 3 hours. The reaction mixture was cooled to 0°C, and sodium triacetoxymethyldride (200 mg, 0.94 mmol) was added. The resulting reaction mixture was allowed to warm to room temperature and stir for 18 hours. The reaction was diluted with ethyl acetate (25 mL) and water (10 mL). The aqueous phase was separated and washed twice with ethyl acetate. The organic layers were combined, dried over magnesium sulfate and evaporated at reduced pressure. Chromatography on silica gel with diethyl ether gave the title compound as a off-white foam, (79 mg, 32%).

MS (ES) 510 (MH+) for C_{28}H_{32}F_{2}N_{4}O_{3} (285)

1H NMR (DMSO-d_6) δ 1.10-1.21 (m, 1H); 1.23-1.34 (m, 1H); 1.44-1.55 (m, 3H); 1.67-1.79 (m, 2H); 1.95-2.07 (m, 1H); 2.18-2.29 (m, 1H); 2.31-2.43 (m, 1H); 2.64-2.70 (m, 1H); 2.71-2.80 (m, 1H); 2.82-2.89 (m, 1H); 3.06-3.17 (m, 2H); 3.57 (d, 3H); 3.84-3.96 (m,
Intermediate 136: Methyl 4-(2-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propyl)piperidine-3-carboxylate

A solution of 1-tert-butyl 3-methyl 4-(3-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propyl)piperidine-1,3-dicarboxylate (Intermediate 131, 220 mg, 0.48 mmol) was reacted as described for Intermediate 106. The crude trifluoroacetate of the title compound was used without further purification for the next step (quantitative).

Intermediate 131: 1-tert-Butyl 3-methyl 4-(3-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propyl)piperidine-1,3-dicarboxylate

A solution of 3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile (Intermediate 68) (265 mg, 1.53 mmol) in dry dimethylformamide (DMF) (5 mL) was treated at 0°C with sodium hydride (105 mg, 60% in oil, 2.63 mmol) and then stirred for 1 hour at room temperature. A solution of 1-tert-butyl 3-methyl 4-(3-[[((methylsulfonyl)oxy]propyl)piperidine-1,3-dicarboxylate in DMF (Intermediate 132, 0.31 mmol, 5 mL, 1.53 mmol) was then added and the resulting mixture was stirred at room temperature for 96 hours. The reaction was diluted with ethyl acetate and water. The aqueous layer was adjusted to pH 3 with 1 N HCl. The layers were separated. The aqueous phase was extracted once with ethyl acetate. The combined organic phases were washed four times with water, dried over magnesium sulfate and evaporated at reduced pressure. Chromatography on silica gel with (10–35%) acetone in hexanes gave 445 mg (64%) of the product as a white semi-solid (as a mixture of diastereomers).

MS (ES): 458 (M+H) for C_{24}H_{30}N_{2}O_{6}

H NMR (CDCl₃) δ: 1.43 and 1.44 (two s, 9H); 1.47-1.9 (m, 7H); 2.56-2.83 (m, 2H); 2.94-3.2 (m, 1H); 3.65 and 3.70 (two s, 3H); 3.76-3.99 (m, 2H); 4.02-4.21 (m, 1H); 4.67 and 4.70 (two s, 2H); 7.04 (m, 1H); 7.11 and 7.18 (two brs, 1H); 7.30 (m, 1H).

Intermediate 132: 1-tert-Butyl 3-methyl 4-(3(((methylsulfonyl)oxy)propyl)piperidine-1,3-dicarboxylate

A mixture of 1-tert-butyl 3-methyl 4-(3-hydroxypropyl)piperidine-1,3-dicarboxylate (Intermediate 133, 460 mg, 1.53 mmol) in dry dichloromethane (5 mL) and triethyl amine
(0.3 mL, 2.14 mmol) was treated at 0°C with a solution of methanesulfonyl chloride (0.14 mL, 1.83 mmol) in dichloromethane (5 mL). After 2 hours minutes the reaction was complete by TLC (dichloromethane : methanol 10:1). The reaction was diluted with ethyl acetate and water. The layers were separated. The organic layer was washed with 0.1N HCl, water, saturated sodium bicarbonate, dried over magnesium sulfate. The solvent was removed under reduced pressure and the crude preparation of the mesylate was used without delay for the next step.

Intermediate 133: 1-tert-Butyl 3-methyl 4-(3-hydroxypropyl) piperidine-1,3-dicarboxylate

A solution of 1-tert-butyl 3-methyl 4-allylpiperidine-1,3-dicarboxylate [WO2002/072572] (715 mg, 2.53 mmol) in tetrahydrofuran (5 mL) at 0°C was treated with a solution of 9-BBN in tetrahydrofuran (0.5M, 10.2 mL, 5.1 mmol). After one hour the reaction mixture was allowed to warm to room temperature for 3 hours. The reaction mixture was cooled to 0°C and treated with water (3 mL), NaOH (3N, 6 mL) and hydrogen peroxide (30% solution, 6 mL). The reaction was allowed to warm to room temperature and stir for one hour. The reaction was diluted with ethyl acetate and water. The layers were separated. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over magnesium sulfate and concentrated at reduced. Chromatography on silica gel with methanol in dichloromethane (0-10%) gave the product as a colorless oil as a mixture of diastereomers (460 mg, 60%).

MS (ES): 302(MH+)+ for C_{15}H_{22}NO_{5}

^1H NMR (CDCl3) δ: 1.28-1.39 (m, 1H); 1.43 and 1.44 (two s, 9H); 1.46-1.54 (m, 2H); 1.56-1.67 (m, 3H); 1.73-1.85 (m, 2H); 2.58-2.63 (m, 1H); 3.02-3.12 (m, 1H); 3.27 (dd, 1H); 3.60-3.64 (m, 2H); 3.65 and 3.69 (two s, 3H); 3.71-3.81 (m, 1H); 3.87-3.98 (m, 1H).

Example 65

4-[(6-Cyano-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propyl]-1-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl] piperidine-3-carboxylic acid

A solution of methyl 1-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]-4-[(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propyl] piperidine-3-carboxylate (Example 64) (73 mg, 0.143 mmol) in methanol (12 mL) and water (5 mL) was treated with sodium hydroxide solution (1N, 1 mL). After 64 hours, the pH was adjusted to 6 with 1N HCl. The mixture was
extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over magnesium sulfate and concentrated at reduced pressure. Chromatography on silica gel using methanol in dichloromethane (0-10%) and trituration with diethyl ether gave the title compound as a colorless solid, mixture of diastereomers, 10 mg (14%).

**MS (ES):** 496 (MH)+ for C₂₇H₂₇F₂N₂O₄

**¹H NMR (CDCl₃)**: δ: 1.40-1.45 (m, 1H); 1.47-1.52 (m, 1H); 1.60-1.65 (m, 1H); 1.65-1.77 (m, 3H); 2.25-2.37 (m, 2H); 2.70-2.77 (m, 1H); 3.08-3.16 (m, 1H); 3.23-3.30 (m, 1H); 3.30-3.40 (m, 2H); 3.64-3.72 (m, 1H); 3.73-3.84 (m, 1H); 3.86-3.95 (m, 1H); 3.95-4.07 (m, 1H); 4.60-4.71 (m, 3H); 6.21-6.31 (m, 1H); 6.67 (d, 1H); 6.87-6.95 (m, 1H); 6.96-7.01 (m, 1H); 7.01-7.07 (m, 1H); 7.09-7.15 (m, 1H); 7.28-7.31 (m, 1H).

**Example 66**

7-Fluoro-3-methyl-1-[2-(4-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino)piperidin-1-yl)ethyl]quinazoline-2,4(1H,3H)-dione

1-[2-(4-Aminopiperidin-1-yl)ethy]-7-fluoro-3-methylquinazoline-2,4(1H,3H)-dione trifluoroacetate salt (Intermediate 134) (0.476 mmol, 380 mg crude) was converted to the free base with N,N-dioisopropylethylamine (0.5 mL, 3.0 mmol) and reacted with 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carboxaldehyde (WO 2004/038144) (102 mg, 0.571 mmol) and sodium triacetoxyl borohydride (222 mg, 1.05 mmol) as described for Example 55. The reaction was diluted with dichloromethane and water. The layers were separated. The aqueous layer was extracted with dichloromethane twice. The combined organic layers were dried over magnesium sulfate and evaporated at reduced pressure. Chromatography on silica gel using methanol in dichloromethane (0-9%) with 1% concentrated ammonium hydroxide (aqueous) gave the product as a waxy material. This material was taken up in dichloromethane and washed well with water. The organic phase was dried over magnesium sulfate and evaporated to obtain the title compound as a colorless solid (48 mg, 21%).

**MS (ES):** 483 (MH)+ for C₂₉H₂₇F₂N₄O₆

**¹H NMR (DMSO-D₆)**: δ: 1.14-1.28 (m, 2H); 1.71-1.82 (m, 2H); 1.94-2.06 (m, 2H); 2.33-2.44 (m, 2H); 2.83-2.92 (m, 2H); 3.26-3.30 (m, 3H); 3.65-3.72 (m, 2H); 4.17 (t, 2H); 4.60 (s, 2H); 7.00 (d, 1H); 7.13 (d, 1H); 7.29 (d, 1H); 7.36 (d, 1H); 8.09 (dd, 1H); 11.18 (s, 1H).
Intermediate 134: 1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-fluoro-3-methylquinazoline-2,4(1H,3H)-dione

tert-Butyl {1-[2-(7-fluoro-3-methyl-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)ethyl]piperidin-4-yl} carbonate (Intermediate 135) (200 mg, 0.476 mmol) was reacted as described for Intermediate 106. The crude trifluoro acetic acid of the title compound was used without further purification for the next step (quantitative).

MS (ES): 321 (M+H)+ for C_{16}H_{21}FN_{4}O_{2}

Intermediate 135: tert-Butyl {1-[2-(7-fluoro-3-methyl-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)ethyl]piperidin-4-yl} carbonate

7-Fluoro-3-methylquinazoline-2,4(1H,3H)-dione (Intermediate 136) (388 mg, 2.0 mmol) was deprotonated with sodium hydride (100 mg, 60% in oil, 2.4 mmol) and alkylated with 2-[4-{(tert-butoxycarbonyl)amino}piperidin-1-yl]ethyl methanesulfonate (Intermediate 6) 2.75 mmol as described for Intermediate 2. Chromatography on silica gel using ethyl acetate in hexanes (10-30%) gave the title compound as a yellow oil (200 mg, 24%).

MS (ES): 421 (M+H)+ for C_{17}H_{22}FN_{4}O_{4}

^1H NMR (CDCl3) δ: 1.2-1.3 (m, 2H); 1.43 (s, 9H); 1.44-1.5 (m, 1H); 1.9-2.0 (m, 2H); 2.15-2.35 (m, 2H); 2.65 (m, 2H); 2.85-3.0 (m, 1H); 3.45 (s, 3H); 3.46-3.52 (m, 1H); 4.15-4.25 (m, 2H); 4.35-4.5 (m, 1H); 6.8-6.9 (m, 1H); 6.91-7.0 (m, 1H); 8.2-8.26 (m, 1H).

Intermediate 136: 7-Fluoro-3-methylquinazoline-2,4(1H,3H)-dione

A suspension of sodium hydride (60% in mineral oil, 368 mg, 9.2 mmol) in dimethylformamide (12 mL) was cooled to 0°C and treated with 2-aminoo-4-fluoro-N-methylbenzamide (Intermediate 137) (0.67 g, 4.0 mmol). Phenyl chloroformate (0.6 mL, 0.73 g, 4.7 mmol) was added over 40 minutes. After 1 hour a further portion of phenyl chloroformate (0.6 mL, 0.73 g, 4.7 mmol) was added. The reaction was allowed to warm to room temperature and stir for two hours. The reaction was slowly added to 200 mL of ice. The solid was filtered, washed with methanol to obtain the product (395 mg, 51%).

MS (ES): 193 (M-H)- for C_{9}H_{17}FN_{2}O_{2}

^1H NMR (DMSO-d_6) δ: 3.23 (s, 3H); 6.89 (dd, 1H); 7.04 (td, 1H); 7.98 (dd, 1H); 11.56 (s, 1H).
Intermediate 137: 2-Amino-4-fluoro-N-methylbenzamide

A mixture of 2-amino 4-fluoro benzoic acid (2.5 g, 16.13 mmol) and 1,3 dimethyl urea (5.85 g, 66.5 mmol) was heated at 150°C for 24 hours. The reaction was diluted with water, filtered and extracted twice with ethyl acetate. The organic extracts were dried over magnesium sulfate and concentrated at reduced pressure. Chromatography on silica gel with ethyl acetate in hexanes (0-50%) gave the title compound as a waxy solid (670 mg, 25%)

MS (ES) : 169 (MH)^+ for C_{9}H_{12}FN_{2}O

^1^H NMR (DMSO-D6) δ: 2.69 (d, 3H); 6.29 (td, 1H); 6.43 (dd, 1H); 6.74 (s, 2H); 7.49 (dd, 1H); 8.08-8.22 (m, 1H).

Example 67

7-Chloro-1-(2-(2,3-dihydro[1,4]dioxino[2,3-ε]pyridin-7-yl)methyl)amino)piperidin-1-yl)ethyl]-1,8-naphthyridin-2(1H)-one

1-[2-(4-Aminopiperidin-l-yl)ethyl]-7-chloro-1,8-naphthyridin-2(1H)-one

trifluoroacetate (Intermediate 138, crude, 405 mg, 0.76 mmol), di-isopropyl ethylamine (0.38 mL, 2.27 mmol), 2,3-dihydro[1,4]dioxino[2,3-ε]pyridine-7-carbalddehyde [WO 2004/058144] (180 mg, 1.1 mmol) and sodium cyanoborohydride (100 mg, 1.56 mmol) were reacted as described for Example 21. Chromatography on silica gel using methanol in dichloromethane (0-20% with 1% aqueous ammonium hydroxide) followed by reverse phase chromatography with 20-75% acetonitrile/water/10 mM NH₄OAc Buffer) gave the title compound (39 mg, 11%).

MS (ES) : 456 (MH)^+ for C_{3}H_{2}ClN_{4}O_{3}

^1^H NMR (CDCl₃) δ 1.32 - 1.43 (m, 2H); 1.87 (d, 2H); 2.10 - 2.21 (m, 2H); 2.51 - 2.61 (m, 1H); 2.69 (t, 2H); 3.08 (d, 2H); 3.81 (s, 2H); 4.21 - 4.32 (m, 4H); 4.58 (t, 2H); 6.68 (d, 1H); 6.78 (s, 1H); 7.11 (d, 1H); 7.58 (d, 1H); 7.75 (d, 1H); 8.05 (s, 1H).

Intermediate 138: 1-[2-(4-Aminopiperidin-l-yl)ethyl]-7-chloro-1,8-naphthyridin-2(1H)-one

tert-Butyl (1-[2-(7-chloro-2-oxo-1,8-naphthyridin-1(2H)-yl)ethyl]piperidin-4-yl) carbamate (Intermediate 139, 308 mg, 0.76 mmol) was reacted as described for Intermediate 106. The crude trifluoro acetate of the title compound was used without further purification for the next step (quantitative).
Intermediate 139: tert-Butyl [1-(2-(7-chloro-2-oxo-1,8-naphthyridin-1(2H)-yl)ethyl)piperidin-4-yl]carbamate

A solution of 7-chloro-1,8-naphthyridin-2(1H)-one [J. Org. Chem. 1990, 55, 4744-4750] in dry DMF (20 mL) (540 mg, 3.0 mmol) at 0°C was treated with sodium hydride (144 mg, 60% in mineral oil, 3.6 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction was cooled using an ice bath. A solution of 2-(4-((tert-butoxycarbonyl)amino)piperidin-1-yl)ethyl methanesulfonate in DMF (Intermediate 6), 0.33 mmol/mL, 1.0 mL, 3.3 mmol) was then added over 1 hour. The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with water and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with saturated sodium chloride solution (3 x 10 mL), dried over sodium sulfate and evaporated. Chromatography on silica gel using methanol in dichloromethane (0-15%) gave the title compound as a brown foam (711 mg, 58%).

MS (ES): 407 (MH)$^+$ for C$_{36}$H$_{47}$ClN$_3$O$_3$.

$^1$H NMR (CDCl$_3$) δ 1.42 (s, 11H); 1.84 - 1.99 (m, 2H); 2.12 - 2.22 (m, 1H); 2.22 - 2.37 (m, 2H); 2.65 - 2.80 (m, 2H); 3.03 - 3.19 (m, 1H); 3.39 - 3.55 (m, 1H); 4.34 - 4.48 (m, 1H); 4.62 (t, 2H); 6.72 (d, 1H); 7.15 (d, 1H); 7.61 (d, 1H); 7.78 (d, 1H).

Example 68

1-(2-(4-{(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino)piperidin-1-yl)ethyl)-7-methoxy-1,8-naphthyridin-2(1H)-one

A solution of 7-chloro-1-(2-{4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl}ethyl)-1,8-naphthyridin-2(1H)-one (Example 67) (95 mg, 0.21 mmol) in methanol (5 mL) was treated with a solution of sodium methoxide (0.5 M, 1 mL, 0.5 mmol). The reaction mixture was sealed in a tube and heated at 150°C for 1 hour using microwave irradiation. The reaction mixture was concentrated at reduced pressure, partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and chloroform/methanol (4:1) (3 x 15 mL). The combined organic extracts were dried over sodium sulfate and concentrated at reduced pressure.

Chromatography on silica gel using methanol in dichloromethane (0-50%) gave the product as a colorless solid (29 mg, 31%)

MS (ES): 452 (MH)$^+$ for C$_{26}$H$_{35}$N$_5$O$_4$. 

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$^1$H NMR (CDCl$_3$) δ 1.39 - 1.54 (m, 2H); 1.90 (d, 2H); 2.13 - 2.28 (m, 2H); 2.47 - 2.62 (m, 1H); 2.64 - 2.76 (m, 2H); 3.06 (d, 2H); 3.80 (s, 2H); 3.99 (s, 3H); 4.26 (dd, 4H); 4.55 - 4.68 (m, 2H); 6.55 (dd, 2H); 6.80 (s, 1H) 7.53 (d, 1H); 7.68 (d, 1H); 8.06 (s, 1H).

Example 69

1-(2-(4-(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl)amino)piperidin-1-yl)ethyl)-7-fluoroquinoxalin-2(1H)-one

A mixture of 1-[2-(4-aminopiperidin-1-yl)ethyl]-7-fluoroquinoxalin-2(1H)-one (Intermediate 140, 85 mg, 0.29 mmol), 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde (WO 2004/053444) (49 mg, 0.29 mmol) and molecular sieves 3 Å in dry methanol/chloroform (1:1, 10 mL) was heated to 70 °C for 3 hours. The reaction was allowed to cool to room temperature and sodium triacetoxycarbonylhydride (190 mg, 0.88 mmol) was added. After 30 minutes, the reaction was filtered through celite, the filtrate was concentrated to dryness, taken up in 15% methanol/chloroform, and washed with saturated sodium bicarbonate solution. The aqueous phase was re-extracted twice with 15% methanol/chloroform. The combined organic phases were dried over magnesium sulfate, filtered, and concentrated to dryness. Chromatography on silica gel with 5% methanol in dichloromethane containing 0.25% ammonium hydroxide gave 70 mg (54%) of the title compound as an off-white solid.

MS (ES): 440 (MH$^+$) for C$_{27}$H$_{34}$FN$_2$O$_3$

$^1$H NMR (DMSO-D$_6$) δ 1.11 - 1.24 (m, 2H); 1.73 (d, 2H); 2.00 (t, 2H); 2.13 (s, 1H); 2.25 - 2.38 (m, 1H); 2.51 - 2.56 (m, 2H); 2.87 (d, 2H); 3.64 (s, 2H); 4.24 - 4.35 (m, 6H); 6.92 (s, 1H); 7.24 (dd, 1H); 7.52 (dd, 1H); 7.87 (dd, 1H); 7.99 (s, 1H); 8.18 (s, 1H).

Intermediate 140: 1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-fluoroquinoxalin-2(1H)-one

A solution of tert-butyl {1-[2-(7-fluoro-2-oxquinolin-1(2H)-yl)ethyl]piperidin-4-yl} carbamate (Intermediate 141, 240 mg, 0.62 mmol) in dichloromethane (20 mL) was treated with trifluoroacetic acid (15 mL). After 45 minutes, the reaction was concentrated to dryness, the residue taken up in methanol/chloroform (15:85, 30 mL) and washed with saturated sodium bicarbonate solution. The aqueous layer was re-extracted with methanol/chloroform (15:85, 3x30 mL). The combined organic phases were dried over magnesium sulfate and concentrated to dryness to give 170 mg (quantitative) of the crude product as an oil.
**Intermediate 141**: tert-Butyl (1H-[7-fluoro-2-oxo-6-quinolinaxin-1(2H)]-yl)ethyl(4-piperidinyl) carbamate

and

**Intermediate 142**: tert-Butyl (1H-[6-fluoro-2-oxo-6-quinolinaxin-1(2H)]-yl)ethyl(4-piperidinyl) carbamate

A suspension of a 1:1 mixture of 7-fluoroquinolinaxin-2(1H)-one (Intermediate 143) and 6-fluoroquinolinaxin-2(1H)-one (Intermediate 144) (1.5 g total, 9.1 mmol) was treated with sodium hydride (60% in oil, 0.44 g, 11.0 mmol) at 0°C. The reaction was allowed to stir at room temperature for 2 hours. The reaction mixture was cooled to 0°C and 2-(4-[[tert-butoxycarbonyl]amino][piperidin-1-yl]ethyl methanesulfonate (Intermediate 6, 1.33 mmol/mL, 11.0 mmol), dissolved in dry DMF (5 mL) was added and it was stirred at room temperature overnight. The reaction mixture was diluted with water and with diethyl ether (5x 50 mL). The combined organic phases were dried over sodium sulfate and concentrated to dryness under reduced pressure. Chromatography with hexanes/acetone (5:1 to 3:1). The higher R₄₉ material was isolated as a mixture of Intermediate 141 with an O-alkylated isomer, which was rechromatographed on silica gel with hexanes/ethyl acetate (1:3) to give pure Intermediate 141 as a colorless solid, 0.24 g, 14%. Isolation of the lower R₄₉ material from the first column gave 0.38 g (21%) of pure Intermediate 142 as a colorless solid.

**Intermediate 141**:

**MS (ES)**: 391 (M⁺) for C₂₃H₂₇F₈N₅O₅

**¹H NMR (DMSO-DS)**: 5.1.25-1.38 (m, 11H); 1.56-1.68 (m, 2H); 2.01 (t, 2H); 2.50-2.56 (m, 2H); 2.82-2.93 (m, 2H); 3.16 (s, 1H); 4.27 (t, 2H); 6.72 (d, 1H); 7.23 (t, 1H); 7.50 (d, 1H); 7.83-7.91 (m, 1H); 8.17 (s, 1H).

**Intermediate 142**:

**MS (ES)**: 391 (M⁺) for C₂₃H₂₇F₈N₅O₅

**¹H NMR (DMSO-DS)**: 5.1.24-1.38 (m, 11H); 1.65 (d, 2H); 2.03 (t, 2H); 2.51-2.58 (m, 2H); 2.88 (d, 2H); 3.11-3.26 (m, 1H); 4.31 (t, 2H); 6.75 (d, 1H); 7.57 (td, 1H); 7.63-7.71 (m, 2H); 8.29 (s, 1H).
**Intermediate 143: 7-Fluoroquinoxalin-2(1H)-one**

and

**Intermediate 144: 6-Fluoroquinoxalin-2(1H)-one**

A mixture of 4-fluorobenzene-1,2-diamine (5.0 g, 39.7 mmol) and ethyl oxoacetate (50 wt % in toluene, 17 mL, 79.4 mmol) in ethanol (100 mL) was stirred for two hours at room temperature. The precipitate was collected by filtration, washed with ethanol, and dried under vacuum giving 4.5 g of a solid. $^1$H NMR revealed a 1:1 mixture of Intermediates 143 and 144. This mixture was used for the next step.

**MS (ES): 165 (MH$^+$) for C$_{8}$H$_{7}$FN$_{2}$O**

**Example 70**

6-[[1-2-(7-Fluoro-2-oxoquinazolin-1(2H)-yl)ethyl]piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

1-[(2-(4-Aminopiperidin-1-y1)ethyl]-7-fluoroquinoxalin-2(1H)-one (Intermediate 148, 85 mg crude, 0.29 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (52 mg, 0.29 mmol) and sodium triacetoxy borohydride (190 mg, 0.88 mmol) were reacted as described according to Example 69 to give 90 mg (69%) of the free base of the product.

**MS (ES): 453 (MH$^+$) for C$_{23}$H$_{27}$FN$_{6}$O$_{3}$**

**$^1$H NMR (DMSO-**d$_6$)** 5 1.12-1.26 (m, 2H); 1.69-1.81 (m, 2H); 2.01 (t, 2H); 2.27-2.42 (m, 1H); 2.51-2.60 (m, 2H); 2.88 (d, 2H); 3.67 (s, 2H); 4.28 (t, 2H); 4.60 (s, 2H); 7.00 (d, 1H); 7.20-7.31 (m, 2H); 7.52 (dd, 1H); 7.88 (dd, 1H); 8.19 (s, 1H); 11.16 (s, 1H).

**Example 71**

1-[(2-(4-(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl)amino)piperidin-1-yl]ethyl]-6-fluoroquinoxalin-2(1H)-one

1-[(2-(4-Aminopiperidin-1-y1)ethyl]-6-fluoroquinoxalin-2(1H)-one (Intermediate 145, 87 mg, 0.30 mmol), 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde (WO 2004/058144) (50 mg, 0.30 mmol), and sodium triacetoxy borohydride (200 mg, 0.90 mmol) were reacted as described for Example 69 to give the free base of the title compound as an oil. The free base was taken up in isopropanol (10 mL) and treated with 2.0M HCl in ether (3 eq). Solvent was removed under reduced pressure. The resulting solid was triturated with...
dichloromethane/hexanes (2mL/10mL). The precipitate was collected by filtration to give 45 mg (29%) of the bis-hydrochloride salt of the product.

\[ \text{MS (ES)}: 440 (M^+ \text{ for C}_{21}H_{26}FN_4O_3} \]
\[ {^1H \text{NMR (D}_2\text{O}) \delta 1.83-2.06 \text{ (m, 2H); 2.42 (d, 2H); 3.17 (t, 2H); 3.48-3.68 (m, 3H); 3.79-4.01 (m, 2H); 4.30-4.41 (m, 4H); 4.43-4.51 (m, 2H); 4.65-4.70 (m, 2H); 7.27-7.30 (m, 1H); 7.44-7.55 (m, 2H); 7.59 (dd, 1H); 8.20-8.25 (m, 2H).} \]

**Intermediate 145**: 1-[2-(4-Aminopiperidin-1-yl)ethyl]-6-fluorquinazolin-2(1H)-one
ter-Butyl [1-[2-(6-fluoro-2-oxoquinazolin-1(2H)-yl)ethyl]piperidin-4-yl] carbamate

(Intermediate 142, 380 mg, 0.97 mmol) was reacted with trifluoroacetic acid in dichloromethane as described for Intermediate 140 to give 260 mg (93%) of the crude product as an oil.

\[ \text{MS (ES)}: 291 (M^+ \text{ for C}_{13}H_{19}FN_4O} \]

**Example 72**

1-[2-[(4-(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl)amino]piperidin-1-yl]ethyl]-7-methoxyquinazolin-2(1H)-one

1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-methoxyquinazolin-2(1H)-one (Intermediate 146, 60 mg crude, 0.20 mmol), 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carboxaldehyde (WO 2004/058144) (33 mg, 0.20 mmol), and sodium triacetoxyl borohydride (130 mg, 0.60 mmol) were reacted as described for Example 69 to give the free base of the title compound as an oil. The free base was taken up in isopropanol and treated with 4.0M HCl in dioxane (3 eq). Solvent was removed under reduced pressure to give 28 mg (27% yield) of the bis-hydrochloride salt of the product.

\[ \text{MS (ES)}: 452 (M^+ \text{ for C}_{24}H_{28}N_4O_4} \]
\[ {^1H \text{NMR (D}_2\text{O}) \delta 1.86-2.02 \text{ (m, 2H); 2.36-2.49 (m, 2H); 3.09-3.23 (m, 2H); 3.52 (t, 2H); 3.56-3.68 (m, 1H); 3.82-3.95 (m, 5H); 4.32-4.40 (m, 4H); 4.43-4.50 (m, 2H); 4.61 (t, 2H); 6.82 (d, 1H); 7.03 (dd, 1H); 7.29 (s, 1H); 7.71 (d, 1H); 7.97 (s, 1H); 8.22 (s, 1H).} \]

**Intermediate 146**: 1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-methoxyquinazolin-2(1H)-one
ter-Butyl [1-[2-(7-methoxy-2-oxoquinazolin-1(2H)-yl)ethyl]piperidin-4-yl] carbamate (Intermediate 147, 190 mg, 0.47 mmol) was reacted with trifluoroacetic acid in
dichloromethane as described for Intermediate 140 to give 110 mg of the crude product as an oil.

**MS (ES):** 303 (MH⁺) for C₁₉H₂₂N₄O₂

**Intermediate 147: tert-Butyl (1-[2-(7-methoxy-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl) carbonate**

7-methoxyquinolin-2(1H)-one (Intermediate 148, 300 mg, 1.70 mmol) was deprotonated with sodium hydride (100 mg, 60% in oil, 2.56 mmol) and alkylated with 2-{4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}ethyl methanesulfonate (Intermediate 6) (3.4 mmol) as described for Intermediate 2. Chromatography on silica gel with 25% acetone in hexanes gave 200 mg (29%) of the product as a colorless solid.

**MS (ES):** 403 (MH⁺) for C₂₃H₂₆N₄O₄

**¹H NMR (DMSO-D₆)**
- 1.26-1.40 (m, 11H);
- 1.57-1.72 (m, 2H);
- 1.97-2.11 (m, 2H);
- 2.51-2.61 (m, 2H);
- 2.85-2.98 (m, 2H);
- 3.19 (s, 1H);
- 3.92 (s, 3H);
- 4.32 (t, 2H);
- 6.76 (d, 1H);
- 6.95-7.04 (m, 2H);
- 7.70-7.78 (m, 1H);
- 8.04 (s, 1H).

**Intermediate 148: 7-Methoxyquinolin-2(1H)-one**

A suspension of 2-chloro-7-methoxyquinoline (Intermediate 149, 720 mg, 3.70 mmol) in 5M HCl (25 mL) was heated to 110 °C for 1 hour. The reaction was cooled to room temperature and let stand for 24 hours. The resulting precipitate was collected by filtration. A second crop of material was collected after concentration the mother liquor. The two crops were combined and crystallized from methanol to give 550 mg (85%) of the product as an off-white solid.

**MS (ES):** 177 (MH⁺) for C₉H₅N₂O₂

**¹H NMR (DMSO-D₆)**
- 3.83 (s, 3H);
- 6.76 (d, 1H);
- 6.91 (dd, 1H);
- 7.69 (d, 1H);
- 7.94-8.00 (m, 1H);
- 12.32 (s, 1H).

**Intermediate 149: 2-Chloro-7-methoxyquinoline**

A solution of 4-methoxybenzene-1,2-diamine (16.8 g, 0.12 mmol) in ethanol (250 mL) was treated with a solution of ethyl oxoacetate (50 wt % in toluene, 50 mL, 0.23 mmol) dropwise with cooling in an ice bath. The reaction was allowed to warm to room temperature and after 2 hours, a precipitate was collected by filtration giving 15 g of a brown solid as a 2:1 mixture of 6-methoxyquinolin-2(1H)-one to 7-methoxyquinolin-2(1H)-one. These
isomers were inseparable by TLC. The mixture was suspended in phosphorus oxychloride (150 mL) and heated to reflux for 1 hour. The reaction was cooled to room temperature and was quenched on ice. The pH of the mixture was adjusted to pH 8 with solid sodium carbonate, it was extracted with ethyl acetate, washed with brine, dried over sodium sulfate, filtered, and concentrated to dryness to give 10.4 g of a crude mixture of 2-chloro-6-methoxyquinoline and the desired 2-chloro-7-methoxyquinoline. Chromatography on silica gel with 5% ethyl acetate in hexanes afforded 0.77 g of the product as a colorless solid.

**MS (ES):** 195 (MH⁺) for C₇H₇ClN₂O

**¹H NMR (CDCl₃) δ 3.96 (s, 3H); 7.29 (d, 1H); 7.41 (dd, 1H); 7.97 (d, 1H); 8.63 (s, 1H).

**Example 73**

6-[(1L-2(7-Methoxy-2-oxoquinazolin-1(2H)-yl)ethyl)piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

1-2-(4-Aminopiperidin-1-yl)ethyl]-7-methoxyquinolin-2(1H)-one (Intermediate 146, 60 mg crude, 0.20 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (36 mg, 0.20 mmol), and sodium triacetoxyl borohydride (130 mg, 0.60 mmol) were reacted as described according to Example 69 to give the free base of the product, which was crystallized from dichloromethane/ethyl acetate to give 45 mg (50%) as a colorless solid.

**MS (ES):** 465 (MH⁺) for C₂₉H₂₃N₆O₄

**¹H NMR (DMSO-D₆) δ 1.06-1.39 (m, 2H); 1.66-1.87 (m, 2H); 2.04 (t, 2H); 2.33-2.49 (m, 1H); 2.56 (t, 2H); 2.92 (d, 2H); 3.70 (s, 2H); 3.92 (s, 3H); 4.32 (t, 2H); 4.61 (s, 2H); 6.86-7.09 (m, 3H); 7.30 (d, 1H); 7.75 (d, 1H); 8.04 (s, 1H); 11.18 (s, 1H).

**Example 74**

6-[(1L-2(7-Methoxy-2-oxoquinazolin-1(2H)-yl)ethyl)piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]thiazin-3(4H)-one

1-2-(4-Aminopiperidin-1-yl)ethyl]-7-methoxyquinolin-2(1H)-one (Intermediate 146, 250 mg crude, 0.83 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-carbaldehyde (WO 2004/058144) (160 mg, 0.83 mmol), and sodium triacetoxyl borohydride (530 mg, 2.50 mmol) were reacted as described according to Example 69. Chromatography on silica gel with 10% methanol in dichloromethane containing 0.25% ammonium hydroxide.
afforded the free base of the product. This was triturated with dichloromethane and the precipitate was collected by filtration giving 230 mg (58%) of the title compound as a colorless solid.

**MS (ES):** 481 (MH⁺) for C₂₃H₂₂N₆O₈S

**¹H NMR (DMSO-D₆) s**
- 1.27 (s, 2H); 1.69 - 1.90 (m, 2H); 2.04 (t, 2H); 2.39-2.48 (m, 1H); 2.56 (t, 2H); 2.93 (d, 2H); 3.53 (s, 2H); 3.75 (s, 2H); 3.92 (s, 3H); 4.33 (t, 2H); 6.91 - 7.05 (m, 2H); 7.10 (d, 1H); 7.67 - 7.83 (m, 2H); 8.04 (s, 1H); 10.88 (s, 1H).

**Example 75**

1-(2-[4-(3,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl)ethyl]-6,7-difluoroquinoxalin-2(1H)-one

1-[2-(4-Aminopiperidin-1-yl)ethyl]-6,7-difluoroquinoxalin-2(1H)-one (Intermediate 150, 190 mg, 0.62 mmol), 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carboxaldehyde (WO 2004/058144) (100 mg, 0.62 mmol), and sodium triacetoxyborohydride (390 mg, 1.90 mmol) were reacted as described according to Example 69. Chromatography on silica gel with 10% methanol in dichloromethane containing 0.25% ammonium hydroxide gave the free base of the product as an oil. The free base was taken up in dichloromethane (2 mL) and diluted with diethyl ether (10 mL). A solution of HCl in diethyl ether (2M, 2.2 eq) was added. The resulting precipitate was collected by filtration to give 180 mg (55%) of the bis-hydrochloride salt of the product.

**MS (ES):** 458 (MH⁺) for C₂₃H₂₃F₂N₆O₃

**¹H NMR (D₂O) δ**
- 1.82 - 2.06 (m, 2H); 2.40 (t, 2H); 3.16 (t, 2H); 3.48-3.68 (m, 3H); 3.89 (d, 2H); 4.27-4.38 (m, 4H); 4.39-4.49 (m, 2H); 4.63 (t, 2H); 7.15-7.28 (m, 1H); 7.44-7.61 (m, 1H); 7.69-7.85 (m, 1H); 8.10-8.28 (m, 2H).

**Intermediate 150: 1-[2-(4-Aminopiperidin-1-yl)ethyl]-6,7-difluoroquinoxalin-2(1H)-one**

tert-Butyl 1-[2-(6,7-difluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl carbamate (Intermediate 151, 500 mg, 1.23 mmol) was reacted with trifluoroacetic acid in dichloromethane as described for Intermediate 140 to give 380 mg (quantitative) of the crude product as an oil.

**MS (ES):** 309 (MH⁺) for C₁₅H₁₆F₂N₄O
Intermediate 151: 2-tert-Butyl 1-(12-(6,7-difluoro-2-oxoquinazolin-1(2H)-yl)ethyl)piperidin-4-yl)carbonyl 155

6,7-Difluoroquinazolin-2(1H)-one (Intermediate 152, 1.0 g, 5.50 mmol) was deprotonated with sodium hydride (60% in oil, 0.26 g, 6.60 mmol) and alkylated with 1-(tert-butoxycarbonyl)amino)piperidin-1-yl)ethyl methanesulfonate (Intermediate 6) (6.6 mmol) as described for Intermediate 2. Chromatography on silica gel with 5% toluene/ethyl acetate gave 300 mg (23%) of the product as a colorless solid.

**MS (ES):** 409 (MH⁺) for C₂₀H₂₃F₃N₂O₃

**¹H NMR (DMSO-δ):** 8 1.10-1.45 (m, 11H); 1.54-1.75 (m, 2H); 1.90-2.13 (m, 2H); 2.52-2.59 (m, 2H); 2.86 (d, 2H); 3.16 (s, 1H); 4.28 (t, 2H); 6.75 (d, 1H); 7.81 (dd, 1H); 7.96 (dd, 1H); 8.25 (s, 1H).

Intermediate 152: 6,7-Difluoroquinazolin-2(1H)-one

To a stirred solution of 4,5-difluorobenzene-1,2-diamine (4.7 g, 32.6 mmol) in ethanol (75 mL) was added ethyl oxoacetate (50 wt % in toluene, 13.3 mL, 65.3 mmol). The reaction was stirred at room temperature overnight. The resulting precipitate was collected by filtration, washed with ethanol, and dried under reduced pressure to give 4.3 g (73%) of the product as a colorless solid.

**MS (ES):** 183 (MH⁺) for C₈H₅F₂N₂O

**¹H NMR (DMSO-δ):** 8 7.23 (dd, 1H); 7.93 (dd, 1H); 8.19 (s, 1H); 12.54 (s, 1H).

Example 76

6-[[1-12-(6,7-Difluoro-2-oxoquinazolin-1(2H)-yl)ethyl]piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazine-3(4H)-one

1-(2-(4-Aminopiperidin-1-yl)ethyl)-6,7-difluoroquinazolin-2(1H)-one (Intermediate 150, 190 mg, 0.62 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carboxaldehyde (WO 2004/058144) (110 mg, 0.62 mmol), and sodium triacetoxysilohydride (390 mg, 1.90 mmol) were reacted as described according to Example 69 to give 180 mg (62%) of the free base of the product as a colorless solid.

**MS (ES):** 471 (MH⁺) for C₂₉H₄₃F₃N₂O₃

**¹H NMR (DMSO-δ):** 8 1.12-1.26 (m, 2H); 1.69-1.83 (m, 2H); 2.01 (t, 2H); 2.42 (s, 1H); 2.53 (t, 2H); 2.88 (d, 2H); 3.69 (s, 2H); 4.29 (t, 2H); 4.60 (s, 2H); 7.01 (d, 1H); 7.30 (d, 1H); 7.82 (dd, 1H); 7.97 (dd, 1H); 8.25 (s, 1H); 11.18 (s, 1H).
Example 77

1-(2-[14-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl methyl]amino]piperidin-1-yl]ethyl)-7,8-difluoroquinoxalin-2(1H)-one

1-[2-(4-Aminopiperidin-1-yl)ethyl]-7,8-difluoroquinoxalin-2(1H)-one (Intermediate 153, 130 mg, 0.42 mmol), 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carboxaldehyde (WO 2004/058144) (70 mg, 0.42 mmol), and sodium triacetoxy borohydride (270 mg, 1.30 mmol) were reacted as described according to Example 71 to give 35 mg (16%) of the bis-hydrochloric salt of the product as a colorless solid.

**MS (ES):** 458 (MH⁺) for C₂₅H₂₅F₂N₃O₂

**¹H NMR (D₂O) δ 1.89-2.02 (m, 2H); 2.43 (d, 2H); 3.18 (t, 2H); 3.52-3.64 (m, 3H); 3.88 (d, 2H); 4.29-4.34 (m, 4H); 4.38-4.43 (m, 2H); 4.71-4.77 (m, 2H); 7.17 (s, 1H); 7.27-7.38 (m, 1H); 7.62-7.69 (m, 1H); 8.15 (s, 2H).

**Intermediate 153:** 1-[2-(4-Aminopiperidin-1-yl)ethyl]-7,8-difluoroquinoxalin-2(1H)-one

**tert-Butyl (1-[2-(7,8-difluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl) carbamate (Intermediate 154, 320 mg, 0.78 mmol)** was reacted with trifluoroacetic acid in dichloromethane as described for Intermediate 140 to give 240 mg (quantitative) of the crude product as an oil.

**MS (ES):** 309 (MH⁺) for C₁₅H₁₈F₂N₄O

**Intermediate 154: tert-Butyl (1-[2-(7,8-difluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl) carbamate**

7,8-Difluoroquinoxalin-2(1H)-one (Intermediate 155 - a mixture of regioisomers containing 30% 5,6-difluoroquinoxalin-2(1H)-one, 1.0 g, 5.50 mmol) was deprotonated with sodium hydride (60% in oil, 0.26 g, 6.60 mmol) and alkylated with 2-[4-[(tert-butoxycarbonyl)amino]piperidin-1-yl]ethyl methanesulfonate (Intermediate 6) (6.6 mmol) as described for Intermediate 2. Chromatography on silica gel with 70-100% ethyl acetate in hexanes gave 320 mg of the product as a colorless solid.

**MS (ES):** 409 (MH⁺) for C₂₀H₂₉F₂NaO₃

**¹H NMR (DMSO-D₄) δ 1.30 (d, 2H); 1.37 (s, 9H); 1.64 (d, 2H); 2.07 (t, 2H); 2.59 (t, 2H); 2.81 (d, 2H); 3.20 (s, 1H); 4.36 (t, 2H); 6.76 (d, 1H); 7.48 (td, 1H); 7.72 (ddd, 1H); 8.23 (s, 1H).
Intermediate 155: 7,8-Difluoroquinoxalin-2(1H)-one
3,4-Difluorobenzene-1,2-diamine (4.6 g, 31.6 mmol) and ethyl oxoaceta (50 wt % in toluene, 13.0 mL, 63.2 mmol) were reacted as described for Intermediate 152 to give 3.7 g of product as an off white solid, mixture with 30% of the regioisomer 5,6-difluoroquinoxalin-2(1H)-one. The mixture was carried on to the next step.

MS (ES): 183 (MH+) for C_{9}H_{7}F_{2}N_{2}O

Example 78
6-{{(1-L2-(7,8-Difluoro-2-oxoquinoline-1(2H)-yl)ethyl}piperidin-4-yl)amino)methyl}-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one
1-[2-(4-Aminopiperidin-1-yl)ethyl]-7,8-difluoroquinoxalin-2(1H)-one (Intermediate 153, 150 mg, 0.42 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-carbaldehyde (WO 2004/058144) (70 mg, 0.42 mmol), and sodium trimetoxo borohydride (270 mg, 1.30 mmol) were reacted as described for Example 69 to give 82 mg (41%) of the free base of the product.

MS (ES): 471 (MH+) for C_{23}H_{21}F_{2}N_{3}O_{3}

1H NMR (DMSO-D6) δ 1.07-1.22 (m, 2H); 1.69 (d, 2H); 1.98 (t, 2H); 2.35 (s, 1H); 2.52 (t, 2H); 2.76 (d, 2H); 3.63 (s, 2H); 4.30 (t, 2H); 4.54 (s, 2H); 6.95 (d, 1H); 7.24 (d, 1H); 7.35-7.47 (m, 1H); 7.61-7.71 (m, 1H); 8.17 (s, 1H); 11.12 (s, 1H).

Example 79
6-{{(1-L2-(6,7-Dimethoxy-2-oxoquinazoline-1(2H)-yl)ethyl}piperidin-4-yl)amino)methyl}-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one
1-[2-(4-Aminopiperidin-1-yl)ethyl]-6,7-dimethoxyquinoxalin-2(1H)-one
(Intermediate 156, 75 mg, 0.23 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-carbaldehyde (WO 2004/058144) (40 mg, 0.23 mmol), and sodium trimetoxo borohydride (150 mg, 0.69 mmol) were reacted as described according to Example 69 to give 78 mg (68%) of the free base of the product as a colorless solid.

MS (ES): 495 (MH+) for C_{29}H_{24}N_{3}O_{3}

1H NMR (DMSO-D6) δ 1.06-1.38 (m, 2H); 1.65-1.85 (m, 2H); 1.95-2.13 (m, 2H); 2.29-2.42 (m, 1H); 2.51-2.64 (m, 2H); 2.92 (d, 2H); 3.67 (s, 2H); 3.85 (s, 3H); 3.88-4.04 (m, 3H); 4.24-4.45 (m, 2H); 4.52-4.66 (m, 2H); 6.94-7.09 (m, 2H); 7.21-7.37 (m, 2H); 7.98-8.11 (m, 1H); 11.06-11.23 (m, 1H).
**Intermediate 156: 1-[2-[(4-Aminopiperidin-1-yl)ethyl]-6,7-dimethoxyquinoxalin-2(1H)-one**

**tert-Butyl [1-[2-(6,7-dimethoxy-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl] carbamale** (Intermediate 157, 100 mg, 0.23 mmol) was reacted with trifluoroacetic acid in dichloromethane as described for Intermediate 140 to give 75 mg (quantitative) of the crude product as an oil.

**MS (ES):** 333 (M+H) for C17H24N4O3

**Intermediate 157: tert-Butyl [1-[2-(6,7-dimethoxy-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl] carbamale**

6,7-Dimethoxyquinoxalin-2(1H)-one (Intermediate 158, 540 mg, 2.60 mmol) was deprotonated with sodium hydride (60% in oil, 2.90 mmol) and alkylation with 2-[(tert-butoxycarbonyl)amino]piperidin-1-yl ethyl methanesulfonate (Intermediate 6) (3.9 mmol) as described for Intermediate 2. Chromatography on silica gel with 20-50% acetone in hexanes gave 310 mg (28%) of the product as an off-white solid.

**MS (ES):** 433 (M+H) for C22H32N4O5

**1H NMR (DMSO-D6) 5 1.25-1.39 (m, 1H); 1.63 (d, 2H); 1.98 - 2.12 (m, 2H); 2.57 (t, 2H); 2.92 (d, 2H); 3.19 (s, 1H); 3.84 (s, 3H); 3.95 (s, 3H); 4.35 (t, 2H); 6.75 (d, 1H); 7.04 (s, 1H); 7.31 (s, 1H); 8.05 (s, 1H).

**Intermediate 158: 6,7-Dimethoxyquinoxalin-2(1H)-one**

A mixture of 1,2-dimethoxy-4,5-dinitrobenzene (5.7 g, 25.0 mmol) in ethanol/ acetic acid (140 mL, 1:1) was hydrogenated over palladium on carbon (10%, 1 g) at normal pressure and room temperature for 3 hours, then filtered through a pad of celite. The filtrate containing the crude diamine was treated with ethyl oxosacetate (50 wt% in toluene, 10 mL, 50 mmol) and the reaction was stirred at room temperature overnight. The resulting precipitate was collected by filtration. This material was suspended in a mixture of methanol/dichloromethane and solvent was removed under reduced pressure to remove traces of acetic acid to give 2.0 g (38%) of product as a solid.

**MS (ES):** 207 (M+H) for C10H10N2O3

**1H NMR (DMSO-D6) 5 3.81-3.83 (m, 3H); 3.83-3.85 (m, 3H); 6.78-6.81 (m, 1H); 7.25-7.27 (m, 1H); 7.97-8.01 (m, 1H); 12.26-12.34 (m, 1H).
Example 80

6-[[1-{2-(7-Methoxy-3-methyl-2-oxoquinazolin-1(2H)-yl)ethyl]piperidin-4-yl}amino]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

1-{2-[4-Aminopiperidin-1-yl]ethyl]-7-methoxy-3-methylquinazolin-2(1H)-one

(Intermediate 159, 75 mg, 0.24 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (42 mg, 0.24 mmol), and sodium triacetoxyborohydride (150 mg, 0.72 mmol) were reacted as described according to Example 69 to give 80 mg (73% yield) of the free base of the product.

MS (ES): 479 (MH⁺) for C₂₅H₂₆N₆O₄

¹H NMR (DMSO-D₆) δ 1.23 (q, 2H); 1.77 (d, 2H); 2.04 (t, 2H); 2.31 - 2.45 (m, 4H); 2.51 - 2.61 (m, 2H); 2.91 (d, 2H); 3.68 (s, 2H); 3.89 (s, 3H); 4.31 (t, 2H); 4.60 (s, 2H); 6.85 - 7.10 (m, 3H); 7.29 (d, 1H); 7.59 - 7.73 (m, 1H); 11.17 (s, 1H).

Intermediate 159: 1-{2-[4-Aminopiperidin-1-yl]ethyl]-7-methoxy-3-methylquinazolin-2(1H)-one

tert-Butyl 1-{2-[7-methoxy-3-methyl-2-oxoquinazolin-1(2H)-yl]ethyl]piperidin-4-yl}carbamate (Intermediate 160, 100 mg, 0.24 mmol) was reacted with trifluoroacetic acid in dichloromethane as described for Intermediate 140 to give 75 mg (99% yield) of the crude product as an oil.

MS (ES): 317 (MH⁺) for C₁₇H₂₄N₄O₂

Intermediate 160: tert-Butyl 1-{2-[7-methoxy-3-methyl-2-oxoquinazolin-1(2H)-yl]ethyl]piperidin-4-yl}carbamate

7-Methoxy-3-methylquinazolin-2(1H)-one (Intermediate 161, 500 mg, 2.60 mmol)

was deprototuated with sodium hydride (60% in oil, 2.90 mmol) and alkylated with 2-{4-[[tert-butoxycarbonyl]amino]piperidin-1-yl}ethyl methanesulfonate (Intermediate 6) (3.9 mmol) as described for Intermediate 2. Chromatography on silica gel with 70% ethyl acetate in hexanes, followed by a second chromatography on silica gel with 20% acetone in hexanes gave 110 mg (10%) of the product as a colorless solid.

MS (ES): 417 (MH⁺) for C₂₂H₂₃N₄O₄

¹H NMR (DMSO-D₆) δ 1.21-1.46 (m, 11H); 1.65 (d, 2H); 2.05 (t, 2H); 2.38 (s, 3H); 2.51-2.59 (m, 2H); 2.92 (d, 2H); 3.18 (s, 1H); 3.90 (s, 3H); 4.31 (t, 2H); 6.77 (d, 1H); 6.91 - 7.00 (m, 2H); 7.58-7.73 (m, 1H).
**Intermediate 161: 7-Methoxy-3-methylquinoxaline-2(1H)-one**

A suspension of 3-chloro-6-methoxy-2-methylquinoxaline (Intermediate 162, 1.5 g, 7.21 mmol) in 5M HCl (30 mL) was heated to 110 °C for 1 hour. The reaction mixture was neutralized with saturated sodium carbonate solution, diluted with water and extracted with ethyl acetate (3 times). The combined organic phases were dried over magnesium sulfate and concentrated to a small volume under reduced pressure. The precipitate was collected by filtration to give 1.0 g (71%) of product as an off-white solid.

**MS (ES):** 191 (MH⁺) for C₁₉H₁₆N₂O₂

**¹H NMR (DMSO-D₆):** 8 2.34 (s, 3H); 3.80 (s, 3H); 6.73 (d, 1H); 6.83-6.89 (m, 1H); 7.59 (d, 1H); 12.19 (s, 1H).

**Intermediate 162: 3-Chloro-6-methoxy-2-methylquinoxaline**

A suspension of 4-methoxybenzene-1,2-diamine (5.0 g, 36.2 mmol) in water (100 mL) was heated under sonication for 5 minutes. 2-Oxopropanoic acid (2.5 mL, 36.2 mmol) was added and it was stirred for 2 hours. The precipitate was collected by filtration and dried under vacuum and heating, over phosphorus pentoxide, to give 3.0 g of a mixture of the product together with 6-methoxy-3-methylquinoxaline-2(1H)-one. This mixture was suspended in phosphorus oxychloride (30 mL) and heated to 115 °C for 30 min. The mixture was quenched on ice and neutralized with solid sodium carbonate. The aqueous mixture was extracted with ethyl acetate (4 times). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated to dryness under reduced pressure. Chromatography on silica gel with 5% ethyl acetate in hexanes and isolation of the higher migrating regioisomer gave 0.9 g of product as an off-white solid.

**MS (ES):** 209 (MH⁺) for C₁₀H₉ClN₂O

**¹H NMR (DMSO-D₆):** 8 2.71 (s, 3H); 3.93 (s, 3H); 7.39 (d, 1H); 7.49 (dd, 1H); 7.95 (d, 1H).

**Example 81**

1-[2-(4-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino)piperidin-1-yl]ethyl]quinolin-2(1H)-one

1-[2-[(4-Aminopiperidin-1-yl)ethyl]quinolin-2(1H)-one (Intermediate 163, 170 mg crude, 0.63 mmol), 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde (WO 2004/058144) (100 mg, 0.63 mmol), and sodium triacetoxyborohydride (400 mg, 1.90 mmol)
were reacted as described according to Example 69 to give the free base of the product as an oil. The free base was taken up in dichloromethane (2 mL) and ethanol (8 mL) and treated with a solution of 4M HCl/dioxane (2 eq). The resulting precipitate was collected by filtration to give 183 mg (60%) of the bis-hydrochloride salt of the product as a colorless solid.

\[ \text{MS (ES): 421 (MH}^+\text{) for C}_{20}\text{H}_{22}\text{N}_{4}\text{O}_3 \]

\[ ^1\text{H NMR (D}_2\text{O)} \delta 1.86 - 2.06 \text{ (m, 2H); 2.36 - 2.54 \text{ (m, 2H); 3.06 - 3.27 \text{ (m, 2H); 3.46 - 3.70 \text{ (m, 3H); 3.89 (dd, 2H); 4.29 - 4.42 \text{ (m, 4H); 4.42 - 4.53 \text{ (m, 2H); 5.65 - 4.70 \text{ (m, 2H); 6.66 (d, 1H); 7.29 (s, 1H); 7.34 (t, 1H); 7.47 (d, 1H); 7.59 - 7.78 (m, 2H); 7.95 (d, 1H); 8.22 (s, 1H).} \]

**Intermediate 162: 1-[2-(4-Aminopiperidin-1-yl)ethyl]quinolin-2(1H)-one**

To a solution of tert-butyl [1-[2-(2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl]carbamate (Intermediate 164, 220 mg, 0.59 mmol) in dioxane (5 mL) was added a solution of HCl in dioxane (4M, 9 mL), followed by water (1 mL) and it was stirred at room temperature overnight. An addition 5 mL of HCl/dioxane was added to the reaction. After 1 hr, the reaction was concentrated to dryness. The crude product was partitioned between 10% methanol/dichloromethane (50 mL) and 1M sodium hydroxide (50 mL). The aqueous phase was back extracted with 10% methanol/dichloromethane (50 mL) and the combined organic phases were washed with brine, dried over sodium sulfate and concentrated under reduced pressure to give 170 mg (quantitative) of the crude product as an oil.

\[ \text{MS (ES): 272 (MH}^+\text{) for C}_{18}\text{H}_{21}\text{N}_{3}\text{O} \]

**Intermediate 164: tert-Butyl [1-[2-(2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl]carbamate**

Quinolin-2(1H)-one (250 mg, 1.7 mmol) was deprotonated with sodium hydride (60% in oil, 70 mg, 1.7 mmol) and alkylated with 2-[4-[[tert-butoxycarbonyl]amino]piperidin-1-yl]ethyl methanesulphonate (Intermediate 6) (1.7 mmol) as described for Intermediate 141. Chromatography on silica gel with 0-5% methanol in dichloromethane gave 220 mg (35%) of product as a colorless solid.

\[ \text{MS (ES): 372 (MH}^+\text{) for C}_{22}\text{H}_{22}\text{N}_{3}\text{O}_7 \]
Example 82

1-(2-{4-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino)piperidin-1-yl}ethyl)quinolin-4(1H)-one

1-[2-{4-Aminopiperidin-1-yl}ethyl]quinolin-4(1H)-one (Intermediate 165, 180 mg crude, 0.66 mmol), 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde (WO 2004/058144) (110 mg, 0.66 mmol), and sodium triacetoxy borohydride (420 mg, 2.0 mmol) were reacted as described according to Example 81 to give the bis-hydrochloride salt of the product 53 mg (16%) as a colorless solid.

MS (ES): 421 (M+H) for C_{21}H_{23}N_{4}O_{3}

^1H NMR (D_{2}O) δ 1.90-2.13 (m, 2H); 2.44 (s, 2H); 3.22 (t, 2H); 3.58-3.70 (m, 3H); 3.77 (s, 2H); 4.33-4.40 (m, 2H); 4.42 (s, 2H); 4.46-4.53 (m, 2H); 4.75-4.86 (m, 2H); 6.47 (d, 1H); 7.36 (s, 1H); 7.51 (t, 1H); 7.68 (d, 1H); 7.77-7.89 (m, 1H); 8.11-8.21 (m, 2H); 8.25 (s, 1H).

Intermediate 165: 1-{2-[4-Aminopiperidin-1-yl]ethyl}quinolin-4(1H)-one
tert-Butyl {1-[2-(4-oxoquinolin-1(4H)-yl)ethyl]piperidin-4-yl} carbonate

(Intermediate 166, 480 mg crude, 1.29 mmol) was reacted with 4M HCl/dioxane in dioxane as described for Intermediate 163 to give 180 mg (51%) of the crude product as an oil.

MS (ES): 272 (M+H) for C_{11}H_{12}N_{2}O

Intermediate 166: tert-Butyl {1-[2-(4-oxoquinolin-1(4H)-yl)ethyl]piperidin-4-yl} carbonate

Quinolin-4(1H)-one (250 mg, 1.7 mmol) was deprotonated with sodium hydride (60% in oil, 70 mg, 1.7 mmol) and alkylated with 2-{4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}ethyl methanesulfonate (Intermediate 6) (1.7 mmol) as described for Intermediate 141. The precipitate formed in the reaction mixture was collected by filtration to give 480 mg (76%) of product as a colorless solid.

MS (ES): 372 (M+H) for C_{21}H_{25}N_{3}O_{3}
Example 83

Cis(±)-[1-[2-(5,7-difluoro-2-oxoquinolin-1-(2H)-yl)ethyl]-3-methoxypiperidin-4-ylamino)methyl]-2H-pyrido[3,2-b][1,4]oxazine-3(4H)-one

Cis(±)-[2-(4-amino-3-methoxypiperidin-1-yl)ethyl]-5,7-difluorquinolin-2(1H)-one

(Intermediate 167, 140 mg, 0.42 mmol), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (75 mg, 0.42 mmol) and sodium triacetoxy borohydride (250 mg, 1.20 mmol) were reacted as described according to Example 69. Chromatography on silica gel with 5% methanol in dichloromethane containing 0.50% ammonium hydroxide gave 120 mg (57%) of the free base of the product.

MS (ES): 500 (M+H+) for C_{25}H_{27}F_{2}N_{3}O_{4}

1H NMR (CDCl_{3}): δ 1.66-1.87 (m, 2H); 2.22-2.44 (m, 2H); 2.55-2.83 (m, 3H); 2.93 (d, 1H); 3.14 (d, 1H); 3.34-3.45 (m, 3H); 3.47-3.56 (m, 1H); 3.80 - 3.86 (m, 2H); 4.25-4.49 (m, 2H); 4.63 (s, 2H); 6.65 (d, 1H); 6.67-6.77 (m, 1H); 6.99 (t, 2H); 7.21 (d, 1H); 7.88 (d, 1H).

Intermediate 167: Cis(±)-[2-(4-amino-3-methoxypiperidin-1-yl)ethyl]-5,7-difluorquinolin-2(1H)-one

Cis(±)-[2-4-(dibenzylamino)-3-methoxypiperidin-1-yl)ethyl]-5,7-difluorquinolin-2(1H)-one (Intermediate 168, 240 mg, 0.46 mmol) was hydrogenated in methanol/acetone (10 mL, 9:1) over palladium hydroxide on carbon (20%, 120 mg) at room temperature and normal pressure for 4 hours. The reaction mixture was filtered through celite and the filtrate was concentrated to dryness under reduced pressure to give 140 mg (90%) of crude product. This was used without further purification.

MS (ES): 338 (M+H+) for C_{14}H_{21}F_{2}N_{3}O_{2}

Intermediate 168: Cis(±)-[2-4-(dibenzylamino)-3-methoxypiperidin-1-yl)ethyl]-5,7-difluorquinolin-2(1H)-one

A solution of 5,7-difluorquinolin-2(1H)-one (Intermediate 25, 300 mg, 1.70 mmol) in dry DMF (10 mL) was treated with sodium hydride (60% in oil, 80 mg, 2.00 mmol) with cooling in an ice bath. The reaction was stirred at room temperature for 90 min. The reaction was again cooled in an ice bath and treated with a solution of cis(±)-[4-(dibenzylamino)-3-methoxypiperidin-1-yl)ethyl methanesulfonate in dry DMF (10 mL) (Intermediate 169, 1.2 eq, 2.00 mmol). The reaction was stirred at room temperature overnight. It was quenched with a small amount of water and concentrated to dryness. Residual DMF was removed by co-

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evaporating with toluene and the residue was partitioned between ethyl acetate (50 mL) and water (20 mL). The biphasic mixture was filtered, the phases separated and the aqueous phase was back extracted two times with ethyl acetate (2 x 50 mL). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated to dryness. Chromatography on silica gel with a gradient of 10-20% acetone in hexanes gave 240 mg (27%) of product as a colorless solid.

**MS (ES)**: 518 (MH+), for C_{31}H_{37}F_{2}N_{3}O_{2}

**1H NMR (DMSO-D6)** δ 1.49-1.60 (m, 1H); 1.70-1.84 (m, 1H); 1.92-2.06 (m, 2H); 2.37-2.47 (m, 2H); 2.99-3.12 (m, 1H); 3.16-3.22 (m, 1H); 3.25 (s, 3H); 3.30-3.40 (m, 1H); 3.56 (s, 1H); 3.59-3.86 (m, 4H); 4.28 (1, 2H); 6.62 (d, 1H); 7.15-7.24 (m, 3H); 7.24-7.41 (m, 9H); 7.96 (d, 1H).

**Intermediate 169**: Cis(±)-2-[4-(dibenzylamino)-3-methoxypiperidin-1-yl]ethyl methanesulfonate

Cis(±)-2-[4-(dibenzylamino)-3-methoxypiperidin-1-yl]ethyl methanesulfonate (Intermediate 170, 740 mg, 2.1 mmol) was reacted with methanesulfonyl chloride (0.20 mL, 2.5 mmol) in the presence of triethylamine (0.41 mL, 2.9 mmol) as described for Intermediate 6. The crude product was presumed to be unstable and was used without further purification directly for the next step.

**Intermediate 170**: Cis(±)-2-[4-(dibenzylamino)-3-methoxypiperidin-1-yl]ethyl methanesulfonate

A mixture of cis(±)-N,N,N,N-dibenzy-3-methoxypiperidin-4-amine (1.7 g, 5.5 mmol) (WO 2005/069461), bromoethanol (0.5 mL, 7.1 mmol), and N,N-dioisopropylethylamine (1.4 mL, 8.3 mmol) were reacted as described for Intermediate 37, but heating for one hour at 70°C. Chromatography on silica gel with 5% methanol in dichloromethane containing 0.25% ammonium hydroxide gave 1.3 g (68%) of product as a colorless solid.

**MS (ES)**: 355 (MH+), for C_{22}H_{30}N_{2}O_{2}

**1H NMR (DMSO-D6)** δ 1.44 - 1.58 (m, 1H); 1.64 (d, 1H); 1.79 - 2.08 (m, 2H); 2.32 (t, 2H); 2.36 - 2.45 (m, 1H); 2.88 (d, 1H); 3.13 (d, 1H); 3.30 (s, 3H); 3.40 - 3.49 (m, 2H); 3.56 (s, 1H); 3.59 - 3.87 (m, 4H); 4.34 (s, 1H); 7.11 - 7.24 (m, 2H); 7.24 - 7.40 (m, 8H)
Example 84
7-Fluoro-2-oxo-1-[2-(4-deoxy-3,4-dihydro-2H-pyridin-3,2-b][1,4]oxazin-6-y1)methylamino]-piperidin-1-y1ethyl]-1,2-dihydroquinoline-5-carbonitrile

Example 85
5-Fluoro-2-oxo-1-[2-(4-deoxy-3,4-dihydro-2H-pyridin-3,2-b][1,4]oxazin-6-y1)methylamino]-piperidin-1-y1ethyl]-1,2-dihydroquinoline-7-carbonitrile

A mixture of the regioisomers 1-[2-(4-aminopiperidin-1-yl)ethyl]-7-fluoro-2-oxo-1,2-dihydroquinoline-5-carbonitrile (major isomer) and 1-[2-(4-aminopiperidin-1-yl)ethyl]-5-fluoro-2-oxo-1,2-dihydroquinoline-7-carbonitrile (minor isomer) (Intermediate 171 and 172, 120 mg, 0.38 mmol), 3-oxo-3,4-dihydro-2H-pyridin-3,2-b][1,4]oxazine-6-carboxaldehyde (WO 2004/058144) (68 mg, 0.38 mmol) and sodium triacetoxyborohydride (230 mg, 1.1 mmol) were reacted as described according to Example 69. Chromatography on silica gel with 10% methanol in dichloromethane containing 0.5% ammonium hydroxide followed by reverse phase HPLC on a 50x250 mm ODS AQ column eluting with an isocratic gradient of 15% acetonitrile in water containing 0.1% TFA to give the bis TFA salts of Example 84 (68 mg) and Example 85 (21 mg), both as colorless solids.

Example 84:

MS (ES): 477 (MH+) for C_{25}H_{23}FN_{4}O_{3}

^1H NMR (DMSO-D_6) δ 1.09 - 1.27 (m, 2H); 1.67 - 1.83 (m, 2H); 2.00 (t, 2H); 2.31 - 2.44 (m, 1H); 2.51 - 2.55 (m, 2H); 2.67 (d, 2H); 3.67 (s, 2H); 4.33 (t, 2H); 4.53 - 4.64 (m, 2H); 6.81 (d, 1H); 7.00 (d, 1H); 7.28 (d, 1H); 7.78 - 7.92 (m, 2H); 7.98 (d, 1H); 11.16 (s, 1H).

Example 85:

MS (ES): 477 (MH+) for C_{25}H_{23}FN_{4}O_{3}

^1H NMR (DMSO-D_6) δ 1.12 - 1.30 (m, 2H); 1.69 - 1.83 (m, 2H); 1.95 - 2.10 (m, 2H); 2.33 - 2.46 (m, 1H); 2.51 - 2.57 (m, 2H); 2.88 (d, 2H); 3.68 (s, 2H); 4.31 - 4.43 (m, 2H); 4.57 - 4.64 (m, 2H); 6.84 (d, 1H); 7.01 (d, 1H); 7.29 (d, 1H); 7.70 (d, 1H); 7.99 (s, 1H); 8.06 (d, 1H); 11.17 (s, 1H).
Intermediate 171: 1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-fluoro-2-oxo-1,2-dihydroquinoline-5-carbonitrile (major isomer)

and

Intermediate 172: 1-[2-(4-Aminopiperidin-1-yl)ethyl]-5-fluoro-2-oxo-1,2-dihydroquinoline-7-carbonitrile

A mixture of tert-butyl {1-[2-(5-cyano-7-fluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl} carbamate and tert-butyl {1-[2-(7-cyano-5-fluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl} carbamate (Intermediates 173 and 174, 170 mg, 0.41 mmol) was reacted with trifuoroacetic acid in dichloromethane as described for Intermediate 140 to give 120 mg (92% yield) of the mixture of regioisomers as an oil. This mixture was carried on without further purification to the next step.

MS (ES): 315 (M+); for C_{17}H_{19}FN_{4}O

Intermediate 173: tert-Butyl {1-[2-(5-cyano-7-fluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl} carbamate

and

Intermediate 174: tert-Butyl {1-[2-(7-cyano-5-fluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl} carbamate

A mixture of tert-butyl {1-[2-(5-bromo-7-fluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl} carbamate and tert-butyl {1-[2-(7-bromo-5-fluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl} carbamate (Intermediates 175 and 176, 460 mg, 0.98 mmol) was reacted with potassium cyanide (96 mg, 1.5 mmol), triethyl tin chloride (14 μL/mL in heptane, 0.90 μL, 0.003 mmol), 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (XANTPHOS) (3.0 mg, 0.005 mmol) and tris(dibenzylideneacetone)dipalladium (0) (5.0 mg, 0.005 mmol) as described for Intermediate 15. Chromatography on silica gel with acetone/hexanes (1:4) gave 170 mg of the mixture of regioisomers. This mixture was carried on directly to the next step.

MS (ES): 415 (M+); for C_{12}H_{27}FN_{4}O
Intermediate 175: tert-Butyl (1-[2-(5-bromo-7-fluoro-2-oxoquinolin-1(2H)-
yl)ethyl]pipridin-4-yl) carbonate

and

Intermediate 176: tert-Butyl (1-[2-(7-bromo-5-fluoro-2-oxoquinolin-1(2H)-
yl)ethyl]pipridin-4-yl) carbonate

A mixture of 5-bromo-7-fluoroquinolin-2(1H)-one and 7-bromo-5-fluoroquinolin-
2(1H)-one (Intermediate 177 and 178, 3.0 g, 9.4 mmol) was reacted with sodium hydride
(60% in oil, 0.20 g, 5.0 mmol) and 2-((tert-butoxycarbonyl)amino)pipridin-1-yl)ethyl
methanesulfonate (Intermediate 6, 9.4 mmol) as described for Intermediate 141.

A mixture of 5-bromo-7-fluoroquinolin-2(1H)-one and 7-bromo-5-fluoroquinolin-
2(1H)-one (Intermediate 177 and 178, 3.0 g, 9.4 mmol) was reacted with sodium hydride
(60% in oil, 0.20 g, 5.0 mmol) and 2-((tert-butoxycarbonyl)amino)pipridin-1-yl)ethyl
methanesulfonate (Intermediate 6, 9.4 mmol) as described for Intermediate 141.

Chromatography on silica gel with a gradient of 50-75% ethyl acetate in hexanes gave 0.63 g
(33%) of the regioisomeric product mixture, which was carried on without further purification
to the next step.

MS (ES): 468, 470 (M+H) for C27H27BrFNO3

Intermediate 177: 5-Bromo-7-fluoroquinolin-2(1H)-one

and

Intermediate 178: 7-Bromo-5-fluoroquinolin-2(1H)-one

The compounds were prepared from (2E)-N-(3-bromo-5-fluorophenyl)-3-
phenylacrylamide (Intermediate 179, 3.0 g, 9.4 mmol) and aluminium trichloride (6.2 g, 46.9
mmol) as described for Intermediate 17, but the reaction mixture was heated to 90 °C for 30
min, to give 1.5 g of 3:1 mixture of 5-Bromo-7-fluoroquinolin-2(1H)-one and 7-bromo-5-
fluoroquinolin-2(1H)-one. This mixture was carried on to the next step without further
purification.

MS (ES): 242, 244 (M+H) for C9H2BrFNO

Intermediate 179: (2E)-N-(3-Bromo-5-fluorophenyl)-3-phenylacrylamide

The compound was prepared from 3-bromo-5-fluorosiline (Intermediate 180, 5.3 g,
27.9 mmol) and cinnaoicloride (5.6 g, 33.5 mmol) in the presence of 2,6-lutidine (5.0 mL,
41.9 mmol) as described for Intermediate 18 to give the product as a colorless solid, 7.6 g
(85% yield).

MS (ES): 320, 322 (M+H) for C13H11BrFNO

1H NMR (DMSO-D6) δ 6.77 (d, 1H); 7.18 - 7.30 (m, 1H); 7.40 - 7.52 (m, 3H); 7.55 -
7.70 (m, 4H); 7.75 (s, 1H); 10.56 (s, 1H).
Intermediate 188: 3-Bromo-5-fluoroaniline

To a solution of N-(3-bromo-5-fluorophenyl)acetamide (Intermediate 181, 8.7 g, 37.4 mmol) in ethanol (30 mL) was added concentrated hydrochloric acid (80 mL). The reaction was heated to 100 °C for 1 hr. It was cooled to room temperature and neutralized with 5N sodium hydroxide. The crude product was extracted with ethyl acetate (2x 100 mL), the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated to dryness. Chromatography on silica gel with a gradient of 5-10% ethyl acetate in hexanes gave 5.3 g (75%) of the product as a yellow oil.

MS (ES): 190, 192 (M+H) for C_{19}H_{14}BrFNO

^1H NMR (DMSO-D6) δ 5.46 - 6.90 (m, 2H); 6.24 - 6.37 (m, 1H); 6.44 - 6.53 (m, 1H); 6.54 - 6.61 (m, 1H).

Intermediate 181: N-(3-Bromo-5-fluorophenyl)acetamide

A mixture of acetamide (2.8 g, 47.2 mmol), palladium acetate (0.50 g, 0.80 mmol), XANTPHOS (0.68 g, 1.2 mmol) and cesium carbonate (18 g, 55.2 mmol) was degassed and purged with nitrogen twice. Dry dioxane (50 mL) was added followed by 1,3-dibromo-5-fluorobenzene (10 g, 39.4 mmol). The reaction was heated to 105 °C overnight and then allowed to cool to room temperature. Dichloromethane was added and the mixture was stirred vigorously for 1 hr. The mixture was filtered. The filtrate was concentrated to dryness.

Chromatography on silica gel with 25% ethyl acetate in hexanes gave 4.0 g (44%) of the product as a colorless solid.

MS (ES): 232, 234 (M+H) for C_{19}H_{14}BrFNO

^1H NMR (DMSO-D6) δ 2.01 - 2.13 (m, 3H); 7.13 - 7.24 (m, 1H); 7.42 - 7.54 (m, 1H); 7.57 - 7.67 (m, 1H); 10.22 - 10.35 (m, 1H).

Example 86

7-Fluoro-1-[2-(4-[(2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino)piperdin-1-yl)ethyl]quinoxalin-2(1H)-one

A mixture of 1-[2-(4-aminopiperdin-1-yl)ethyl]-7-fluoroquinoxalin-2(1H)-one (Intermediate 140, 130 mg, 0.448 mmol), 2-oxo-1,2-dihydroquinoline-3-carbaldehyde (65 mg, 0.448 mmol) and 3Å molecular sieves (100 mg) in methanol (6.0mL) was heated at reflux for 2.5 hours under nitrogen atmosphere. It was cooled to 0°C and sodium triacetoxoborohydride (189.5 mg, 0.996 mmol) was added and the mixture was allowed to warm to
room temperature and stirred overnight. The mixture was filtered and purified through silica
plug (eluting with 15% methanol in methylene chloride) to give title compound (71 mg).

**MS (ES):** 448.52 (MH⁺) for C_{25}H_{28}FN_{4}O_{2}  

**^1H NMR (DMSO-D6) δ ppm:** 1.13 - 1.32 (m, 2H); 1.79 (d, 2H); 2.02 (t, 2H); 2.35 - 2.45 (m, 5H); 2.52 - 2.59 (m, 2H); 2.90 (d, 2H); 3.61 (s, 2H); 4.27 (t, 2H); 7.15 (t, 1H); 7.24 - 7.33 (m, 2H); 7.43 (t, 1H); 7.51 (d, 1H); 7.63 (d, 1H); 7.79 - 7.92 (m, 2H); 8.17 (s, 1H).

**Examples 87-96**

The following compounds were synthesized following the procedure described for Example 86, except the compounds were purified by reverse phase HPLC with methanol/water, containing 0.1% TFA to give the TFA salts of the final products.

<table>
<thead>
<tr>
<th>Ex</th>
<th>Compound</th>
<th><strong>^1H NMR (DMSO-D6) δ ppm</strong></th>
<th>ES</th>
<th>Aldehyde</th>
</tr>
</thead>
<tbody>
<tr>
<td>87</td>
<td>1-[2-(4-[(2,2-Dimethyl-3,4-dihydro-2H-chromen-6-yl)methyl]amino)pyrroldin-1-yl)ethyl]-5,7-difluoroquinolin-2(1H)-one</td>
<td>1.27 (s, 6H); 1.64 - 1.89 (m, 4H); 2.21 - 2.39 (m, 2H); 2.73 (t, 2H); 2.95 - 3.18 (m, 2H); 3.80 (s, 2H); 4.08 (s, 2H); 4.53 (s, 2H); 6.67 (d, 1H); 6.76 (d, 1H); 7.19 (d, 1H); 7.24 (s, 1H); 7.31 (t, 1H); 7.43 (d, 1H); 8.03 (d, 1H); 9.02 (s, 2H); 9.75 (s, 1H)</td>
<td>482</td>
<td>2,2-dimethylchormosane-6-carbaldehyde</td>
</tr>
<tr>
<td>88</td>
<td>1-[2-(4-[(1,3-Dimethyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)methyl]amino)pyrroldin-1-yl)ethyl]-5,7-difluoroquinolin-2(1H)-one</td>
<td>1.80 (s, 2H); 2.34 (s, 2H); 3.01 - 3.18 (m, 2H); 3.45 (s, 6H); 3.80 (s, 2H); 4.24 (s, 2H); 4.53 (s, 2H); 6.67 (d, 1H); 7.22 (s, 2H); 7.25 - 7.36 (m, 2H); 7.43 (d, 1H); 8.03 (d, 1H); 9.18 (s, 2H)</td>
<td>482</td>
<td>1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-carbaldehyde</td>
</tr>
<tr>
<td>Ex</td>
<td>Compound</td>
<td>$^1$H NMR (DMSO-D6) δ ppm</td>
<td>ES</td>
<td>Alddehyde</td>
</tr>
<tr>
<td>----</td>
<td>---------</td>
<td>--------------------------</td>
<td>----</td>
<td>-----------</td>
</tr>
<tr>
<td>89</td>
<td>5,7-Difluoro-1-(2-{4-[(5,6,7,8-tetrahydro-naphthalen-2-ylmethyl)amino]piperidin-1-yl}ethyl)quinolin-2(1H)-one</td>
<td>1.72 (s, 4H); 1.77 - 1.92 (m, 2H); 2.32 (s, 2H); 2.71 (s, 4H); 3.09 (s, 2H); 3.58 (s, 2H); 3.79 (s, 2H); 4.12 (s, 2H); 4.54 (s, 2H); 6.66 (d, 1H); 7.07 - 7.14 (m, 1H); 7.20 (s, 2H); 7.30 (t, 1H); 7.43 (d, 1H); 8.02 (d, 1H); 9.23 (s, 2H)</td>
<td>452</td>
<td>5,6,7,8-tetrahydro-naphthalene-2-carbaldehyde</td>
</tr>
<tr>
<td>90</td>
<td>5,7-Difluoro-1-{2-{4-[[6-fluoro-4H-1,3-benzodioxin-8-y1]methyl]amino}piperidin-1-yl}ethyl)quinolin-2(1H)-one</td>
<td>1.84 (d, 2H); 2.33 (s, 2H); 3.09 (s, 2H); 3.29 - 3.44 (m, 2H); 3.80 (s, 2H); 4.16 (s, 2H); 4.54 (s, 2H); 4.91 (s, 2H); 5.32 (s, 2H); 6.66 (d, 1H); 7.01 - 7.14 (m, 1H); 7.19 - 7.34 (m, 2H); 7.43 (d, 1H); 8.01 (d, 1H); 9.35 (s, 2H)</td>
<td>474</td>
<td>6-fluoro-4H-1,3-benzodioxine-8-carbaldehyde</td>
</tr>
<tr>
<td>91</td>
<td>5,7-Difluoro-1-{2-{4-[(1H-indol-6-ylmethyl)amino]piperidin-1-yl}ethyl)quinolin-2(1H)-one</td>
<td>1.65 (d, 2H); 2.35 (s, 2H); 3.09 (s, 2H); 3.31 (s, 2H); 3.80 (s, 2H); 4.30 (s, 2H); 4.54 (s, 2H); 6.45 (s, 1H); 6.66 (d, 1H); 7.13 (d, 1H); 7.29 (t, 1H); 7.42 (s, 2H); 7.50 - 7.68 (m, 2H); 8.01 (d, 1H); 9.22 (s, 2H); 11.39 (s, 1H)</td>
<td>437</td>
<td>1H-indole-6-carbaldehyde</td>
</tr>
<tr>
<td>92</td>
<td>1-{2-{4-{4-[2,3-Dihydro-1H-inden-5-ylmethyl)amino]piperidin-1-yl}ethyl}-5,7-difluoroquinolin-2(1H)-one</td>
<td>1.73 - 1.89 (m, 2H); 1.94 - 2.09 (m, 2H); 2.22 - 2.41 (m, 2H); 2.86 (t, 4H); 3.28 (s, 2H); 3.43 - 3.54 (m, 2H); 3.78 (s, 2H); 4.16 (s, 2H); 4.53 (s, 2H); 6.67 (d, 1H); 7.20 - 7.31 (m, 3H); 7.37 (s, 1H); 7.42 (d, 1H); 8.02 (d, 1H); 9.15 (s, 2H)</td>
<td>438</td>
<td>Indane-5-carbaldehyde</td>
</tr>
<tr>
<td>Ex</td>
<td>Compound</td>
<td>H NMR (DMSO-D6) δ ppm</td>
<td>ES</td>
<td>Aldehyde</td>
</tr>
<tr>
<td>----</td>
<td>---------------------------------------------------------------------------</td>
<td>------------------------</td>
<td>----</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>93</td>
<td>5,7-Difluoro-1-[2-([1-methyl-1H-1,2,3-benzotriazol-5-yl)methyl]amino)piperidin-1-yl]ethyl</td>
<td>1.72 - 1.95 (m, 2H); 2.35 (s, 2H); 2.99 - 3.18 (m, 2H); 3.31 (s, 2H); 3.79 (s, 2H); 4.32 (s, 3H); 4.41 (s, 2H); 4.54 (s, 2H); 6.66 (d, 1H); 7.29 (t, 1H); 7.42 (d, 1H); 7.69 (d, 1H); 7.84 (d, 1H); 8.02 (d, 1H); 8.23 (s, 1H); 9.43 (s, 2H)</td>
<td>453 (MH)⁺</td>
<td>1-methyl-1H-1,2,3-benzotriazole-5-carbaldehyde</td>
</tr>
<tr>
<td>94</td>
<td>5,7-Difluoro-1-[2-([1H-indol-5-ylmethyl]amino)piperidin-1-yl]ethyl</td>
<td>1.80 (s, 2H); 2.36 (s, 2H); 3.11 (s, 2H); 3.40 (s, 2H); 3.80 (s, 2H); 4.26 (s, 2H); 4.52 (s, 2H); 6.47 (s, 1H); 6.67 (d, 1H); 7.21 (d, 1H); 7.31 (t, 1H); 7.37 - 7.52 (m, 3H); 7.70 (s, 1H); 8.03 (d, 1H); 9.04 (s, 1H); 11.28 (s, 1H)</td>
<td>437 (MH)⁺</td>
<td>1H-indole-5-carbaldehyde</td>
</tr>
<tr>
<td>95</td>
<td>5,7-Difluoro-1-[2-([4-methyl-3,4-dihydro-2H,1,4-benzoxazin-7-yl)methyl]amino)piperidin-1-yl]ethyl</td>
<td>1H NMR (DMSO-D6) δ ppm 1.73 (s, 2H); 2.30 (s, 2H); 2.83 (s, 3H); 2.97 - 3.15 (m, 2H); 3.24 (s, 2H); 3.30 - 3.38 (m, 2H); 3.79 (s, 2H); 4.03 (s, 2H); 4.22 (s, 2H); 4.53 (s, 2H); 6.63 - 6.75 (m, 2H); 6.85 (s, 1H); 6.90 (d, 1H); 7.31 (t, 1H); 7.43 (d, 1H); 8.04 (d, 1H); 8.90 (s, 1H)</td>
<td>469 (MII)⁺</td>
<td>4-methyl-3,4-dihydro-2H-1,4-benzoxazine-7-carbaldehyde</td>
</tr>
<tr>
<td>96</td>
<td>1-[2-([2,1,3-Benzoxadiazol-5-ylmethyl]amino)piperidin-1-yl]ethyl</td>
<td>1.13 - 1.29 (m, 2H); 1.78 (d, 2H); 1.95 - 2.07 (m, 2H); 2.31 - 2.43 (m, 1H); 2.51 - 2.58 (m, 2H); 2.89 (d, 2H); 3.82 (s, 2H); 4.27 (t, 2H); 7.23 (td, 1H); 7.51 (dd, 1H); 7.58 (d, 1H); 7.80 - 7.89 (m, 2H); 7.96 (d, 1H); 8.18 (s, 1H)</td>
<td>423 (MH)⁺</td>
<td>2,1,3-benzoxadiazole-5-carbaldehyde</td>
</tr>
</tbody>
</table>
Example 97

N-(1-[2-(7-Fluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl)-2,3-dihydro-1,4-benzodioxine-6-sulfonylamide

To a solution of 1-[2-(4-aminopiperidin-1-yl)ethyl]-7-fluoroquinoxalin-2(1H)-one (Intermediate 140, 130 mg, 0.448 mmol) in methylene chloride (10 mL) was added diisopropyl ethylamine (0.156 mL, 0.996 mmol) and 2,3-dihydro-1,4-benzodioxine-6-sulfonyl chloride (116 mg, 0.493 mmol) and the reaction was stirred for 2.5 hours at room temperature. It was washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate, and concentrated. The residue was dissolved in HCl in dioxane (4M, 8.0 mL), concentrated, suspended in ethyl acetate and filtered to give the HCl salt of title compound (15.9 mg).

**MS (ES):** 489 (M+H) for C_{21}H_{25}FN_{4}O_{2}S

**{1H NMR (DMSO-D6) $\delta$:** 1.62 - 1.83 (m, 3H); 2.92 - 3.11 (m, 2H); 3.16 - 3.28 (m, 3H); 3.41 - 3.50 (m, 3H); 3.59 (d, 2H); 4.47 - 4.59 (m, 2H); 7.05 (d, 1H); 7.23 - 7.34 (m, 2H); 7.78 (dd, 1H); 7.83 - 7.96 (m, 2H); 8.15 - 8.23 (m, 1H); 10.61 (s, 1H).

Example 98

N-(1-[2-(7-Fluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl)-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-sulfonylamide

1-[2-(4-Aminopiperidin-1-yl)ethyl]-7-fluoroquinoxalin-2(1H)-one (Intermediate 140, 130 mg, 0.448 mmol) was reacted as described for Example 97 with 3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-sulfonyl chloride (122 mg, 0.493 mmol) to give the HCl salt of title compound (89 mg).

**MS (ES):** 502 (M+H) for C_{22}H_{27}FN_{4}O_{3}S

**{1H NMR (DMSO-D6) $\delta$:** 1.55 - 1.93 (m, 3H); 2.94 - 3.09 (m, 2H); 3.17 - 3.30 (m, 2H); 3.50 (d, 1H); 3.61 (d, 2H); 4.53 (d, 2H); 4.69 (s, 2H); 7.12 (d, 1H); 7.28 (t, 1H); 7.32 - 7.42 (m, 2H); 7.73 (d, 1H); 7.83 - 7.95 (m, 1H); 8.02 (d, 1H); 8.20 (s, 1H); 10.14 (s, 1H); 11.04 (s, 1H).
Example 99
5-Fluoro-N-[1-[2-(7-fluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl]-1H-indole-2-carboxamide

A mixture of 1-[2-(4-aminopiperidin-1-yl)ethyl]-7-fluoroquinolin-2(1H)-one (Intermediate 140, 130 mg, 0.448 mmol), 5-fluoro-1H-indole-2-carboxylic acid (0.538 mmol), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide (EDC)(124 mg, 0.645 mmol) and 1-Hydroxybenzotriazole hydrate (HOBT) (87 mg, 0.645 mmol) in dichloromethane/DMF (4:1, 10 mL) was stirred for 2.5 hours at room temperature. The solvent was removed under reduced pressure and the residue was suspended in methanol, stirred for 45 minutes and then filtered to give title compound (161 mg).

**MS (ES):** 452 (M+H) for C_{29}H_{35}F_{2}N_{3}O_{2}

**1H NMR (DMSO-D_6):** 6 1.78 - 2.15 (m, 4H); 3.10 - 3.29 (m, 2H); 3.57 (s, 1H); 3.75 (d, 2H); 4.07 (s, 1H); 4.61 (s, 2H); 6.95 - 7.10 (m, 1H); 7.19 (s, 1H); 7.23 - 7.34 (m, 1H); 7.39 (d, 2H); 7.75 - 7.88 (m, 1H); 7.88 - 7.98 (m, 1H); 8.23 (s, 1H); 8.67 (d, 1H); 10.44 (s, 1H); 11.74 (s, 1H).

Example 100
N-(1-[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl)-6-morpholin-4-ylnicotinamide

1-[2-(4-Aminopiperidin-1-yl)ethyl]-5,7-difluoroquinolin-2(1H)-one (Intermediate 23, 100 mg, 0.326 mmol) was reacted as described for Example 99 with 6-morpholin-4-ylnicotinic acid (81 mg, 0.391 mmol), EDC (94 mg, 0.489 mmol) and HOBT (66 mg, 0.489 mmol) to give title compound (43.6 mg).

**MS (ES):** 493 (M+H) for C_{29}H_{35}F_{2}N_{3}O_{2}

**1H NMR (DMSO-D_6):** 6 1.81 - 2.12 (m, 5H); 3.09 - 3.24 (m, 2H); 3.46 - 3.60 (m, 4H); 3.62 - 3.78 (m, 6H); 3.97 - 4.18 (m, 1H); 4.63 (s, 2H); 6.67 (d, 1H); 6.85 (d, 1H); 7.30 (t, 1H); 7.74 (d, 1H); 7.93 - 8.07 (m, 2H); 8.37 (d, 1H); 8.63 (s, 1H); 10.66 (s, 1H).

Example 101
N-(1-[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl)-2,3-dihydro-1,4-benzodioxine-2-carboxamide

1-[2-(4-Aminopiperidin-1-yl)ethyl]-5,7-difluoroquinolin-2(1H)-one (Intermediate 23, 100 mg, 0.326 mmol) was reacted as described for Example 99 with 2,3-dihydro-1,4-
benzodioxane-2-carboxylic acid (71 mg, 0.391 mmol), EDC (94 mg, 0.489 mmol) and HOBT (66 mg, 0.489 mmol) to give title compound (73.9 mg).

**Example 102**

N\{1-[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl\}-1-methyl-1H-1,2,3-benzotriazole-5-carboxamide

1-[2-(4-Aminopiperidin-1-yl)ethyl]-5,7-difluoroquinolin-2(1H)-one (Intermediate 23, 100 mg, 0.326 mmol) was reacted as described for Example 99 with 1-methyl-1H-1,2,3-benzotriazole-5-carboxylic acid (70 mg, 0.391 mmol), EDC (94 mg, 0.489 mmol) and HOBT (66 mg, 0.489 mmol) to give title compound (67.6 mg).

**Example 103**

N\{1-[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl\}-3-(2-methyl-1,3-thiazol-4-yl)benzamide

1-[2-(4-Aminopiperidin-1-yl)ethyl]-5,7-difluoroquinolin-2(1H)-one (Intermediate 23, 100 mg, 0.326 mmol) was reacted as described for Example 99 with 3-(2-methyl-1,3-thiazol-4-yl)benzoic acid (86 mg, 0.391 mmol), EDC (94 mg, 0.489 mmol) and HOBT (66 mg, 0.489 mmol). Solvent removed and the obtained solids were stirred in HCl/dioxane (8.0 mL, 4M) and then filtered to give the HCl salt of title compound (39 mg).
Example 104

N-(1-[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl)-4-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide

1-[2-(4-Aminopiperidin-1-yl)ethyl]-5,7-difluoroquinolin-2(1H)-one (Intermediate 23, 100 mg, 0.326 mmol) was reacted as described for Example 99 with 4-(5-methyl-1,2,4-oxadiazol-3-yl)benzoic acid (80 mg, 0.391 mmol), EDC (94 mg, 0.489 mmol) and HOBT (66 mg, 0.489 mmol). Solvent removed and the obtained solids were suspended in ethyl acetate and then filtered to give title compound (71.9 mg).

MS (ES): 494 (M+H) for C_{26}H_{21}F_{2}N_{3}O_{1}

\textsuperscript{1}H NMR (DMSO-\text{d}_{6}) \delta 1.77 - 1.97 (m, 2H); 1.98 - 2.15 (m, 2H); 2.66 (s, 3H); 3.10 - 3.27 (m, 2H); 3.75 (ddd, 2H); 4.05 (s, 1H); 4.60 (t, 2H); 6.69 (d, 1H); 7.32 (t, 1H); 7.46 - 7.68 (m, 1H); 7.96 - 8.15 (m, 5H); 8.72 (d, 1H); 9.86 (s, 1H).

Example 105

3-Oxo-4-[2-((2R,5S)-5-(((3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl)amino)piperidin-2-yl)ethyl]-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile

To a solution of tert-butyl (2R,5S)-2-[2-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]-5-(((3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl)amino)piperidine-1-carboxylate (Intermediate 182, 0.138 g) in dioxane (2 mL) was added 4M HCl/dioxane (1 mL). After 1 hour at room temperature, the reaction was concentrated and evaporated twice from methanol. The solid was suspended in methanol and filtered to yield 73 mg of the name compound as a bis HCl salt.

MS (ES): 463 (M+H') for C_{26}H_{21}N_{6}O_{4}

\textsuperscript{1}H NMR (DMSO-\text{d}_{6}) \delta 1.58 - 1.63 (m, 1H); 1.65 - 1.74 (m, 1H); 1.75 - 1.86 (m, 1H); 1.92 - 2.03 (m, 1H); 2.13 - 2.23 (m, 1H); 2.29 - 2.38 (m, 1H); 3.02 - 3.14 (m, 1H); 3.14 - 3.24 (m, 3H); 3.59 - 3.70 (m, 1H); 3.70 - 3.78 (m, 1H); 4.01 - 4.13 (m, 2H); 4.18 - 4.28 (m, 2H); 4.70 (s, 2H); 4.82 (s, 2H); 7.19 (d, 1H); 7.26 (d, 1H); 7.46 (d, 1H); 7.54 (dd, 1H); 7.77 (d, 1H); 9.51 (s, 1H); 9.70 (s, 1H); 9.82 (s, 1H); 11.36 (s, 1H).
**Intermediate 182: tert-Butyl (2R,5S)-2-[2-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoazin-4-yl)ethyl]-5-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-yl]methyl][amino] piperidine-1-carboxylate**

A mixture of tert-butyl (2R,5S)-5-amino-2-[2-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoazin-4-yl)ethyl]piperidine-1-carboxylate (Intermediate 183, 0.14 g), 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (75 mg) and 3 Å molecular sieves powder (70 mg) in methanol (8 mL) was heated at 80 °C for 1 hour. The solution was cooled to 0°C and NaN₃BH₃ (33 mg) was added. After stirring at room temperature overnight, the reaction was filtered and concentrated. The residue was purified chromatography on silica gel with a gradient of 0-5% methanol in methylene chloride to give 0.14 g.

**MS (ESI) 563 (MH⁺)** for C₂₅H₃₂N₇O₆

**¹H NMR (CDCl₃)**
- 1.37 - 1.43 (m, 1H); 1.44 - 1.51 (s, 9H); 1.70 - 1.81 (m, 2H); 2.11 (m, 1H); 2.89 - 3.00 (m, 1H); 3.01 - 3.12 (m, 1H); 3.94 - 4.05 (m, 1H); 4.20 - 4.32 (m, 1H); 4.33 - 4.44 (m, 1H); 4.64 (s, 2H); 4.67 (s, 2H); 6.99 (d, 1H); 7.04 (d, 1H); 7.17 - 7.24 (m, 2H); 7.32 (dd, 1H).

**Intermediate 183: tert-Butyl (2R,5S)-5-amino-2-[2-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoazin-4-yl)ethyl]piperidine-1-carboxylate**

tert-Butyl (2R,5S)-5-azido-2-[2-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoazin-4-yl)ethyl]piperidine-1-carboxylate (Intermediate 184, 0.31 g) was hydrogenated in methanol (10 mL) over 10% Pd/C (90 mg) at normal pressure and room temperature overnight. The reaction was degassed, filtered and purified by chromatography on silica gel with a gradient of 0-10% methanol in methylene chloride to give 0.29 g.

**MS (ESI) 401 (MH⁺)** for C₂₁H₂₈N₄O₄

**Intermediate 184: tert-Butyl (2R,5S)-5-azido-2-[2-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoazin-4-yl)ethyl]5-hydroxypiperidine-1-carboxylate**

To a solution of tert-butyl (2R,5R)-2-[2-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoazin-4-yl)ethyl]-5-hydroxypiperidine-1-carboxylate (Intermediate 185, crude, 0.8 g) in THF (20 mL) were successively added triphenylphosphine (1.30 g), diisopropylazodicarboxylate (1 mL) and diphenyl phosphoryl azide (0.90 g). After 4 hours, the reaction was diluted with ethyl acetate, washed with saturated solution of sodium
hydrogen carbonate (NaHCO₃) and brine, dried over sodium sulfate and concentrated.
Chromatography on silica gel with a gradient of 0-5% methanol in methylene chloride gave
0.31 g of product.

MS (ESI) 427 (MH⁺) for C₂₉H₂₃N₆O₉

Intermediate 185: tert-Butyl (2R,5R)-2-[(6-cyano-3-oxo-2,3-dihydro-4H-1,4-
benzoazin-4-yl)ethyl]-5-hydroxypiperidine-1-carboxylate

To a solution of tert-butyl (2R,5R)-5-[(tert-butyl(dimethyl)silyl)oxy]-2-[(6-
cyano-3-oxo-2,3-dihydro-4H-1,4-benzoazin-4-yl)ethyl]piperidine-1-carboxylate (Intermediate
186, 1.01 g) in THF (10 mL) was added tetraethylammonium fluoride (TBAF) (4 mL). After
5 hours, the reaction was diluted with ethyl acetate, washed with NaHCO₃ and brine, dried
over sodium sulfate and concentrated. The crude reaction mixture was used without further
purification in the next step.

MS (ESI) 402 (MH⁺) for C₂₁H₂₇N₃O₉

Intermediate 186: tert-Butyl (2R,5R)-5-[(tert-butyl(dimethyl)silyl)oxy]-2-[(6-
cyano-3-oxo-2,3-dihydro-4H-1,4-benzoazin-4-yl)ethyl]piperidine-1-carboxylate

To a solution of tert-butyl (2R,5R)-5-[(tert-butyl(dimethyl)silyl)oxy]-2-[(6-
hydroxyethyl)piperidine-1-carboxylate (Intermediate 187, 1.27 g) in methylene chloride (15
mL) at 0 °C were added disopropylethylamine (1.2 mL) and methanesulfonyl chloride (0.50
mL). At the same time in a separate flask, to a solution of 3-oxo-3,4-dihydro-2H-1,4-
benzoazine-6-carbonitrile (Intermediate 60) (0.66 g) in DMF (8 mL) at 0 °C was added
60% suspension in oil of NaH (0.25 g). After 30 minutes, the mesylate solution was diluted
with methylene chloride, washed with NaHCO₃ and brine, dried over sodium sulfate and
concentrated. This residue was dissolved in DMF (5 mL) and added to the sodium salt of
Intermediate 60. The reaction was stirred over the weekend, diluted with ethyl acetate,
 washed with NaHCO₃ and brine, dried over sodium sulfate and concentrated to give the
product.

MS (ESI) 516 (MH⁺) for C₂₇H₄₁N₇O₃Si
**Intermediate 187: tert-Butyl (2R,5R)-5-\{\text{tert-butyl(dimethyl)silyl]oxy}\}-2-(2-hydroxyethyl)piperidine-1-carboxylate**

To a solution of tert-butyl (2R,5R)-5-\{\text{tert-butyl(dimethyl)silyl]oxy}\}-2-vinylpiperidine-1-carboxylate (Intermediate 188, 1.39 g) in THF (20 mL) at 0 °C was added 9-BBN (0.5 M, 15 mL). After 45 minutes, the reaction was diluted with water (3 mL), 3 N NaOH (12 mL) and 30% H₂O₂ (12 mL). After 15 minutes, the reaction was allowed to warm to room temperature. After 30 minutes, the reaction was diluted with ethyl acetate, washed with 1 N HCl, NaHCO₃ and brine, dried (Na₂SO₄), filtered and concentrated. Chromatography on silica gel with a gradient of 0-5% methanol in methylene chloride gave 1.27 g of product.

**MS (ESI) 360 (M+H)⁺** for C₁₈H₂₅NO₄Si

**Intermediate 188: tert-Butyl (2R,5R)-5-\{\text{tert-butyl(dimethyl)silyl]oxy}\}-2-vinylpiperidine-1-carboxylate**

To a suspension of zinc dust (12.2 g) in THF (200 mL) and diiodomethane (5 mL) at 0 °C was added trimethylaluminium (2M in hexanes, 6 mL). After the addition the reaction was carefully warmed to room temperature (exothermic reaction!). The reaction was then cooled with an ice bath and a solution of tert-butyl (2R,5R)-5-\{\text{tert-butyl(dimethyl)silyl]oxy}\}-2-formylpiperidine-1-carboxylate (Intermediate 189, 6.34 g) in THF (40 mL) was added. After 6 hours it was warmed to room temperature, the reaction was diluted with ethyl acetate and slowly quenched with a saturated aqueous solution of NaHCO₃. The organic phase was collected and washed with NaHCO₃ and brine, dried (Na₂SO₄), filtered and concentrated. Chromatography on silica gel with a gradient of 0-100% methylene chloride in hexanes gave 3.96 g of product.

**MS (ESI) 341 (M+H)⁺** for C₁₆H₂₃NO₃Si

**¹H NMR (CDCl₃)** δ 0.06 (s, 6H); 0.87 (s, 9H); 1.42 - 1.44 (m, 1H); 1.44 (s, 9H); 1.63 - 1.81 (m, 2H); 2.44 - 2.73 (m, 1H); 3.43 - 3.63 (m, 1H); 3.77 - 4.16 (m, 1H); 4.50 - 4.92 (m, 1H); 4.97 - 5.13 (m, 1H); 5.13 - 5.26 (m, 1H); 5.58 - 5.84 (m, 1H).

**Intermediate 189: tert-Butyl (2R,5R)-5-\{\text{tert-butyl(dimethyl)silyl]oxy}\}-2-formylpiperidine-1-carboxylate**

To a solution of oxalyl chloride (2.4 mL) in methylene chloride (75 mL) at -78 °C was slowly added dimethylsulfoxide (3 mL) in methylene chloride (25 mL). After 10 minutes,
a solution of tert-butyl (2R,5R)-5-[(tert-butyl(dimethyl)silyl)oxy]-2-(hydroxymethyl)piperidine-1-carboxylate (Intermediate 190, 7.60 g) in methylene chloride (40 mL) was slowly added. After 30 minutes at -78 °C, diisopropylethylamine (10 mL) was added and the reaction warmed to room temperature. The reaction was diluted with ethyl acetate, washed with 0.5 M HCl, NaHCO₃ and brine solutions, dried (Na₂SO₄), filtered and concentrated. Chromatography on silica gel with a gradient of 0-30% ethyl acetate in hexanes gave 6.84 g of product.

**MS (ESI) 344 (M+H)⁺ for C₁₁H₁₃NO₄Si**

**Intermediate 190: tert-Butyl (2R,5R)-5-[(tert-butyl(dimethyl)silyl)oxy]-2-(hydroxymethyl)piperidine-1-carboxylate**

To a solution of 1-tert-butyl 2-ethyl (2R,5R)-5-[(tert-butyl(dimethyl)silyl)oxy]piperidine-1,2-dicarboxylate (Intermediate 191, 9.99 g) in THF (100 mL) was added lithium aluminium hydride (1M in THF, 30 mL). After 2 hours, the reaction was quenched with ethyl acetate, washed with 1 N HCl, NaHCO₃ and brine solutions, dried (Na₂SO₄), filtered and concentrated yielding 7.9 g of product.

**MS (ESI) 346 (M+H)⁺ for C₁₁H₁₅NO₄Si**

**Intermediate 191: 1-tert-Butyl 2-ethyl (2R,5R)-5-[(tert-butyl(dimethyl)silyl)oxy]piperidine-1,2-dicarboxylate**

To a solution of 1-tert-butyl 2-ethyl (2R)-5-oxopiperidine-1,2-dicarboxylate (8.3 g) (Bioorganic & Medicinal Chemistry Letters (2002), 12(10), 1387-1390) in methanol (200 mL) at 0 °C was added sodium borohydride (1.80 g). After 2 hours, the reaction was concentrated to dryness. The residue was dissolved in ethyl acetate and washed with 1 N HCl, NaHCO₃ and brine solutions, dried (Na₂SO₄), filtered and concentrated. The crude alcohol was dissolved in DMF (200 mL) and treated with imidazole (7.5 g) and t-BDMSCl (11.5 g). After stirring overnight at room temperature, the reaction was diluted with ethyl acetate and washed with 1 N HCl, NaHCO₃ and brine solutions, dried (Na₂SO₄), filtered and concentrated. Chromatography on silica gel with a gradient of 0-25% ethyl acetate in hexanes gave 9.99 g of product.

**MS (ESI) 388 (M+H)⁺ for C₁₉H₁₇NO₄Si**

**1H NMR (CDCl₃) δ (rotamers) 0.06 (m, 6H); 0.86 & 0.87 (s, 9H); 1.22 - 1.30 (m, 3H); 1.42 & 1.46 (s, 9H); 1.61 - 1.73 (m, 1H); 1.77 - 1.91 (m, 1H); 2.18 - 2.31 (m, 1H); 2.58 &
Example 106

3-Oxo-4-{2-{2S,5R}-5-[[3-oxo-3,4-dihydro-2H-pyrrole][3,2-b][1,4]oxazin-6-yl]methyl]amino}piperidin-2-yl)(ethyl)-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile

The title compound was prepared following the procedure described for Example 105, except, starting from 1-tert-butyl 2-methyl (2S)-5-oxopiperidine-1,2-dicarboxylate (Bioorganic & Medicinal Chemistry Letters (2002), 12(10), 1387-1390).

\[ \text{MS (ESI)} 463 (M^+ \text{ for } C_{34}H_{43}N_{13}O_4) \]

\[ \text{^1H NMR (DMSO-D_6)} \delta 1.58 - 1.63 (m, 1H); 1.65 - 1.74 (m, 1H); 1.75 - 1.86 (m, 1H); 1.92 - 2.03 (m, 1H); 2.13 - 2.23 (m, 1H); 2.29 - 2.38 (m, 1H); 3.02 - 3.14 (m, 1H); 3.14 - 3.24 (m, 3H); 3.59 - 3.70 (m, 1H); 3.70 - 3.78 (m, 1H); 4.01 - 4.13 (m, 2H); 4.18 - 4.28 (m, 2H); 4.70 (s, 2H); 4.82 (s, 2H); 7.19 (d, 1H); 7.25 (d, 1H); 7.46 (d, 1H); 7.54 (dd, 1H); 7.77 (d, 1H); 9.51 (s, 1H); 9.70 (s, 1H); 9.82 (s, 1H); 11.36 (s, 1H).

Example 107

6-[[1-2-{5,7-Difluoro-2-oxoquinazolin-1(2H)-yl]ethyl}piperidin-4-yl]amino)methyl]-2H-pyrrole[3,2-b][1,4]oxazin-3(4H)-one

To a solution of 1-[2-(4-aminopiperdin-1-yl)ethyl]-5,7-difluoroquinazolin-2(1H)-one (Intermediate 192; 0.158 g) in methanol (10 mL) were added 3 Å molecular sieve power (0.15 g) and 3-oxo-3,4-dihydro-2H-pyrrole[3,2-b][1,4]oxazine-6-carboxaldehyde (WO 2004/058144) (92 mg). After 2 hours at reflux, the reaction was cooled to 0°C and NaN₃(OAc)₃ (0.19 g) was added. The reaction was allowed to warm to room temperature and was stirred overnight. It was diluted with ethyl acetate, filtered, washed with saturated solutions of Na₂CO₃ and brine, dried over sodium sulfate and concentrated. Chromatography on silica gel with 0-20% methanol in dichloromethane. Fractions containing product were collected, concentrated, dissolved in a minimum of CH₂Cl₂, precipitated with diethyl ether, and filtered to yield 104 mg of product.

\[ \text{MS (ESI)} 471 (M^+) \text{ for } C_{26}H_{27}N_{13}O_3 \]

\[ \text{^1H NMR (CDCl}_3) \delta 1.15 - 1.35 (m, 2H); 1.73 - 1.88 (m, 2H); 1.93 - 2.09 (m, 2H); 2.51 - 2.58 (m, 2H); 2.83 - 2.95 (m, 2H); 3.16 (s, 1H); 3.71 - 3.84 (m, 1H); 4.21 - 4.34 (m, 2H); 4.61 (s, 2H); 7.02 (d, 1H); 7.26 - 7.48 (m, 1H); 8.19 (s, 1H). \]
Intermediate 192: 1-[2-((4-Aminopiperidin-1-yl)ethyl)-5,7-difluoroquinoxalin-2(1H)-one

To a solution of tert-butyl 1-[2-(5,7-difluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl] carbamate (Intermediate 193, 0.21 g) in dioxane (3 mL) and water (1 mL) was added 4 M HCl in dioxane (1 mL). After 30 minutes, additional 4 M HCl/dioxane (3 mL) was added. After 1 hour, the reaction was diluted with chloroform and poured into a saturated solution of Na₂CO₃. The organic solution was collected, dried (Na₂SO₄), filtered and concentrated yielding 0.158 g of crude titled compound.

MS (ESI) 309 (MH⁺) for C₁₅H₁₆F₂N₄O

Intermediate 193: tert-Butyl 1-[2-(5,7-difluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl] carbamate

and

Intermediate 194: tert-Butyl 1-[2-(6,8-difluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl] carbamate

A mixture of 5,7-difluoroquinoxalin-2(1H)-one and 6,8-difluoroquinoxalin-2(1H)-one (Intermediate 195) (1.05 g, 5.77 mmol) was deprotonated with sodium hydride (0.31 g, 60% in oil, 7.75 mmol) and alkylated with 2-[(tert-butoxycarbonylamino)piperidin-1-yl] ethyl methanesulfonate (Intermediate 6) (5.8 mmol) as described for Intermediate 2. The residue obtained after aqueous workup was triturated in diethyl ether and filtered yielding 0.73 g of tert-butyl 1-[2-(5,7-difluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl] carbamate (Intermediate 193). The filtrate was concentrated and the residue was purified by chromatography on silica gel with 0-20% acetone in dichloromethane to yield 111 mg of tert-butyl 1-[2-(6,8-difluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl] carbamate (Intermediate 194).

Intermediate 193:

MS (ESI) 409 (MH⁺) for C₅₀H₃₆F₂N₄O₃

¹H NMR (CDCl₃) δ 1.33 - 1.42 (m, 2H); 1.44 (s, 9H); 1.89 - 1.97 (m, 2H); 2.24 (td, 2H); 2.65 (t, 2H); 2.84 - 2.89 (m, 2H); 3.41 - 3.52 (m, 1H); 4.27 (t, 2H); 4.41 (s, 1H); 6.87 (td, 1H); 6.93 (dt, 1H); 8.23 (s, 1H).

Intermediate 194:

MS (ESI) 409 (MH⁺) for C₅₀H₃₆F₂N₄O₃
Intermediate 195: 5,7-Difluoroquinazolin-2(1H)-one and 6,8-difluoroquinazolin-2(1H)-one

To a solution of 1,2-diamino-3,5-difluorobenzene (5.11 g) in methanol (100 mL) was added ethylglyoxalate (16 mL). After 6 hours at room temperature, the precipitate was collected by filtration and washed with methanol yielding 2.1 g products, 1:1 mixture of 5,7-difluoroquinazolin-2(1H)-one and 6,8-difluoroquinazolin-2(1H)-one.

MS (ESI) 182 (M+H)\(^+\) for C\(_{12}\)H\(_{14}\)F\(_2\)N\(_2\)O

Example 108

6-{[1-[[2-(6,8-Difluoro-2-oxoquinazolin-1(2H)-yl)ethyl]piperidin-4-yl]amino]methyl]-2H-pyrido[3,2-b][1,4]oxazine-3(4H)-one

1-[2-(4-Aminopiperidin-1-yl)ethyl]-6,8-difluoroquinazolin-2(1H)-one (Intermediate 196, 52 mg) was reacted with 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carboxaldehyde (WO 2004/058144) and sodium acetoxymethylylcarbodimide as described for Example 107 yielding 29 mg of the title compound.

MS (ESI) 471 (M+H)\(^+\) for C\(_{23}\)H\(_{24}\)F\(_2\)N\(_3\)O\(_3\)

\(^1\)H NMR (DMSO-D\(_6\)) 8 1.16 - 1.28 (m, 2H); 1.71 - 1.82 (m, 2H); 2.04 (t, 2H); 2.35 - 2.47 (m, 2H); 2.54 - 2.61 (m, 2H); 2.81 - 2.90 (m, 2H); 3.70 (s, 2H); 4.32 - 4.42 (m, 2H); 4.61 (s, 2H); 7.02 (d, 1H); 7.30 (d, 1H); 7.61 (d, 1H); 7.72 (ddd, 1H); 8.33 (s, 1H); 11.17 (s, 1H).

Intermediate 196: 1-[2-(4-Aminopiperidin-1-yl)ethyl]-6,8-difluoroquinazolin-2(1H)-one

tert-Butyl \{1-[2-(6,8-difluoro-2-oxoquinazolin-1(2H)-yl)ethyl]piperidin-4-yl\} carbonate

(Intermediate 194) was deprotected with HCl in dioxane as described for

Intermediate 192.

MS (ESI) 309 (M+H)\(^+\) for C\(_{15}\)H\(_{15}\)F\(_2\)N\(_2\)O
Example 109

2-Oxo-1-{2-(4-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl]methyl]amino)piperidin-1-yl]ethyl}-1,2-dihydroquinoxaline-6-carbonitrile

1-{2-(4-Aminopiperidin-1-yl)ethyl}-2-oxo-1,2-dihydroquinoxaline-6-carbonitrile

(Intermediate 197, 0.125 g) was reacted with 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carboxaldehyde (WO 2004/058144) (0.17 g) and NaBH(OAc)₃ (0.27 g) as described for Example 107. The residue was purified by reverse phase HPLC with acetonitrile in water containing 0.1% TFA. Fractions containing product were concentrated to remove acetonitrile, neutralized with Na₂CO₃ solid, extracted with ethyl acetate, dried (Na₂SO₄), filtered and concentrated. The residue was suspended in diethyl ether and filtered to yield 127 mg of a colorless solid.

**MS (ESI)** 460 (M⁺) for C₂₉H₂₉N₂O₃

**¹H NMR (DMSO-δ6) δ** 1.14 - 1.25 (m, 2H); 1.70 - 1.80 (m, 2H); 1.96 - 2.07 (m, 2H); 2.33 - 2.43 (m, 1H); 2.51 - 2.57 (m, 2H); 2.87 (d, 2H); 3.67 (s, 2H); 4.33 (t, 2H); 4.61 (s, 2H); 7.01 (d, 1H); 7.30 (d, 1H); 7.79 (d, 1H); 8.05 (dd, 1H); 8.36 (d, 2H); 11.16 (s, 1H).

**Intermediate 197:** 1-{2-(4-Aminopiperidin-1-yl)ethyl}-2-oxo-1,2-dihydroquinoxaline-6-carbonitrile

To a solution of tert-butyl {1-{2-(6-cyano-2-oxoquinolin-1(2H)-yl)ethyl}piperidin-4-yl} carbamate (Intermediate 198, 0.38 g) in methylene chloride (4 mL) was added at 0°C TFA (2 mL). After 1 hour, the reaction was diluted with chloroform, washed with saturated solution of Na₂CO₃ dried (Na₂SO₄), filtered and concentrated yielding 0.25 g of crude product.

**MS (ESI)** 298 (M⁺) for C₁₆H₁₈N₂O

**Intermediate 198:** tert-Butyl {1-{2-(6-cyano-2-oxoquinolin-1(2H)-yl)ethyl}piperidin-4-yl} carbamate

and

**Intermediate 199:** tert-Butyl {1-{2-(7-cyano-2-oxoquinolin-1(2H)-yl)ethyl}piperidin-4-yl} carbamate

A mixture of 2-oxo-1,2-dihydroquinoline-6-carbonitrile and 3-oxo-3,4-dihydroquinoline-6-carbonitrile (Intermediate 200, 0.83 g, 4.8 mmol) was deprotonated with sodium hydride (0.30 g, 60% in oil) and alkylated with 2-{4-{(tert-
butoxycarbonyl)amino[4]piperidin-1-yl]ethyl methanoso1fonate (Intermediate 6) (4.8 mmol) as described for Intermediate 2. Chromatography on silica gel with 0-25% acetone in dichloromethane gave 38 mg of tert-butyl {1-[2-(7-cyano-2-oxoquinoxalin-1(2H)-yl)ethyl][piperidin-4-yl] carbamate (Intermediate 199) and 0.39 g of tert-butyl {1-[2-(6-cyano-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl] carbamate (Intermediate 198).

**MS (ESI) 398 (M+H)⁺ for C₂₅H₂₉N₅O₃**

*Intermediate 198:*

\[ ^1H \text{NMR (CDCl}_3\] δ 1.31 - 1.41 (m, 2H); 1.44 (s, 9H); 1.88 - 1.98 (m, 2H); 2.19 - 2.29 (m, 2H); 2.67 (t, 2H); 2.83 - 2.93 (m, 2H); 3.41 - 3.52 (m, 1H); 4.35 (t, 2H); 4.43 (m, 1H);

7.48 (d, 1H); 7.80 (dd, 1H); 8.20 (d, 1H); 8.35 (s, 1H).

*Intermediate 199:*

\[ ^1H \text{NMR (CDCl}_3\] δ 1.32 - 1.42 (m, 2H); 1.44 (s, 9H); 1.89 - 1.97 (m, 2H); 2.19 - 2.30 (m, 2H); 2.68 (t, 2H); 2.83 - 2.93 (m, 2H); 3.42 - 3.53 (m, 1H); 4.33 (t, 2H); 4.42 (s, 1H); 7.59 (dd, 1H); 7.79 (d, 1H); 7.97 (d, 1H); 8.37 (s, 1H).

*Intermediate 200: 2-Oxo-1,2-dihydroquinoxaline-6-carbonitrile and 3-oxo-3,4-dihydroquinoxaline-6-carbonitrile*

To a solution of 3,4-diaminobenzonitrile (0.99 g) in methanol (20 mL) was added ethylglyoxalate (3.5 mL). After stirring overnight at room temperature, the precipitate was collected and washed with methanol. The filtrate was concentrated to give a second crop of product yielding 0.83 g from both batches, 1:1 mixture of 2-oxo-1,2-dihydroquinoxaline-6-carbonitrile and 3-oxo-3,4-dihydroquinoxaline-6-carbonitrile as a brown solid.

MS (ESI) 172 (MH⁺) for C₉H₇N₂O

*Example 110*

3-Oxo-4-[2-(4-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4] oxazin-6-yl]methyl]amino)piperidin-1-yl]ethyl]-3,4-dihydroquinoxaline-6-carbonitrile

1-[2-(4-Aminopiperidin-1-yl)ethyl]-2-oxo-1,2-dihydroquinoxaline-7-carbonitrile (Intermediate 201, 0.11 g) was reacted with 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4] oxazine-6-carbaldehyde (WO 2004/058144) and sodium acetoxycobaldehyde as described for Example 107 yielding 17 mg of a colorless solid.

MS (ESI) 460 (MH⁺) for C₃₄H₅₆N₇O₃
1H NMR (DMSO-D6) δ 1.22 - 1.33 (m, 2H); 1.80 - 1.91 (m, 2H); 1.98 - 2.08 (m, 2H);
2.55 - 2.67 (m, 3H); 2.90 - 3.01 (m, 2H); 3.79 - 3.90 (m, 1H); 4.35 (t, 2H); 4.64 (s, 2H); 7.05
(d, 1H); 7.34 (d, 1H); 7.79 (d, 1H); 7.99 (d, 1H); 8.21 (s, 1H); 8.38 (s, 1H); 11.23 (s, 1H).

**Intermediate 201**: 1-[2-(4-Aminopiperidin-1-yl)ethyl]-2-oxo-1,2-dihydroquinoxaline-7-carbonitrile

tert-Butyl (1-[2-(7-cyano-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl) carbonate

(Intermediate 199) was deprotected with TFA as described for Intermediate 197 to
give the crude free base of the product.

**Example 111**

6-[(1-[2-(6-Methoxy-3-oxopyrido[2,3-b]pyrazin-4(3H)-yl)ethyl]piperidin-4-yl)amino]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

4-[2-(4-Aminopiperidin-1-yl)ethyl]-6-methoxypyrrolo[2,3-b]pyrazin-3(4H)-one

(Intermediate 202, 0.125 g) was reacted with 3-oxo-3,4-dihydro-2H-pyrido[3,2-
b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (50 mg) and sodium acetoxylborohydride
(110 mg) as described for Example 107. Chromatography on silica gel with 0-20% methanol
in dichloromethane and trituration of the product from ether gave 37.6 mg of the title

compound as acetic acid salt.

**MS (ESI) 466 (M+H) for C_{25}H_{27}N_{7}O_{4}**

1H NMR (DMSO-D6) δ 1.18 (q, 2H); 1.74 (d, 2H); 2.03 (t, 2H); 2.32 - 2.41 (m, 1H);
2.61 (t, 2H); 2.90 (d, 2H); 3.66 (s, 2H); 3.98 (s, 3H); 4.41 (t, 2H); 4.59 (s, 2H); 6.83 (d, 1H);
6.99 (d, 1H); 7.27 (d, 1H); 8.10 (s, 1H); 8.12 (d, 1H); 11.15 (s, 1H).

**Intermediate 202**: 4-[2-(4-Aminopiperidin-1-yl)ethyl]-6-methoxypyrrolo[2,3-
b]pyrazin-3(4H)-one

tert-Butyl (1-[2-(6-methoxy-3-oxopyrido[2,3-b]pyrazin-4(3H)-yl)ethyl]piperidin-4-
yl) carbonate (Intermediate 203, 0.213 g) was deprotected with TFA as described for

Intermediate 197 to give the crude free base of the product, 0.15 g.

**MS (ESI) 304 (M+H) for C_{16}H_{22}N_{2}O_{2}**
**Intermediate 203: ( tert-Butyl) (1H-[2-(6-methoxy-3-oxopyrido[2,3-b]pyrazin-4(3H)-yl]ethyl)piperidin-4-yl) carbonate**

6-Methoxypyrido[2,3-b]pyrazin-3(4H)-one (Intermediate 204, 0.085 g, 0.48 mmol) was deprotonated with sodium hydride (0.030 g, 60% in oil, 0.75 mmol) and alkylated with 2-[(tert-butoxycarbonylamino)piperidin-1-yl]ethyl methanesulfonate (Intermediate 6) (1.05 mmol) as described for Intermediate 2. Chromatography on silica gel with 0-25% acetone in dichloromethane gave 0.13 g of the title compound.

**MS (ESI) 404 (M+H)⁺ for C₂₅H₂₆N₄O₄**

**¹H NMR (CDCl₃) δ 1.31 - 1.40 (m, 2H); 1.40 - 1.46 (m, 9H); 1.87 - 1.95 (m, 2H); 2.15 - 2.27 (m, 2H); 2.69 - 2.75 (m, 2H); 2.93 - 3.02 (m, 2H); 3.40 - 3.51 (m, 1H); 4.02 (s, 3H); 4.35 - 4.46 (m, 1H); 4.51 - 4.60 (m, 2H); 6.73 (d, 1H); 8.02 (d, 1H); 8.15 (s, 1H).

**Intermediate 204: 6-Methoxypyrido[2,3-b]pyrazin-3(4H)-one**

To a solution of 3,4-diamino-6-methoxypyridine (1.11 g) in methanol (20 mL) was added ethylglyoxalate (3.5 mL). After stirring overnight at room temperature, it was filtered and washed with methanol (the precipitate contained the undesired regioisomer, 6-methoxypyrido[2,3-b]pyrazin-2(1H)-one). The filtrate was concentrated and suspended in diethyl ether to give 0.18 g product.

**MS (ESI) 178 (M+H)⁺ for C₉H₁₄N₂O**

**¹H NMR (DMSO-D₆) δ 6.77 (d, 1H); 8.01 (s, 1H); 8.07 (d, 1H); 12.83 (s, 1H).**

**Example 112**

4-(2-(4-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl]amino)piperidin-1-yl)ethyl)-6-methoxypyrido[2,3-b]pyrazin-3(4H)-one

4-[(2-(4-Aminopiperidin-1-yl)ethyl)-6-methoxypyrido[2,3-b]pyrazin-3(4H)-one (Intermediate 202, 75 mg) was reacted with 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde (WO 2004/058144) (48 mg) and sodium acetoxyborohydride (0.11) as described for Example 107. Chromatography on silica gel with 0-2% methanol in dichloromethane to give 72 mg of the product.

**MS (ESI) 453 (M+H)⁺ for C₂₅H₂₈N₄O₄**

**¹H NMR (DMSO-D₆) δ 1.18 (q, 2H); 1.74 (d, 2H); 2.02 (t, 2H); 2.30 - 2.40 (m, 1H); 2.60 (t, 2H); 2.89 (d, 2H); 3.65 (s, 2H); 3.98 (s, 3H); 4.26 (d, 2H); 4.29 - 4.34 (m, 2H); 4.40 (t, 2H); 6.83 (d, 1H); 6.92 (s, 1H); 7.98 (s, 1H); 8.10 (s, 1H); 8.12 (d, 1H).**
Example 113

6-[[1-[2-[(6-Chloro-1-oxido-3-oxo-1,2,4-benzotriazin-4(3H)-yl)ethyl]piperidin-4-yl]amino]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

4-[2-(4-Aminopiperidin-1-yl)ethyl]-6-chloro-1,2,4-benzotriazin-3(4H)-one 1-oxide

(Intermediate 205, 0.517 g) was reacted with 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-carboxaldehyde (WO 2004/053144) (117 mg) and sodium acetoxymethyleneborohydride (340 mg) as described for Example 107. Chromatography on silica gel with 0-20% methanol in dichloromethane gave 60 mg of the title compound as acetic acid salt.

**MS (ESI)** 486 (MH+) for C_{12}H_{24}ClN_{3}O_{4}

**{1H NMR (DMSO-D6)}** δ 1.13 - 1.24 (m, 2H); 1.69 - 1.79 (m, 2H); 2.02 (t, 2H); 2.31 - 2.42 (m, 1H); 2.57 (t, 2H); 2.88 (d, 2H); 3.27 - 3.39 (m, 2H); 3.67 (s, 2H); 4.26 (t, 2H); 4.60 (s, 2H); 7.00 (d, 1H); 7.28 (d, 1H); 7.43 (dd, 1H); 7.91 (d, 1H); 8.20 (d, 1H); 11.15 (s, 1H).

**Intermediate 205**: 4-[2-(4-Aminopiperidin-1-yl)ethyl]-6-chloro-1,2,4-benzotriazin-3(4H)-one 1-oxide

**tert-Butyl (1-[2-[(6-chloro-1-oxido-3-oxo-1,2,4-benzotriazin-4(3H)-yl)ethyl]piperidin-4-yl]carbamate** (Intermediate 206, 0.65 g) was deprotected with TFA as described for Intermediate 197 to give the crude free base of the product, 0.517 g.

**MS (ESI)** 324 (MH+) for C_{14}H_{22}ClN_{3}O_{2}

**Intermediate 206**: **tert-Butyl (1-[2-[(6-chloro-1-oxido-3-oxo-1,2,4-benzotriazin-4(3H)-yl)ethyl]piperidin-4-yl]carbamate**

6-Chloro-1,2,4-benzotriazin-3(4H)-one 1-oxide (FR 2621583, 1.50 g) was deprotonated with sodium hydride (0.42 g, 60% in oil) and alkylated with 2-{(4-[[tert-butoxy carbonyl]amino]piperidin-1-yl)ethyl methanesulfonate (Intermediate 6) (1 equivalent) as described for Intermediate 2. The residue obtained after aqueous work up was suspended in diethyl ether and filtered to yield 1.30 g of product.

**MS (ESI)** 424 (MH+) for C_{16}H_{26}ClN_{3}O_{4}

**{1H NMR (CDCl3)}** δ 1.30 - 1.41 (m, 2H); 1.44 (s, 9H); 1.88 - 1.96 (m, 2H); 2.21 - 2.30 (m, 2H); 2.74 (t, 2H); 2.83 - 2.92 (m, 2H); 3.41 - 3.52 (m, 1H); 4.27 (t, 2H); 4.34 - 4.45 (m, 1H); 7.30 (dd, 1H); 7.53 (d, 1H); 8.27 (d, 1H).
Example 114

6-Chloro-4-{2-[2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl]amino}piperidin-1-yl)ethyl]-1,2,4-benzotriazin-3(4H)-one 1-oxide

4-[2-{4-Aminopiperidin-1-yl)ethyl]-6-chloro-1,2,4-benzotriazin-3(4H)-one 1-oxide

(Intermediate 205, 0.25 g) was reacted with 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde (WO 2004/058144) (0.14 g) and sodium acetoxyborohydride (0.34 g) as described for Example 107. Chromatography on silica gel with 0-20% methanol in dichloromethane gave 60 mg of the title compound as acetic acid salt (0.37 g).

MS (ESI) 473 (MH⁺) for C₂₅H₂₂CIN₄O₄

1H NMR (DMSO-D₆) δ 1.14 - 1.25 (m, 2H); 1.68 - 1.78 (m, 2H); 2.02 (t, 2H); 2.31 - 2.42 (m, 1H); 2.57 (t, 2H); 2.88 (d, 2H); 3.67 (s, 2H); 4.22 - 4.30 (m, 4H); 4.33 (dd, 2H); 6.93 (s, 1H); 7.44 (dd, 1H); 7.91 (d, 1H); 8.00 (s, 1H); 8.21 (d, 1H).

Example 115

6-{[(1-[2-(6-Chloro-3-oxo-1,2,4-benzotriazin-4(3H)-yl)ethyl]piperidin-4-yl)methyl]amino}ethyl]-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (Intermediate 207, 67 mg) was reacted with 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (360 mg) and sodium acetoxyborohydride (76 mg) as described for Example 107. Chromatography on silica gel with 0-20% methanol in dichloromethane and trituration from other gave 33 mg of the title compound.

MS (ESI) 470 (MH⁺) for C₂₇H₂₃CIN₅O₃

1H NMR (DMSO-D₆) δ 1.30 - 1.42 (m, 2H); 1.88 - 1.97 (m, 2H); 1.98 - 2.08 (m, 2H); 2.58 - 2.67 (m, 2H); 2.90 - 3.02 (m, 2H); 3.28 - 3.34 (m, 2H); 3.95 - 4.07 (m, 2H); 4.26 (t, 2H); 4.66 (s, 2H); 7.08 (d, 1H); 7.39 (d, 1H); 7.56 (dd, 1H); 7.87 (d, 1H); 8.43 (d, 1H); 11.27 (s, 1H).

Intermediate 207: 4-[2-{4-Aminopiperidin-1-yl)ethyl]-6-chloro-1,2,4-benzotriazin-3(4H)-one

 tert-Butyl {1-[2-(6-chloro-3-oxo-1,2,4-benzotriazin-4(3H)-yl)ethyl]piperidin-4-yl} carbamate (Intermediate 208, 74 mg) was deprotected with TFA as described for Intermediate 197 to give the crude free base of the product, 67 mg.

MS (ESI) 307 (MH⁺) for C₁₄H₁₈CIN₃O
Intermediate 208: tert-Butyl (1-[2-(6-chloro-1-oxido-3-oxo-1,2,4-benzo triazin-4(3H)-yl]ethyl)piperidin-4-yl)carbamate

To a solution of tert-butyl (1-[2-(6-chloro-1-oxido-3-oxo-1,2,4-benzo triazin-4(3H)-yl]ethyl)piperidin-4-yl)carbamate (Intermediate 206) (0.43 g) in acetic acid (8 mL) and water (2 mL) was added zinc dust (0.50 g). After 30 minutes, the solution was filtered and the filtrate concentrated. The residue was then treated with potassium ferricyanide (1.0 g) in water (20 mL). After 2 hours, the reaction was diluted with ethyl acetate. The aqueous layer was collected, the pH adjusted with solid Na₂CO₃ and extracted with ethyl acetate. The combined organic washes were dried (Na₂SO₄), filtered and concentrated. The residue was purified by chromatography on silica gel with 0-25% acetone in dichloromethane to yield 66 mg of the product.

**MS (ESI) 407 (M+H)⁺** for C₁₉H₂₆ClN₃O₁

**¹H NMR (CDCl₃) δ 1.32 - 1.40 (m, 2H); 1.44 (s, 9H); 1.91 (d, 2H); 2.20 - 2.30 (m, 2H); 2.75 (t, 2H); 2.87 (d, 2H); 3.40 - 3.52 (m, 1H); 4.24 (t, 2H); 4.40 (s, 1H); 7.42 (dd, 1H); 7.46 (s, 1H); 8.38 (d, 1H).

Example 116

4-(2-[(2S,5R)-5-[(1,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-2-yl]ethyl)-3-oxo-3,4-dihydro-2H-1,4-benzoazine-6-carbonitrile

The product was obtained following the procedure described for Example 105, except, the enantiomer of Intermediate 183, tert-butyl (2S,5R)-5-amino-2-[2-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoazin-4-yl)ethyl]piperidine-1-carboxylate (prepared by the exact route as Intermediate 183, but starting from 1-tert-butyl 2-ethyl (2S,5S)-5-[(tert-butyl(dimethyl)silyl)oxy]piperidin-1,2-dicarboxylate, the enantiomer of Intermediate 191) was reacted with 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carboxaldehyde to yield the named compound.

**MS (ESI) 449 (M+H)⁺** for C₂₄H₂₅N₅O₄

**¹H NMR (DMSO-D₆) δ ppm 1.42 - 1.81 (m, 3H); 1.85 - 2.03 (m, 1H); 2.16 (d, 1H); 2.28 (d, 1H); 2.98 - 3.11 (m, 1H); 3.38 - 3.58 (m, 1H); 3.68 (d, 2H); 4.28 (s, 2H); 4.38 (dd, 4H); 4.80 (s, 1H); 7.18 (d, 1H); 7.31 (s, 1H); 7.52 (d, 1H); 7.75 (s, 1H); 8.26 (s, 1H); 9.46 - 9.79 (m, 2H); 9.98 (s, 1H).
Example 117

6-[[1-2-(7-Bromo-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-1-yl)ethyl]piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

1-2-[4-Aminopiperidin-1-yl]ethyl]-7-bromo-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one

(Intermediate 209) (2.0 mmol), (3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carboxaldehyde (WO 2004/058144) (356 mg, 2.0 mmol) and sodium cyanoborohydride (496 mg, 4 equiv) were reacted as described under Example 21 to give the product as an off-white solid 420 mg (41% yield).

**MS (ESP):** 517.52 (MH⁺) for C₂₂H₂₃BrN₆O₄

**¹H-NMR (DMSO-d₆) δ:** 1.13 (t, 2H); 1.34 (q, 5H); 1.85 (d, 2H); 1.98 (t, 2H); 2.45 (m, 2H); 2.71 (m, 1H); 2.91 (d, 2H); 3.00 (m, 2H); 3.89 (m, 2H); 3.99 (m, 2H); 4.63 (s, 2H); 4.85 (s, 2H); 7.05 (d, 1H); 7.35 (d, 1H); 7.94 (dd, 1H); 11.25 (bs, 1H).

**Intermediate 209:** 1-2-[4-Aminopiperidin-1-yl]ethyl]-7-bromo-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one

** tert-Butyl** (1-2-(7-bromo-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-1-yl)ethyl]piperidin-4-yl) carbamate (Intermediate 210) (0.85 g) was reacted as described for Intermediate 14. The crude trifluoro acetate of the title compound was used without further purification for the next step (quantitative yield).

**MS (ESP):** 355/357 (MH⁺) for C₂₁H₁₉BrN₄O₂

**Intermediate 210:** tert-Butyl (1-12-(7-bromo-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-1-yl)ethyl]piperidin-4-yl) carbamate

6-Bromo-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one (Intermediate 211) (460 mg, 2.0 mmol) was deprotonated with sodium hydride and acylated with 2-(4-[[tert-butoxycarbonyl]amino)piperidin-1-yl]ethyl methanesulfonate (Intermediate 6) (2.1 mmol) as described for Intermediate 2. Chromatography on silica gel with methanol/dichloromethane gave the product as an oil (0.85 g, 93% yield).

**MS (ESP):** 455, 457 (MH⁺) for C₂₁H₂₇BrN₄O₄

**Intermediate 211:** 7-Bromo-1H-pyrido[2,3-b][1,4]oxazin-2(3H)-one

Ethyl [(5-bromo-3-uracil-2-yl)oxy]acetate (Intermediate 212) (4.3 g, 14.1 mmol) was dissolved in anhydrous THF (10 mL) and concentrated HCl (10 mL) was added at
0 °C. Tin chloride (5.0 g, 26.4 mmol) was added in small portions. The reaction was stirred for 1 hr and heated at 65 °C overnight. The reaction mixture was concentrated under reduced pressure, extracted with chloroform, dried over magnesium sulfate and concentrated. Chromatography on silica gel with methanol/ chloroform gave the product as a light pink solid (1.2 g, 37% yield).

**MS (ESP):** 229/231(MH+)** for C7H5BrN2O2

**1H-NMR (DMSO-d6)** δ: 5.80 (s, 2H); 7.32 (s, 1H); 7.87 (s, 1H); 10.94 (bs, 1H).

**Intermediate 211: Ethyl (6-bromo-3-nitropyridin-2-yl)oxyacetate**

A mixture of 6-bromo-2-chloropyridin-3-ol (4.73 g, 19.9 mmol) and ethyl glycolate (2.9 g, 27.8 mmol) in anhydrous dioxane (20 mL) was treated with sodium hydride (1.12 g, 60% in mineral oil, 28 mmol) in portions (exothermic reaction!). The reaction was then quenched with water and extracted with chloroform and dried over magnesium sulfate. Chromatography on silica gel with ethyl acetate/ hexanes gave the product as a light yellow solid (4.8 g, 79% yield).

**MS (ESP):** 305, 307(MH+)** for C9H5BrN2O2

**1H-NMR (DMSO-d6)** δ ppm: 1.17 (t, 3H); 4.12 (q, 2H); 5.10 (s, 2H); 8.64 (s, 1H); 8.76 (s, 1H).

**Example 118**

2-Oxo-1-[2-(4-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino)piperidin-1-yl]ethyl]-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine-7-carboxamide and

**Example 119**

2-Oxo-1-[2-(4-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino)piperidin-1-yl]ethyl]-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine-7-carboxamide

A mixture of 6-[{1-[2-(7-bromo-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-1-yl)ethyl]piperidin-4-yl]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one (Example 117) (110 mg, 0.21 mmol), zinc cyanide (80 mg, 0.683 mmol) and tetrakis(triphenylphosphine) palladium(0) (25 mg, 0.0215 mmol) in anhydrous DMF (2.5 mL) over molecular sieves 3Å was vortexed and then heated in the microwave at 200 °C for one
hour. Reverse phase chromatography and generation of the free base as described for Example 21 gave 20 mg (20%) of Example 118 and 20 mg (20%) of Example 119, both as off-white solids.

**Example 118**

MS (ESP): 464 (MH+), for C23H22N4O4

1H-NMR (DMSO-d6) δ: 1.74 (m, 2H); 2.18 (m, 2H); 3.02 (m, 2H); 3.80 (m, 2H); 3.90 (m, 2H); 4.23 (m, 4H); 4.70 (s, 2H); 5.01 (s, 2H); 7.11 (d, 1H); 7.44 (d, 1H); 8.08 (s, 1H); 8.40 (s, 1H); 9.28 (s, 1H); 9.75 (bs, 1H); 11.35 (bs, 1H).

**Example 119:**

MS (ESP): 482 (MH+), for C22H22N4O5

1H-NMR (DMSO-d6) δ: 1.74 (m, 2H); 2.36 (m, 2H); 3.10 (m, 2H); 3.80 (m, 2H); 4.23 (m, 2H); 4.32 (m, 4H); 4.56 (s, 2H); 4.70 (s, 2H); 4.94 (s, 4H); 7.11 (d, 1H); 7.44 (d, 1H); 7.62 (s, 1H); 7.91 (s, 1H); 8.08 (s, 1H); 8.38 (s, 1H); 9.30 (bs, 2H); 9.60 (bs, 1H); 11.35 (bs, 1H).

**Example 120**

1-(2-(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino)-2-methylpyridin-1-yl)ethyl)-5,7-difluoroquinolin-2(1H)-one

A solution of 1-(2-(4-aminomethyl)pyridin-1-yl)ethyl)-5,7-difluoroquinolin-2(1H)-one (Intermediate 213, crude, 220 mg, 0.69 mmol) and 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carbaldehyde (WO 2004/058144) (114 mg, 0.69 mmol) in dry dichloromethane/methanol (4 mL, 4:1) was heated over 3 Å molecular sieves at 80 °C for 3 hours. The reaction mixture was cooled to 0°C, and sodium trimethoxy borohydride (299 mg, 1.38 mmol) was added. The resulting reaction mixture was stirred at room temperature for 16 hours and then was filtered through a 0.45 μm membrane and concentrated to dryness under reduced pressure. The residue was taken up in dichloromethane (20 mL) and saturated aqueous sodium hydrogen carbonate solution (5 mL). The pH of the aqueous phase was adjusted to pH~10 with 1M aqueous sodium hydroxide solution. The aqueous phase was back extracted twice with dichloromethane (4x 20 mL) and the combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. Chromatography on silica gel with dichloromethane/methanol (17:3) gave 195 mg (69%) of the title compound as a white foam.

MS (ESP): 471 22 (MH+), for C32H28F2 N4O5
- 174 -

^1^H NMR (300 MHz, DMSO-d_6) δ: 0.82-0.91 (m, 4H); 1.16-1.26 (m, 1H); 1.74-1.90 (m, 2H); 2.16-2.25 (m, 2H); 2.34-2.42 (m, 2H); 2.85-2.95 (m, 1H); 3.08 (d, 1H, J = 11.5 Hz); 3.76 (s, 2H); 4.27-4.34 (m, 6H); 6.63 (d, 1H, J = 9.8 Hz); 6.96 (s, 1H); 7.18-7.32 (m, 2H); 7.94 (d, 1H, J = 9.8 Hz); 8.03 (s, 1H).

The intermediates for Example 120 were prepared as follows:

**Intermediate 213**: 1-[2-(4-Aminophenyl)-2-methylpiperidin-1-yl]ethyl]-5,7-difluoroquinolin-2(1H)-one

A solution of 1-{2-[4-(dibenzylandino)-2-methylpiperidin-1-yl]ethyl]-5,7-

difluoroquinolin-2(1H)-one (Intermediate 214 358 mg, 0.71 mmol) in methanol (6 mL) was

treated with palladium hydroxide on carbon (100 mg). The reaction was stirred at room

temperature under hydrogen gas for 18 hours, filtered through celite, rinsed with methanol

(100 mL), and concentrated under reduced pressure to afford 225 mg (96%) of a yellow oil.

**MS** (ESI): (M+H)\(^+\) for C\(_{21}\)H\(_{21}\)F\(_{2}\)N\(_{5}\)O.

^1^H-NMR (DMSO-d_6) δ: 0.74-0.87 (m, 4H); 1.04-1.17 (dq, 1H, J = 12.1, 11.9, 3.7 Hz);

1.54-1.67 (m, 2H); 2.16-2.26 (m, 2H); 2.30-2.39 (m, 1H); 2.84-2.95 (m, 1H); 3.02-3.08 (m, 1H); 4.26 (t, 2H, J = 6.7 Hz); 6.63 (d, 1H, J = 9.8 Hz); 7.17-7.31 (m, 2H); 7.94 (d, 1H, J = 9.8 Hz).

**Intermediate 214**: 1-{2-(Benzylamino)-2-methylpiperidin-1-yl]ethyl}-5,7-
difluoroquinolin-2(1H)-one

A solution of 5,7-difluoroquinolin-2(1H)-one (40 mg, 1.9 mmol) in dry

dimethylformamide (DMF) (5 mL) was treated at 0 °C with a cooling bath under stirring with

sodium hydride (80 mg, 60% in oil, 2.0 mmol). The cooling bath was removed and the

mixture was stirred for 30 minutes at room temperature. A solution of 2-[4-(bocylamino)]-2-

methylpiperidin-1-yl]ethyl methanesulfonate in DMF (Intermediate 215, 0.58 mmol/mL, 3.5

mL, ~2.03 mmol) was then added and the resulting mixture was stirred overnight at room

temperature. The DMF was removed under reduced pressure, and the residue was taken up in

ethyl acetate (100 mL) and saturated aqueous sodium hydrogen carbonate solution (30 mL).

The aqueous phase was back extracted once with ethyl acetate (50 mL). The combined

organic phases were dried over sodium sulfate and concentrated under reduced pressure.

Chromatography on silica gel with hexanes/acetone (2:1) gave 365 mg (39% yield) of the

product as a yellow solid.
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**Intermediate 215**: 2-[(4-(Dibenzylationino)-2-methylpiperidin-1-yl)ethyl methanesulfonate

A mixture 2-[(4-dibenzylationino)-2-methylpiperidin-1-yl)ethylmethanol (Intermediate 216, 660 mg, 1.9 mmol) in dry dichloromethane (6 mL) and triethyl amine (0.375 mL, 2.7 mmol) was treated at 0°C with methanesulfonyl chloride (0.175 mL, 8.4 mmol). After 45 minutes the reaction was complete by TLC (chloroform/methanol 6:1, r.f. 0.54). Potassium phosphate buffer (pH 7, 1 M, 25 mL) was added, dichloromethane was removed under reduced pressure and it was extracted with ice cold ethyl acetate (2 x 100 mL) and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude preparation of the mesylate was used without delay for the next step.

**MS (ESP)**: 417.18 (MH⁺) for C₂₃H₁₇N₃O₃S.

**Intermediate 216**: 2-[(4-(Dibenzylationino)-2-methylpiperidin-1-yl)ethanol

To a solution of N,N-dibenzyll-2-methylpiperidin-4-amine (Intermediate 217, 880 mg, 3.0 mmol) in acetonitrile (6 mL) was added triethylamine (0.85 ml, 6.0 mmol) and 2-bromomethanol (0.32 mL, 4.5 mmol). The reaction is stirred at 70°C at 300 watts in the microwave for 20 minutes. Acetonitrile was removed under reduced pressure, the residue was taken up in dichloromethane (100 mL) and saturated aqueous sodium hydrogen carbonate solution (30 mL) and the aqueous phase was back extracted thrice with dichloromethane (3 x 70 mL). The combined organic phases were dried over sodium sulfate and concentrated to dryness under reduced pressure. Chromatography of the residue on silica gel with dichloromethane/methanol (10:1) gave 660 mg (65% yield) of the product as an orange solid.

**MS (ESP)**: 339.22 (MH⁺) for C₂₂H₂₃N₂O₂.

**¹H-NMR (DMSO-d₆)** δ: 1.01 (d, 3H, J = 5.8 Hz), 1.22-1.34 (m, 1H), 1.48-1.56 (m, 1H); 1.69 (d, 2H, J = 11.1 Hz); 1.95-2.11 (m, 2H), 2.14-2.30 (m, 1H); 2.38-2.43 (m, 1H), 2.64-2.80 (m, 1H); 2.84-3.00 (m, 1H); 3.37-3.41 (m, 1H); 3.55 (s, 4H), 4.24-4.35 (m, 1H); 7.15-7.22 (m, 2H); 7.24-7.34 (m, 8H).
**Intermediate 217: N,N-Dibenzyl-2-methylpiperidin-4-amine**

A mixture of ethyl 4-(dibenzylamino)-2-methylpiperidine-1-carboxylate (Intermediate 218, 1.28 g, 3.78 mmol) in dry isopropyl alcohol (30 mL) was added potassium hydroxide (0.65 mL, 8.4 mmol). The reaction was stirred at 105 °C for 6 hours. 2-Propanol was removed under reduced pressure, the residue was taken up in dichloromethane (100 mL), filtered through a 0.5 μm membrane, and concentrated under reduced pressure. Chromatography of the residue on silica gel with dichloromethane/methanol/ammonium hydroxide (85:15:0.1) gave 392 mg (79% yield) of the product as a red oil.

**MS (ESI):** 295.18 (MH⁺) for C₂₀H₂₆N₂.

**¹H-NMR (DMSO-d₆):** 0.98 (d, 3H, J = 5.8 Hz); 1.07-1.14 (m, 1H); 1.37 (dq, 1H, J = 12.0, 4.2 Hz); 1.68 (t, 2H, J = 13 Hz); 2.26-2.36 (m, 2H); 2.40-2.46 (m, 1H); 2.91-2.97 (m, 1H); 3.56 (s, 4H); 7.16-7.20 (m, 2H); 7.25-7.34 (m, 8H).

**Intermediate 218: Ethyl 4-(dibenzylamino)-2-methylpiperidine-1-carboxylate**

A mixture of ethyl 4-(benzylamino)-2-methylpiperidine-1-carboxylate (Intermediate 219, 1.57 g, 5.7 mmol), cesium carbonate (3.72 g, 11.4 mmol) and benzyl bromide (1.36 mL, 11.4 mmol) in dry DMF (20 mL) was heated at 80°C for 16 hours. The DMF was removed under reduced pressure, the residue was taken up in ethyl acetate (150 mL) and water (75 mL) and the aqueous phase was back extracted once with ethyl acetate (3x150 mL). The combined organic phases were washed with brine (100 mL) and were dried over sodium sulfate. Chromatography on silica gel with hexanes/ethyl acetate (3:2) gave 1.43 g (68% yield) of the product as a yellow oil.

**MS (ESI):** 367 (MH⁺) for C₂₉H₃₀N₂O₂.

**¹H-NMR (DMSO-d₆):** 1.07-1.16 (m, 6H); 1.47-1.61 (m, 2H); 1.72-1.93 (m, 2H); 2.56-2.70 (m, 1H); 3.11-3.19 (m, 1H); 3.48-3.63 (m, 6H); 3.89-4.00 (m, 2H); 7.17-7.21 (m, 2H); 7.29-7.38 (m, 8H).

**Intermediate 219: Ethyl 4-(benzylamino)-2-methylpiperidine-1-carboxylate**

A solution of ethyl 2-methyl-4-oxopiperidine-1-carboxylate (2.20 grams, 11.9 mmol) and benzyl benzylamine in dichloroethane/methanol (4:1, 50 mL) was heated over 3 Å molecular sieves at 90°C for 16 hours. The reaction mixture was cooled to 0°C and sodium triacetate borohydride (5.03 g, 23.8 mmol) was added. The resulting reaction mixture was stirred at room temperature for 30 minutes and then was filtered through a 0.45 μm membrane.
and concentrated to dryness under reduced pressure. The residue was taken up in aqueous 1N HCl solution and washed with ether (2 x 50 mL). The pH of the aqueous phase was adjusted to a pH of approximately 7 with 1M aqueous sodium bicarbonate solution. The aqueous phase was back extracted twice with ether (4 x 50 mL) and the combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. Chromatography on silica gel with dichloromethane/methanol (94:6) gave 1.57 g (47% yield) of a yellow oil.

**MS (ESP):** 277 (MH+) for C_{16}H_{24}N_{2}O_{2}.

**^{1}H-NMR (DMSO-d_{6})**: 8: 1.15 (t, 3H, J = 7.1 Hz); 1.30 (d, 3H, J = 6.8 Hz); 1.52-1.59 (m, 3H); 1.61-1.71 (m, 1H); 2.80-2.82 (m, 1H); 3.22-3.27 (m, 1H); 3.57-3.73 (m, 3H); 3.95-4.06 (m, 3H); 7.18-7.34 (m, 5H).

**Example 121**

1-(2-{4-[2-(3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino}piperidin-1-yl)ethyl)-2-oxo-1,2-dihydroquinolin-7-carboxylate

A mixture of 7-chloro-1-(2-{4-[2-(3-dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino}piperidin-1-yl)ethyl)quinolin-2(1H)-one (2.11 g, crude, ~3.47 mmol) and zinc cyanide (244 mg, 2.1 mmol) in dry DMF (8 mL) was degassed and flushed with nitrogen three times. Zinc (174 mg, 0.059 mmol, 51.6 mM solution in heptane) was added, followed by 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (63 mg, 0.11 mmol) and tris(dibenzylideneacetone)dipalladium (0) (100 mg, 0.11 mmol) and it was degassed and flushed with nitrogen like above. The mixture was stirred for 30 minutes at room temperature and then degassed and flushed with nitrogen again. It was heated at 120°C for 3 hours. The solvent was removed under reduced pressure and the residue taken up in chloroform/isopropyl alcohol (3:1, 50 mL) and filtered through celite and concentrated under reduced pressure. Chromatography by reverse phase (Column: Atlantis Hilic; Gradient: 90% ACE/0.1% TFA; 5% Water/0.1% TFA; and 5% Isopropanol/0.1% TFA; Flow Rate: 1 mL/min.) afforded 418 mg (20%) of a brown oil as a TFA salt.

**MS (ESP):** 447.14 (MH+) for C_{32}H_{36}N_{2}O_{3}.

**^{1}H-NMR (300 MHz, DMSO-d_{6})**: 8: 1.75-1.87 (m, 2H); 2.29-2.38 (d, 2H, J = 12.6 Hz); 3.00-3.20 (m, 2H); 3.37-3.49 (m, 2H); 3.90 (d, 2H, J = 12.6 Hz); 4.24 (br s, 2H); 4.35 (d, 2H, J = 4.6 Hz); 4.39 (d, 2H, J = 4.6 Hz); 4.62-4.72 (m, 2H); 6.95 (d, 1H, J = 9.6 Hz); 7.12 (s, 1H); 8.02 (d, 1H, J = 7.7 Hz); 8.11 (d, 1H, J = 9.6 Hz); 8.21 (s, 1H); 8.47 (d, 1H, J = 7.7 Hz); 9.18-9.45 (m, 2H).
Example 122

\[
\text{Cis=I-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]4-[3-(6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propyl]piperidine-3-carboxylic acid}
\]

A solution of methyl Cis(±)-1-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]4-[3-(6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propyl]piperidine-3-carboxylate (Example 123) (105 mg, 0.204 mmol) in methanol (1 mL) was treated with a solution of sodium hydroxide (1N, 1 mL) the reaction was warmed to 30 °C for 18 hours. The temperature was increased to 60 °C for 6 hours. The solvents were evaporated, the reaction was diluted with ethyl acetate and water. The pH was adjusted to 7 with 1N HCl. The layers were separated. The aqueous phase was extracted with ethyl acetate (2 X 20 mL). The organic layers were combined dried over magnesium sulfate and concentrated at reduced pressure. The residue was taken up and dichloromethane and precipitated with ether in a dry ice/acetone bath. The solvent was decanted. The solid was dried under high vacuum to obtain 21 mg (20%) of an off-white solid.

**MS(RP):** 501 (M+), for C_{27}H_{30}F_{2}N_{2}O_{3}

**1H-NMR (400 MHz, DMSO-d_6):** 8.14 - 1.26 (m, 1H) 1.41 - 1.53 (m, 1H) 1.57 - 1.68 (m, 2H) 1.74 - 1.84 (m, 1H) 1.98 - 2.10 (m, 1H) 2.89 - 2.97 (m, 1H) 2.98 - 3.04 (m, 1H) 3.04 - 3.12 (m, 1H) 3.12 - 3.20 (m, 1H) 3.22 - 3.34 (m, 1H) 3.34 - 3.45 (m, 2H) 3.71 (s, 3H) 3.81 - 3.86 (m, 1H) 3.88 - 3.96 (m, 3H) 4.46 (s, 2H) 6.47 - 6.58 (m, 2H) 6.63 (s, 1H) 6.85 (d, 2H) 7.06 - 7.18 (m, 2H) 7.39 - 7.48 (m, 1H) 8.11 (s, 1H)

Example 123

**Methyl cis(±)-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]4-[3-(6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propyl]piperidine-3-carboxylate**

A solution of methyl 4-[3-(6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propyl]piperidine-3-carboxylate (Intermediate 228) (150 mg, 0.414 mmol) in ethanol (2 mL) was treated with K_{2}CO_{3} (63 mg, 0.455 mmol) followed by a solution of 2-[(1E)-3-chloroprop-1-en-1-yl]1,4-difluorobenzene (Intermediate 124) (86 mg, 0.455 mmol) in ethanol (1 mL). The reaction was warmed to 40°C for 18 hours. The reaction was partitioned between ethyl acetate and water. The aqueous layer was extracted with dichloromethane (2 X 20 mL). The organic extracts were combined, dried over MgSO_{4} and concentrated at reduced pressure to obtain a yellow oil. Chromatography on silica gel eluting with (0-2.5%) methanol in dichloromethane gave the title compound as a yellow oil (120 mg, 56%).
\textbf{Intermediate 220: Methyl 4-[1-(6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propyl]piperidine-3-carboxylate}

To an ice-cooled solution of 6-methoxy-2H-1,4-benzoxazin-3(4H)-one (Intermediate 48) (407 mg, 2.29 mmol) in DMF was added sodium hydride (110 mg, 2.75 mmol). After stirring for 2 hours a solution of 1-tert-butyl 3-methyl 4-[(methylsulfonyl)oxy]propyl)piperidine-1,3-dicarboxylate (868 mg, ~2.29 mmol) (Intermediate 132) in DMF (5 mL) was added. The reaction was allowed to stir at room temperature for five days. The reaction was diluted with ethyl acetate and water. The pH was adjusted to approximately 3 with 1N HCl. The layers were separated. The aqueous layer was extracted with ethyl acetate (3 X 30 mL). The combined organic layers were washed with water (4X 50 mL), dried over magnesium sulfate and concentrated at reduced pressure to obtain a semi-solid. Chromatography on silica gel eluting with (0-2.5 %) methanol in dichloromethane gave the product as a mixture of diastereomers. Reverse phase separation using a 50-60 % gradient of acetonitrile in water with 0.1% trifluoroacetic acid gave the cis diastereomer as the faster eluting peak. Upon evaporation of the organic components and extraction of the aqueous with 20% methanol in dichloromethane 150 mg of the cis diastereomer was obtained.

$^1$H NMR (CDCl$_3$): 8 1.19 - 1.30 (m, 1H); 1.32 - 1.40 (m, 2H); 1.64 - 1.75 (m, 2H); 1.77 - 1.89 (m, 2H); 1.94 - 2.04 (m, 1H); 2.93 - 3.01 (m, 1H); 3.06 - 3.11 (m, 1H); 3.13 - 3.20 (m, 1H); 3.47 - 3.53 (m, 1H); 3.54 - 3.60 (m, 1H); 3.74 (s, 3H); 3.79 (s, 3H); 3.82 - 3.90 (m, 1H); 3.90 - 4.00 (m, 1H); 4.49 - 4.57 (m, 2H); 6.49 - 6.56 (m, 2H); 6.89 - 6.97 (m, 1H).

The trans compound was obtained as a mixture of amine and Boc protected material (138 mg) through neutralization of the aqueous layer with sodium bicarbonate before extraction with 20% methanol in dichloromethane. The mixture was dissolved in ethanol (3 mL) and heated in the microwave at 150°C for four hours.
Example 124

1-(2-[(4-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl)ethyl]-7-methoxy-3,4-dihydroquinazolin-2(1H)-one

To a solution of 1-[(2-[(4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl)ethyl]-7-methoxyquinazolin-2(1H)-one (Example 72, 0.125 g) in ethanol (4 mL) was added sodium borohydride (40 mg). After 3 hours at room temperature, additional sodium borohydride (47 mg) was added. After 30 minutes the reaction was quenched with acetone and concentrated. Chromatography on silica gel with a gradient of dichloromethane to 20% methanol in dichloromethane gave 108 mg of the product as a colorless solid.

MS (ES) 454 (M+H) for C_{24}H_{31}N_{3}O_{3}

^1H-NMR (DMSO-d_6) δ (ppm): 1.36 (m, 2H); 1.78 - 1.88 (m, 2H); 1.98 (t, 2H); 2.41 (t, 2H); 2.52 - 2.60 (m, 1H); 2.89 (d, 2H); 3.63 (d, 2H); 3.67 (s, 3H); 3.77 - 3.87 (m, 2H); 3.88 - 3.95 (m, 2H); 4.25 - 4.30 (m, 2H); 4.51 - 4.56 (m, 2H); 4.87 (s, 1H); 6.46 (d, 1H); 6.62 (d, 1H); 6.66 (d, 1H); 6.95 - 7.01 (m, 1H); 8.05 (s, 1H).

Example 125

5,7-Difluoro-1-[(4-[(1-oxo-1,3-dihydro-2-benzofuran-5-yl)methyl]amino]piperidin-1-yl)ethyl]quinolin-2(1H)-one

The compound was prepared following the procedure described for Examples 87-96.

MS (ES) 454 (M+H) for C_{25}H_{31}N_{3}O_{3}

^1H-NMR (DMSO-d_6) δ (ppm): 1.83 (s, 2H); 2.32 (s, 2H); 3.07 (s, 1H); 3.31 (s, 2H); 3.45 (s, 2H); 3.80 (s, 2H); 4.39 (s, 2H); 4.53 (s, 2H); 5.45 (s, 2H); 6.66 (d, 1H); 7.29 (t, 1H); 7.42 (d, 1H); 7.73 (d, 1H); 7.80 (s, 1H); 7.94 (d, 1H); 8.01 (d, 1H); 9.49 (s, 1H).

Example 126

6-[(1-[(2-[(7-Methoxy-2-oxoquinazolin-1(2H)-yl)propyl]piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one

1-[2-[(4-aminopiperidin-1-yl)-1-methylethyl]-7-methoxyquinazolin-2(1H)-one (Intermediate 221) (160 mg crude, 0.51 mmol), 3-oxo-3,4-dihydro-2H-pyrrolo[3,2-b][1,4]oxazine-6-carbaldehyde (WO 2004/058144) (91 mg, 0.51 mmol), and sodium...
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triacetoxy borohydride (320 mg, 1.5 mmol) were reacted as described according to Example 69. Chromatography on silica gel eluting with 5% methanol/dichloromethane containing 0.25% ammonium hydroxide gave 105 mg (63%) of the title compound as an off-white solid.

MS (ESP): 479 (M+) for C23H38N6O4

\[ ^1H \text{NMR (DMSO-D}_6) \delta (\text{ppm}): 0.96 \text{ (d, 3H); 0.99 - 1.14 (m, 2H); 1.71 (t, 2H); 1.95 (s, 1H); 2.10 (t, 1H); 2.22 - 2.41 (m, 2H); 2.89 - 3.01 (m, 1H); 3.03 - 3.14 (m, 1H); 3.64 (s, 2H); 3.90 (s, 3H); 4.11 (q, 1H); 4.27 - 4.40 (m, 1H); 4.55 - 4.66 (m, 2H); 6.93 - 7.04 (m, 3H); 7.23 - 7.33 (m, 1H); 7.69 - 7.80 (m, 1H); 8.04 (s, 1H); 11.16 (s, 1H). \]

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**Intermediate 221: 1-[[2-(4-Aminopiperidin-1-yl)-1-methylethyl]amino]quinaxolin-2(1H)-one**

A solution of tert-butyl (1-[[2-(7-methoxy-2-oxoquinaxalin-1(2H)-yl)propyl]piperidin-4-yl]carbamate (Intermediate 222, 200 mg, 0.48 mmol) in dichloromethane (30 mL) was treated with trifluoroacetic acid (3 mL). After 2 hours, the reaction was concentrated to dryness. The residue was partitioned between 15% methanol/chloroform. The aqueous phase was re-extracted 3x with 15% methanol/chloroform. The combined organic phases were dried over magnesium sulfate, filtered, and concentrated to dryness giving 160 mg (100%) of the crude product as an oil.

MS (ESP): 317 (M+) for C17H26N4O2

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**Intermediate 222: tert-Butyl (1-[[2-(7-methoxy-2-oxoquinaxalin-1(2H)-yl)propyl]piperidin-4-yl]carbamate**

A solution of 7-methoxyquinaxalin-2(1H)-one (Intermediate 148, 590 mg, 3.35 mmol) in dry DMF (10 mL) was cooled in an ice bath under nitrogen and treated with sodium hydride (60%, 160 mg, 4.02 mmol). The reaction was stirred at room temperature for ~90 minutes. The reaction was again cooled in an ice bath and treated with a solution of 2-[[tert-butoxycarbonyl]amino]piperidin-1(2H)-yl)-1-methylethyl methanesulfonate in dry DMF (Intermediate 223, ~0.43 mmol/mL, 4.3 mmol). The reaction was stirred at room temperature overnight. The reaction mixture was concentrated to dryness. Residual DMF was co-evaporated 3x with toluene. The resulting residue was partitioned between ethyl acetate and water. The aqueous phase was re-extracted 3x with ethyl acetate. The organic phases were combined, dried over magnesium sulfate, filtered, and concentrated to dryness. Chromatography on silica gel with 25% acetone/benzene gave 410 mg (29%) of product.
which contained ~10% starting material (7-methoxyquinoxalin-2(1H)-one). This material was used directly in the next step.

\[ \text{MS (ESPI): 417 (MH\textsuperscript+)} \text{ for C}_{22}\text{H}_{23}\text{N}_{4}\text{O}_{4} \]

\[ \text{'H NMR (DMSO-D_6) \delta (ppm): 0.96 (d, 3H); 1.10 - 1.26 (m, 2H); 1.31 - 1.42 (m, 9H); 1.53 - 1.72 (m, 2H); 2.14 (t, 1H); 2.37 (t, 1H); 2.94 (d, 1H); 3.04 - 3.15 (m, 2H); 3.87 - 3.96 (m, 3H); 4.06 - 4.20 (m, 2H); 4.32 (dd, 1H); 6.71 (d, 1H); 6.95 - 7.05 (m, 2H); 7.71 - 7.78 (m, 1H); 8.04 (s, 1H).} \]

Intermediate 223: 2-[(4-[( tert-Butyloxycarbonyl)amino]piperidin-1-yl)-1-methyl]ethanol methanesulfonate

\[ \text{tert-Butyl [1-(2-hydroxypropyl)piperidin-4-yl]carbamate (Intermediate 224, 1.1 g, 4.3 mmol), triethylamine (0.90 mL, 6.5 mmol) and methanesulfonyl chloride (0.37 mL, 4.7 mmol). Were reacted as described for Intermediate 6. The crude mesylate was directly used for the next step.} \]

Intermediate 224: tert-Butyl [1-(2-hydroxypropyl)piperidin-4-yl]carbamate

\[ \text{tert-Butyl piperidin-4-ylcarbamate (2.0 g, 10.0 mmol), 1-bromopropan-2-ol (2.8 g, 20.0 mmol, commercial product which also contained 30% of the regioisomer 2-bromopropan-1-ol), triethylamine (4.2 mL, 30.0 mmol), and acetonitrile (15 mL) were combined in a microwave vial and heated to 70 °C for 4 hours. The reaction mixture was concentrated to dryness. The crude product was partitioned between ethyl acetate/water. The aqueous phase was re-extracted 2x with ethyl acetate. The combined organic phases were dried over magnesium sulfate, filtered, and concentrated to dryness. The product was purified by flash chromatography on silica gel eluting with a gradient of 20-30% methanol in dichloromethane to give 1.7 g of the desired product as an oil.} \]

\[ \text{'H NMR (DMSO-D_6) \delta ppm: 1.01 (d, 3H); 1.26 - 1.48 (m, 11H); 1.64 (d, 2H); 1.85 - 2.04 (m, 2H); 2.03 - 2.27 (m, 2H); 2.78 (d, 2H); 3.09 - 3.29 (m, 1H); 3.62 - 3.81 (m, 2H); 4.23 (d, 1H); 6.75 (d, 1H).} \]
Example 127

5,7-Difluoro-1-(2-[4-[[5,6,7,8-tetrahydro-1,8-naphthyridin-2-ylmethyl]amino]piperidin-1-yl]ethyl)quinolin-2(1H)-one

1-[2-(4-Aminopiperidin-1-yl)ethyl]-5,7-difluoroquinolin-2(1H)-one (Intermediate 23) (126 mg, 0.410 mmol), 5,6,7,8-tetrahydro-1,8-naphthyridine-2-carboxaldehyde (JOC 2004, 69, 1959-1966) (66 mg, 0.410 mmol) and sodium triacetoxyborohydride (52 mg, 0.22 mmol) were reacted as described for Example 6, to give 84.82 mg of the mono acetate salt of the product as a pale yellow foam.

MS (ES): 454.54 (MH⁺) for C₂₅H₂₅F₂N₄O

¹H NMR (DMSO-d₆) δ (ppm): 1.12 - 1.27 (m, 2H); 1.67 - 1.79 (m, 4H); 2.01 (t, 2H); 2.29 - 2.42 (m, 1H); 2.60 (t, 2H); 2.88 (d, 2H); 3.22 (t, 2H); 3.51 (s, 2H); 4.29 (t, 2H); 6.28 (s, 1H); 6.40 (d, 1H); 6.61 (d, 1H); 7.05 (d, 1H); 7.16 - 7.26 (m, 1H); 7.31 (d, 1H); 7.96 (d, 1H).

All cited publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.
CLAIMS

What is claimed is:

1. A compound of formula I:

   \[ L - U_1 - M - U_2 - R \]

   [Diagram]

   or a pharmaceutically acceptable salt thereof, or N-oxides thereof, wherein:

   L is a group of formula L1-L15:

   [Diagrams L1-L15]

   wherein "−" indicates the point of attachment;

   Z₂, Z₆, and Z₇ are C or N provided that when Z₃, Z₆, or Z₇ is N, then R₂a, R₂c, or R₂d are absent; and

   R₂a, R₂b, R₂c, R₂d, R₂e, and R₂f, are each independently H, halo, cyano, carboxy,

   nitro, carbamoyl, \((C_1-C_6)\)alkanoyl, \((C_1-C_6)\)alkoxycarbonyl, \((C_1-C_6)\)alkyl, hydroxy,
halo(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy, (C₁-C₆)alkoxy, NHCO-(C₁-C₆)alkyl, SO₂(C₁-C₆)alkyl, SO₂NH(C₁-C₆)alkyl, or SO₂N((C₁-C₆)alkyl);  
R₂g, R₂g', and R₂g'' are each independently H, (C₁-C₆)alkyl, or halo(C₁-C₆)alkyl;  
U₁ is CRₐR₉—CR₉R₉, or CRₐR₉—CR₉R₉—CR₉R₉, wherein Ra, Rb, Rc, Rd, Re, and  
Rf are each independently hydrogen or (C₁-C₆)alkyl;  
M is a group of formula M₁-M₅:

![Chemical Structures](image)

Wherein R₂ is H or carboxy, and wherein “—X—” indicate points of attachment;  
Ry and Ry' are each independently 1H, halo, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy,  
CO₂Rₙ, wherein Rₙ is H, (C₁-C₆)alkyl, or halo(C₁-C₆)alkyl, or Ry and Ry' together with the  
carbon to which they are attached form C=O; or Ry and Ry' together form a bridge;  
X and Y are each independently CH₃, O, or NRₚ;  
“—” is a bond or is absent;  
n is 1, or 2, or 3;  
when M is a group of formula M₁ or M₄, U₂ is NRₚ—W, wherein W is CH₂, CO, SO₂,  
\[\text{CH}_2\text{HC-CH}_2\text{CH}_2\text{HC-CH}_2\text{CH} = \text{CH}_2\text{CH} = \text{C} = \text{C}\text{H},\text{ or }\text{CH}_2\text{C} = \text{C},\text{ wherein each hydrogen may be optionally}\]  
replaced by halo or (C₁-C₆)alkyl;  
when M is a group of formula M₂, M₃, or M₅, U₂ is W wherein W is as defined  
herein above;  
R' at each occurrence is independently H, (C₁-C₆)alkyl, -CO-(C₁-C₆)alkyl,  
-CO(C₁-C₆)alkylcarboxy, -CO₂(C₁-C₆)alkyl, -CO-NH(C₁-C₆)alkyl, -CO-N(N((C₁-C₆)alkyl)₂, or  
SO₂(C₁-C₆)alkyl, any of which may be optionally substituted on carbon with halo, hydroxy,  
(C₁-C₆)alkyl, (C₁-C₆)alkoxy, SO₂(C₁-C₆)alkyl, NH₂, NH(C₁-C₆)alkyl, or N(N((C₁-C₆)alkyl)₂;
when W is \( \text{CH}_2, \text{CO} \) or \( \text{SO}_2 \), R is aryl, heteroaryl, heterocyclyl or ortho-fused bicyclic heteroaryl, or when W is \( \text{CH}_2\text{HC} = \text{CH} \), \( \text{CH}_2\text{CH}_2 \), \( \text{CH}_2\text{CH} = \text{CH} \), or \( \text{CH}_2\text{C} = \text{C} \), R is aryl, heteroaryl, heteroaryloxy, heteroarylsulfinyl, heteroarylsulfonyl, heteroarylamino; wherein any R may be optionally substituted on carbon; and wherein any ring nitrogen in R may be optionally substituted by \((\text{C}_1\text{-C}_6)\text{alkyl}\); and

any of L, U₁, M, U₂, or R may be optionally substituted on carbon by one, two or three substituents selected from halo, nitro, cyano, hydroxy, oxo, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphanoyl, methyl, ethyl, ethenyl, ethynyl, methoxy, ethoxy, methoxycarbonyl, ethoxycarbonyl, heteroaryl, heterocyclyl, acetyl, acetoxy, methylnitramino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, or acetylamino;

with the proviso that when L is a group of formula L₈ or L₁₅, W is not CO.

2. A compound or a pharmaceutically acceptable salt thereof, according to claim 1,

wherein

\[
L \text{ is:}
\]

\[
\text{R}_2^b, \text{R}_2^c, \text{R}_2^d
\]

\[
\text{Z is CH or N when " \( \ldots \) " is a bond, or Z is O or NH when " \( \ldots \) " is absent; and R}_2^a, \text{R}_2^b, \text{R}_2^c, \text{and R}_2^d \text{ are each independently H, halo, cyano, } (\text{C}_1\text{-C}_6)\text{alkanoyl, (C}_1\text{-C}_6)\text{alkoxycarbonyl, (C}_1\text{-C}_6)\text{alkyl, halo(C}_1\text{-C}_6)\text{alkyl, halo(C}_1\text{-C}_6)\text{alkoxy, (C}_1\text{-C}_6)\text{alkoxy, NHCO-(C}_1\text{-C}_6)\text{alkyl, SO}_2(C}_1\text{-C}_6)\text{alkyl, SO}_2\text{NH(C}_1\text{-C}_6)\text{alkyl, or SO}_3\text{N(C}_1\text{-C}_6)\text{alkyl)_2.}
3. A compound or a pharmaceutically acceptable salt thereof, according to either claim 1 or 2, wherein

![Chemical Structure]

L is ---, wherein "---" indicates the point of attachment; and Z is CH or N when "---" is a bond, or, when "---" is absent, Z is O or NH.

5. A compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1-3, wherein U₁—M—U₂ is:

![Chemical Structure]

wherein "---" indicates the point of attachment;

Ry is H, F, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, or carboxy; and

R' is H, (C₁-C₆)alkyl, -(C₁-C₆)alkylcarboxy, -CO-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl,
-CO-NH(C₁-C₆)alkyl, -CO-N((C₁-C₆)alkyl)₂, or SO₂(C₁-C₆)alkyl.

10. A compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1-4, wherein Ry is H, hydroxy, fluoro, or methoxy.

15. A compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1-5, wherein R is

2,1,3-benzothiadiazol-5-yl;
3-oxo-3,4-dihydro-2H-1,4-benzothiazin-6-yl;
2,3-dihydro-benzo[1,4]dioxin-6-yl;
1,2,3-benzothiadiazol-5-yl;
3-oxo-3,4-dihydro-2H-1,4-benzoazin-6-yl;
7-fluoro-3-oxo-3,4-dihydro-2H-1,4-benzoazin-6-yl;
2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl;
2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl;
3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl;
[1,2,3]thiadiazolo[5,4-b]pyridin-6-yl;
3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl;
7-chloro-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl;
7-fluoro-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl;
2-thienylthio; or
2,5-difluorophenyl.

7. A compound or a pharmaceutically acceptable salt thereof, according to any one of
   claims 1-6, wherein R is

   \[
   \begin{align*}
   \text{H} & \quad \text{N} \\
   \text{O} & \quad \text{N} \\
   \text{O} & \quad \text{S}
   \end{align*}
   \]

   \[
   \begin{align*}
   \text{H} & \quad \text{N} \\
   \text{O} & \quad \text{N} \\
   \text{O} & \quad \text{S}
   \end{align*}
   \]

   or

   \[
   \begin{align*}
   \text{H} & \quad \text{N} \\
   \text{O} & \quad \text{N} \\
   \text{O} & \quad \text{S}
   \end{align*}
   \]

   wherein

   "-\ldots-" indicates the point of attachment.

8. A compound, or a pharmaceutically acceptable salt thereof, according to any one of
   claims 1-3 which is a compound of formula II:

   \[
   \begin{align*}
   R_2a & \quad \text{U} \quad \text{M} \quad \text{U}_2 \quad \text{R} \\
   R_2b & \quad \text{R}_c \\
   R_2c & \quad \text{Z} \\
   R_2d & \quad \text{O}
   \end{align*}
   \]

   \[
   \begin{align*}
   R_2a, R_2b, R_2c, \text{ and } R_2d \text{ are each independently H, fluoro, chloro, cyano, (C}_1\text{-C}_6\text{)alkyl,}
   \\
   \text{halo(C}_1\text{-C}_6\text{)alkyl, halo(C}_1\text{-C}_6\text{)alkoxy, (C}_1\text{-C}_6\text{)alkoxy;}
   \\
   Z \text{ is CH or N when "-\ldots-" is a bond, or Z is O or NH when "-\ldots-" is absent;}
   \\
   M \text{ is a group of formula M1a or M2-M5.}
   \end{align*}
   \]
in the trans configuration relative to "Y".

Ry and Ry' are each independently H, hydroxy, fluoro, chloro, methoxy, carboxy, CO₂(C₁-C₆)alkyl, or (C₁-C₆)alkyl, or together with the carbon to which they are attached form C=O; or Ry and Ry' together form a bridge;

X is CH₂, NH, N(C₁-C₆)alkyl, N[CO-(C₁-C₆)alkyl], N[SO₂(C₁-C₆)alkyl] or O;

Y is CH₂, NH, N(C₁-C₆)alkyl, N[CO-(C₁-C₆)alkyl], N[SO₂(C₁-C₆)alkyl] or O;

when M is a group of formula M₁a or M₄, U₁ is NR₁, wherein R₁ is H,
(C₁-C₆)alkyl, -(C₁-C₆)alkylecboxy, -CO-(C₁-C₆)alkyl, -CO₂(C₁-C₆)alkyl,
-CO-NH(C₁-C₆)alkyl, -CO-N[(C₁-C₆)alkyl]₂, any of which may be optionally substituted on carbon with halo, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, SO₂(C₁-C₆)alkyl, NH₃,

NH(C₁-C₆)alkyl, or N[(C₁-C₆)alkyl]₂; and W is CH₃, CO, SO₂, CH₂CH₃, CH₂CH=CH, or CH₃C≡C, wherein each hydrogen may be optionally replaced by halo or (C₁-C₆)alkyl;

when M is a group of formula M₂, M₃, or M₅, U₃ is W wherein W is as defined herein above; and

when W is CH₃, CO or SO₂, R is aryl, heteroaryl, heterocyclyl or ortho-fused bicyclic heteroaryl, or when W is CH₂CH₃, CH₂CH=CH, or CH₂C≡C, R is aryl, heteroaryl,
heteroaryl(C₁-C₆)alkyloxy, heteroaryl(C₁-C₆)alkylthio, heteroaryl(C₁-C₆)alkylsulfinyl,
heteroaryl(C₁-C₆)alkylsulfonyl, heteroaryl(C₁-C₆)alkylamino; wherein any R may be optionally substituted on carbon; and wherein any ring nitrogen in R may be optionally substituted by (C₁-C₆)alkyl.
9. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-3 or 5-7 which is a compound of formula III:

```
   R4b      R2  
   R2a----N----R4     R2d
   R2c       U2----R
```

wherein

- R2a, R2b, R2c, and R2d are each independently H, fluoro, chloro, cyano, (C1-C6)alkyl, halo(C1-C6)alkyl, halo(C1-C6)alkoxy, (C1-C6)alkoxy;
- Z is CH or N when "----" is a bond, or, when "----" is absent, Z is O or NH;
- Y is N or CR2, wherein R2 is H, hydroxy, or carboxy;
- U2 is NR'-W, wherein W is CH2, CO, SO2, CH2CH2, CH2CH=CH, or CH2CS=C,

10 wherein each hydrogen may be optionally replaced by halo or (C1-C6)alkyl; and

```
   R is
   N
   O
```

or

```
   R is
   N
   S
```

wherein "~~~" indicates the point of attachment.

10. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-7 which is a compound of formula IV:

```
   R2b      R2  
   R2a----N----N----R
   R2c       R'----W
```

IV
wherein

R₁, R₂b, R₂c, and R₂d are each independently H, fluoro, chloro, cyano, nitro,
(C₁-C₆)alkanoyl, (C₁-C₆)alkoxy carbonyl, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy,
(C₁-C₆)alkoxy, NHCO-(C₁-C₆)alkyl, SO₂(C₁-C₆)alkyl, SO₂NH(C₁-C₆)alkyl, or

SO₂N((C₁-C₆)alkyl)₂;

Z is CH or N when "-----" is a bond, or, when "-----" is absent, Z is O or NH;
R' is H or (C₁-C₆)alkyl;
W is CO, SO₂, or CH₂₅ wherein each hydrogen may be optionally replaced by halo or
(C₁-C₆)alkyl; and

R is

\[ \text{, or } \]

wherein "-----" indicates the point of attachment.

11. A compound according to any one of claims 1-7 or 9, or a pharmaceutically acceptable
salt thereof, which is a compound of formula V:

\[ \text{V} \]

wherein

R₂b, R₂c, and R₂d are each independently H, fluoro, chloro, cyano, nitro,
(C₁-C₆)alkanoyl, (C₁-C₆)alkoxy carbonyl, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy,
(C₁-C₆)alkoxy, NHCO-(C₁-C₆)alkyl, SO₂(C₁-C₆)alkyl, SO₂NH(C₁-C₆)alkyl, or

SO₂N((C₁-C₆)alkyl)₂;

Z is CH or N when "-----" is a bond, or, when "-----" is absent, Z is O or NH; and

R is

\[ \text{, or } \]
12. A compound, or a pharmaceutically acceptable salt thereof, which is
1-(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl)ethyl]-7-methoxyquinolin-2(1H)-one;
1-(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl)ethyl]-7-methoxyquinolin-4(1H)-one;
Methyl 1-(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl)ethyl]-6-methoxy-1H-indole-2-carboxylate;
6-[[1-[(2-(7-Methoxy-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl)amino]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
1-(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl)ethyl]-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
2-Oxo-1-[2-(4-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl]methyl]amino]piperidin-1-yl)ethyl]-1,2-dihydroquinoline-7-carbonitrile;
6-[[1-[(2-(7,8-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl)amino]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
6-[[1-[(2-(7-Fluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl)amino]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
1-(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl)ethyl]-7-fluoroquinolin-2(1H)-one;
6-[[1-[(2-(7-Methoxy-2-oxo-3,4-dihydroquinolin-1(2H)-yl)ethyl]piperidin-4-yl)amino]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
(3S,4R)-1-[(2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]-4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidine-3-carboxylic acid;
(3S,4R)-1-[(2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl))-4-[[2E]-3-(2,5-difluorophenyl)prop-2-en-1-yl]amino]piperidine-3-carboxylic acid;
Methyl (3S,4R)-1-[(2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl])-4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidine-3-carboxylate;
Methyl (3S,4R)-1-[(2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl))-4-[[2E]-3-(2,5-difluorophenyl)prop-2-en-1-yl]amino]piperidine-3-carboxylate;
(3R,4R)-1-[(2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl])-4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidine-3-carboxylic acid;
(3R,4R)-1-[(2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl)-4-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]amino]piperidine-3-carboxylic acid;
Methyl (3R,4R)-1-[(2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl)-4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino]piperidine-3-carboxylate;
Methyl (3R,4R)-1-[(2-(5,7-difluoro-2-oxoquinolin-1(2H)-yl)ethyl)-4-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]amino]piperidine-3-carboxylate;
Cis(+)6-[(1-[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]-3-hydroxy-piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
4-(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl)ethyl]-6-methoxy-2H-1,4-benzoxazin-3(4H)-one;
6-[(1-[(2-(6-Methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
6-[(1-[2-(6-Methoxy-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
4-(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl)ethyl]-6-methoxy-2H,1,4-benzothiazin-3(4H)-one;
6-[(1-[2-(6-Fluoro-3-oxo-2,3-dihydro-4H-1,4-benzothiazin-4-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
4-(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl)ethyl]-6-fluoro-2H-1,4-benzoxazin-3(4H)-one;
6-[(1-[2-(6-Chloro-3-oxo-2,3-dihydro-4H-1,4-benzoaxazin-4-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
6-[(1-[2-(6-Methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoaxazin-4-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]thiazin-3(4H)-one;
3-Oxo-4-[2-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino]piperidin-1-yl]ethyl]-3,4-dihydro-2H-1,4-benzoxazin-6-carbonitrile;
6-[(1-[2-[3-Oxo-6-(trifluoromethoxy)-2,3-dihydro-4H-1,4-benzoaxazin-4-yl]ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
6-[(1-[2-(6-Fluoro-3-oxo-2,3-dihydro-4H-1,4-benzoaxazin-4-yl)ethyl]piperidin-4-yl)amino)methyl]-2H-pyrido[3,2-b][1,4]thiazin-3(4H)-one;
4-(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino]piperidin-1-yl)ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazin-6-carbonitrile;
6-[(1-[2-(6-Bromo-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl)amino]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
6-[(1-[2-(6-Hydroxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl)amino]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
4-[(2-[4-(((2,5-Difluorophenyl)cyclopropyl)methyl)amino)piperidin-1-yl]ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile;
6-[(1-[2-(6,8-Difluoro-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl)amino]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
4-[(2-((2E)-3-(2,5-Difluorophenyl)prop-2-en-1-yl)amino)piperidin-1-yl]ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile;
6-[(trans-4-[2-(6-Methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]cyclohexyl)amino]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
3-Oxo-4-[(2-[trans-4-(((3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl)amino)cyclohexyl)ethyl]-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile;
6-Bromo-4-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino)piperidin-1-yl]ethyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
6-[(1-[2-(6-Nitro-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)ethyl]piperidin-4-yl)amino]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
3-Oxo-4-[(2-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino)piperidin-1-yl]ethyl]-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-carboxamide;
3-Oxo-4-[(2-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino)piperidin-1-yl]ethyl]-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-carboxylate;
Methyl 3-oxo-4-[(2-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino)piperidin-1-yl]ethyl]-3,4-dihydro-2H-1,4-benzoxazine-6-carboxylate;
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3-Oxo-4-[2-(6-[[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-
yl)methyl]amino]-3-azabicycle[3.1.0]hex-3-yl]ethyl]-3,4-dihydro-2H,1,4-benzoxazine-6-
carbonitrile;

4-(2-{{2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino}piperidin-1-
yl)ethy]-2H,1,4-benzoxazin-3(4H)-one;

5-[[1-(2-[6-(1-Hydroxyethyl)-3-oxo-2,3-dihydro-4H,1,4-benzoxazin-4-

Ethyl N-[[1-(2-[6-(3-cyano-3-oxo-2,3-dihydro-4H,1,4-benzoxazin-4-yl]ethyl]piperidin-4-
yl)]-N'-(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]glycinate;

6-[[1-[2-[6-(Methylsulfonyl)-3-oxo-2,3-dihydro-4H,1,4-benzoxazin-4-

7-Methoxy-3-methyl-1-[2-(4-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-
yl)methyl]amino}piperidin-1-yl]ethyl]quinazoline-2,4(1H,3H)-dione;

8-{{2-[4-(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino]-2-oxopiperidin-1-
yl]ethyl]-6-methoxy-2H,1,4-benzoxazin-3(4H)-one;

9-[[1-[2-[6-Methoxy-3-oxo-2,3-dihydro-4H,1,4-benzoxazin-4-yl]ethyl]-2-
oxopiperidin-4-yl]amino]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;

3-Oxo-4-[2-(2-oxo-4-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-
yl)methyl]amino}piperidin-1-yl]ethyl]-3,4-dihydro-2H,1,4-benzoxazine-6-carbonitrile;

6-[[4-(3-(7-Methoxy-2-oxo-2H-furan-3,1-benzoxazin-1(4H)-yl)propyl]piperazin-1-
yl)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;

4-(3-[4-(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]piperazin-1-yl]propyl]-6-
methoxy-2H,1,4-benzoxazin-3(4H)-one;

4-[2-[(2E)-3-(2,5-Difluorophenyl)prop-2-en-1-yl]piperidin-4-yl]amino]ethyl]-6-
methoxy-2H,1,4-benzoxazin-3(4H)-one;

4-(3-[4-(2E)-3-(2,5-Difluorophenyl)prop-2-en-1-yl]piperazin-1-yl]propyl]-6-
methoxy-2H,1,4-benzoxazin-3(4H)-one;

6-[[1-[2-[6-Methoxy-2-oxo-1,7-naphthyridin-1(2H)-yl]ethyl]piperidin-4-
yl]amino]methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;

4-(2-{{2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino}piperidin-1-
yl)ethy]-2H,1,4-benzoxazin-3(4H)-one;
Methyl 1-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]-4-{3-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propyl]piperidine-3-carboxylate; 4-{3-(6-cyano-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propyl]-1-[(2E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]piperidine-3-carboxylic acid; 7-Fluoro-3-methyl-1-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino)piperidin-1-yl)ethyl]quinazolone-2,4(1H,3H)-dione; 7-Chloro-1-[(2-(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino)piperidin-1-yl)ethyl]-1,8-naphthyridin-2(1H)-one; 1-[(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino)piperidin-1-yl)ethyl]-7-methoxy-1,8-naphthyridin-2(1H)-one; 1-[(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino)piperidin-1-yl)ethyl]-7-fluoroquinoxalin-2(1H)-one; 6-[(1-[(2-(7-Fluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one; 1-[(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino)piperidin-1-yl)ethyl]-6-fluoroquinoxalin-2(1H)-one; 1-[(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino)piperidin-1-yl)ethyl]-7-methoxyquinoxalin-2(1H)-one; 6-[(1-[(2-(7-Methoxy-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one; 6-[(1-[(2-(7-Methoxy-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl amino)methyl]-2H-pyrido[3,2-b][1,4]thiazin-3(4H)-one; 1-[(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino)piperidin-1-yl)ethyl]-6,7-difluoroquinoxalin-2(1H)-one; 6-[(1-[(2-(6,7-Difluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one; 1-[(2-[(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino)piperidin-1-yl)ethyl]-7,8-difluoroquinoxalin-2(1H)-one; 6-[(1-[(2-(7,8-Difluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one; 6-[(1-[(2-(6,7-Dimethoxy-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
6-{[(1-[2-(7-Methoxy-3-methyl)-2-oxoquinazolin-1(2H)-yl)ethyl]piperidin-4-yl]amino}methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;

1-(2-{4-[[2,3-Dihydro[1,4]dioxino(2,3-c)pyridin-7-ylmethyl]amino]piperidin-1-yl}ethyl)quinolin-2(1H)-one;

1-(2-{4-[[2,3-Dihydro[1,4]dioxino(2,3-c)pyridin-7-ylmethyl]amino]piperidin-1-yl}ethyl)quinolin-4(1H)-one;

Cis(±)-6-{{1-[[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]-3-methoxypiperidin-4-yl]amino}methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;

7-Fluoro-2-oxo-1-(2-[(4-{{[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl]methyl}amino]piperidin-1-yl}ethyl]-1,2-dihydroquinoline-5-carbonitrile;

5-Fluoro-2-oxo-1-(2-[(4-{{[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl]methyl}amino]piperidin-1-yl}ethyl]-1,2-dihydroquinoline-7-carbonitrile;

7-Fluoro-1-[2-(4-{{[2-oxo-1,2-dihydroquinolin-3-yl]methyl}amino]piperidin-1-yl}ethyl]quinolin-2(1H)-one;

1-[2-(4-{{[2,2-Dimethyl-3,4-dihydro-2H-chromen-6-yl]methyl}amino]piperidin-1-yl}ethyl]-5,7-difluoroquinolin-2(1H)-one;

1-[2-(4-{{[(1,3-Dimethyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)methyl}amino]piperidin-1-yl}ethyl]-5,7-difluoroquinolin-2(1H)-one;

5,7-Difluoro-1-(2-[(5,6,7,8-tetrahydro-1-quinolin-2-yl)methyl]amino]piperidin-1-yl}ethyl]quinolin-2(1H)-one;

5,7-Difluoro-1-(2-[(4-{{[6-fluoro-4H-1,3-benzodioxin-8-yl]methyl}amino]piperidin-1-yl}ethyl]quinolin-2(1H)-one;

5,7-Difluoro-1-(2-[(4-[[1H-indol-6-ylmethyl]amino]piperidin-1-yl}ethyl]quinolin-2(1H)-one;

1-(2-{4-[[2,3-Dihydro-1H-inden-5-ylmethyl]amino]piperidin-1-yl}ethyl)-5,7-difluoroquinolin-2(1H)-one;

5,7-Difluoro-1-(2-[(4-{{[1-methyl-1H-1,2,3-benzotriazol-5-yl]methyl}amino]piperidin-1-yl}ethyl]quinolin-2(1H)-one;

5,7-Difluoro-1-(2-[(4-[[1H-indol-5-ylmethyl]amino]piperidin-1-yl}ethyl]quinolin-2(1H)-one;

5,7-Difluoro-1-{[2-(4-{{[4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl]methyl}amino]piperidin-1-yl}ethyl]quinolin-2(1H)-one;
1-(2-[(4-[(2,1,3-Benzoxadiazol-5-ylmethyl)amino]piperidin-1-yl)ethyl]-7-fluoroquinoxalin-2(1H)-one;
N-1-(2-[[(7-Fluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl]-2,3-dihydro-1,4-benzodioxine-6-sulfonamide;
N-1-[2-[7-Fluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-sulfonamide;
5-Fluoro-N-1-[2-(7-fluoro-2-oxoquinoxalin-1(2H)-yl)ethyl]piperidin-4-yl]-1H-indole-2-carboxamide;
N-1-[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl]-6-morpholin-4-ylnicotinamide;
N-1-[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl]-2,3-dihydro-1,4-benzodioxine-2-carboxamide;
N-1-[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl]-1-methyl-1H-indole-2,3-benzothiazole-5-carboxamide;
N-1-[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl]·2-(2-methyl-1,3-thiazol-4-yl)benzamide;
N-1-[2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl]-4-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide;
3-Oxo-4-[2-[(2R,5S)-5-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino]piperidin-2-yl]ethyl]-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile;
3-Oxo-4-[2-[(2S,5R)-5-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino]piperidin-2-yl]ethyl]-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile;
6-[[1-2-(5,7-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
6-[[1-2-(6,8-Difluoro-2-oxoquinolin-1(2H)-yl)ethyl]piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
2-Oxo-1-[2-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino]piperidin-1-yl)(ethyl]-1,2-dihydroquinoxaline-6-carbonitrile;
3-Oxo-4-[2-[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino]piperidin-1-yl)(ethyl]-3,4-dihydroquinoxaline-6-carbonitrile;
6-[[1-2-(6-Methoxy-3-oxopyrido[2,3-b]pyrazin-4(3H)-yl)ethyl]piperidin-4-yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
4-(2-4-{(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino}piperidin-1-yl)ethyl)-6-methoxypyrido[2,3-b]pyrazin-3(4H)-one;  
6-{[(1-[2-(6-Chloro-1-oxido-3-oxo-1,2,4-benzotriazin-4(3H)-yl)ethyl]piperidin-4-yl)amino]methyl}-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;  
6-Chloro-4-(2-4-{(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino}piperidin-1-yl)ethyl]-1,2,4-benzotriazin-3(4H)-one 1-oxide;  
6-{[(1-[2-(6-Chloro-3-oxo-1,2,4-benzotriazin-4(3H)-yl)ethyl]piperidin-4-yl)amino]methyl}-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;  
4-(2-4-(2S,5R)-5-{(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino}piperidin-2-yl)ethyl)3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile;  
6-{[(1-[2-(7-Bromo-2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-1-yl)ethyl]piperidin-4-yl)amino]methyl}-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;  
2-Oxo-1-[2-(4-{[(3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino}piperidin-1-yl)ethyl]-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazine-7-carboxamide;  
1-(2-4-{(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino}-2-methyl)piperidin-1-yl)ethyl)-5,7-difluorooquinolin-2(1H)-one;  
1-(2-4-{(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino}piperidin-1-yl)ethyl)-2-oxo-1,2-dihydroquinoline-7-carbonitrile;  
Cis\(\text{4}(1-[2(E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]-4-3-(6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propyl)piperidine-3-carboxylic acid;  
Methyl (Cis\(\text{4})-1-[2(E)-3-(2,5-difluorophenyl)prop-2-en-1-yl]-4-3-(6-methoxy-3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)propyl)piperidine-3-carboxylate;  
Cis\(\text{1}(2-4-{(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino}-3-hydroxy)piperidin-1-yl)ethyl]-2-oxo-1,2-dihydroquinoline-7-carbonitrile;  
Cis\(\text{1}(2-3-hydroxy-4-[((3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl)methyl]amino}piperidin-1-yl)ethyl]-2-oxo-1,2-dihydroquinoline-7-carbonitrile;  
5,7-Difluoro-1-(2-4-{(5,6,7,8-tetrahydro-1,8-naphthyridin-2-ylmethyl)amino}piperidin-1-yl)ethyl)quinolin-2(1H)-one;
Cis±1-2-({2-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino}-3-
methoxy-piperidin-1-yl)ethyl]-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
Cis±1-2-[(3-methoxy-4-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-
yl)methyl]amino]piperidin-1-yl)ethyl]-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
Cis±1-2-[4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino]-3-
fluoropiperidin-1-yl)ethyl]-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
Cis±1-2-[(3-fluoro-4-[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-
yl)methyl]amino]piperidin-1-yl)ethyl]-2-oxo-1,2-dihydroquinoline-7-carbonitrile;
Cis±1-2-[4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino]-3-
hydroxy-piperidin-1-yl)ethyl]-7-fluoroquinoxalin-2(1H)-one;
Cis±6-[[2-[(7-fluoro-2-oxoquinazolin-1(2H)-yl)ethyl]-3-hydroxy-piperidin-4-
yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
Cis±1-2-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino]-3-
fluoropiperidin-1-yl)ethyl]-7-fluoroquinoxalin-2(1H)-one;
Cis±6-[[2-[(7-fluoro-2-oxoquinazolin-1(2H)-yl)ethyl]-3-fluoropiperidin-4-
yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
Cis±1-2-[4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino]-3-
hydroxy-piperidin-1-yl)ethyl]-7-methoxyquinoxalin-2(1H)-one;
Cis±6-[[2-[(7-methoxy-2-oxoquinazolin-1(2H)-yl)ethyl]-3-hydroxy-piperidin-4-
yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
Cis±1-2-[4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino]-3-
fluoropiperidin-1-yl)ethyl]-7-methoxyquinoxalin-2(1H)-one;
Cis±6-[[2-[(7-methoxy-2-oxoquinazolin-1(2H)-yl)ethyl]-3-methoxy-piperidin-4-
yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
Cis±1-2-[4-[(2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-yl)methyl]amino]-3-
fluoropiperidin-1-yl)ethyl]-7-methoxyquinoxalin-2(1H)-one;
Cis±6-[[2-[(7-methoxy-2-oxoquinazolin-1(2H)-yl)ethyl]-3-fluoropiperidin-4-
yl]amino)methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one;
Cis&4-[2-(3-hydroxy-4-{{[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl]methyl}amino}piperidin-1-yl)ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile;

Cis&4-[2-(3-methoxy-4-{{[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl]methyl}amino}piperidin-1-yl)ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile;

Cis&4-[2-(3-fluoro-4-{{[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl]methyl}amino}piperidin-1-yl)ethyl]-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbonitrile;

1-(2-{4-[2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl]amino}piperidin-1-yl)ethyl]-7-methoxy-3,4-dihydroquinoxalin-2(1H)-one;

5,7-Difluoro-1-[2-{4-[(1-oxo-1,3-dihydro-2-benzofuran-5-yl)methyl]amino}piperidin-1-yl]ethyl]quinolin-2(1H)-one;

6-{{[1-{2-(7-Methoxy-2-oxoquinoxalin-1(2H)-yl)propyl}piperidin-4-yl]amino}methyl}-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one; or

5,7-Difluoro-1-{2-{4-[(5,6,7,8-tetrahydro-1,8-naphthyridin-2-ylmethyl)amino}piperidin-1-yl]ethyl]quinolin-2(1H)-one.

13. A pharmaceutical composition comprising a compound according to any one of claims 1-12, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable adjuvant, carrier, or excipient.

14. A method of treating a bacterial infection comprising administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-12 to a mammal in need thereof.

15. A method of treating a bacterial infection in a warm-blooded animal, such as a human being, in need of such treatment, which comprises administering to said animal an effective amount of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-12 or a pharmaceutically-acceptable salt thereof.

16. A method for inhibiting bacterial DNA gyrase in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-12 or a pharmaceutically acceptable salt.
17. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-12 or a pharmaceutically acceptable salt thereof for use as a medicament.

18. The use of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-12 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an anti-bacterial effect in a warm-blooded animal such as a human being.

19. The use of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-12 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of a bacterial infection in a warm-blooded animal such as a human being.

20. A process for making a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-12, comprising one of the following:

(a) N-alkylation of $L$ with $X \cdot U_1 \cdot M$, wherein $X$ is a leaving group in the presence of a base to form $LU_1 \cdot M$, wherein $U_1$ is $\text{CH}_3\text{CH}_2$, followed by attachment of $U_2$ and $R$ via functional group manipulation, alkylation, or reductive amination;

\[
\begin{array}{ccc}
L & \xrightarrow{X \cdot U_1 \cdot M} & LU_1 \cdot M & \xrightarrow{U_2} \\
\text{Base} & & & \\
L \cdot U_1 \cdot M & \xrightarrow{R} & L \cdot U_1 \cdot M \cdot U_2 \cdot R
\end{array}
\]

(b) N-alkylation of $L$ with $HO \cdot U_1 \cdot M$, under Mitsunobu conditions to form $LU_1 \cdot M$, followed by attachment of $U_2$ and $R$ via functional group manipulation, alkylation, or reductive amination;

\[
\begin{array}{ccc}
L & \xrightarrow{HO \cdot U_1 \cdot M} & LU_1 \cdot M & \xrightarrow{U_2} \\
\text{Mitsunobu} & & & \\
L \cdot U_1 \cdot M \cdot U_2 & \xrightarrow{R} & L \cdot U_1 \cdot M \cdot U_2 \cdot R
\end{array}
\]

(c) N-alkylation of $L$ with bromo- or chloroacetic acid or a derivative thereof to form $L \cdot \text{CH}_2\text{CO}_2\cdot H$ followed by
i) activation of the acid moiety in \( \text{L-CH}_2\text{CO}_2\text{H} \); 

ii) amide coupling to form \( \text{LU}_1\text{M} \), wherein \( \text{U}_1 \) is \( \text{CH}_2\text{CO} \),

iii) attachment of \( \text{U}_2 \) and \( \text{R} \) via functional group manipulation, alkylation, or reductive amination, and

iv) optional reduction of the carbonyl moiety in \( \text{U}_1 \) to form a compound wherein \( \text{U}_1 \) is \( \text{CH}_2\text{CH}_2 \).

\[
\begin{align*}
\text{L} & \xrightarrow{\text{Base}} \text{L-CH}_2\text{CO}_2\text{H} \quad \xrightarrow{\text{M}} \text{L-CH}_2\text{CO}_2\text{M} \\
& \quad \xrightarrow{\text{U}_2} \text{L-CH}_2\text{CO-U}_2 \quad \xrightarrow{\text{R}} \text{L-CH}_2\text{CO-U}_2\text{R}
\end{align*}
\]

(d) \( \text{N-alkylation of L with X-(CH}_2)_n\text{CH=CH}_2 \) wherein \( \text{X} \) is a leaving group and \( n \) is 1 or 2 to form \( \text{L-(CH}_2)_n\text{CH=CH}_2 \), followed by:

i) oxidative cleavage using an oxidant such as ozone or sodium periodate (with reductive workup) to form \( \text{L-(CH}_2)_n\text{CH}_2\text{OH} \); 

ii) conversion of the alcohol moiety in \( \text{L-(CH}_2)_n\text{CH}_2\text{OH} \) to a leaving group;

iii) reaction of \( \text{L-(CH}_2)_n\text{CH}_2\text{-Y} \) with \( \text{M} \), in the presence of a base to form \( \text{LU}_1\text{M} \); and

iv) attachment of \( \text{U}_2 \) and \( \text{R} \) via functional group manipulation, alkylation, or reductive amination;

\[
\begin{align*}
\text{L} & \xrightarrow{\text{Base}} \text{L-(CH}_2)_n\text{CH=CH}_2 \quad \xrightarrow{[\text{O}]} \text{L-(CH}_2)_n\text{OH} \\
& \quad \xrightarrow{\text{M}} \text{L-U}_1\text{M} \\
& \quad \xrightarrow{\text{U}_2} \text{L-U}_1\text{M-U}_2 \quad \xrightarrow{\text{R}} \text{L-U}_1\text{M-U}_2\text{R}
\end{align*}
\]

\( \text{X, Y = leaving group} \quad n = 1 \) or 2
N-alkylation of L with X-(CH₂)ₙCH=CH₂ wherein X is a leaving group and n is 1 or 2 to form L-(CH₂)ₙCH=CH₂, followed by:

i) hydroboration followed by an oxidative workup to form to form L-CH₂CH₂OH;

ii) conversion of the alcohol moiety in L-CH₂CH₂OH to a leaving group;

iii) reaction of L-CH₂CH₂-"LG" with M, in the presence of a base to form LU₁M;

and

iv) followed by attachment of U₂ and R via functional group manipulation, alkylation, or reductive amination; or

\[
\begin{align*}
L & \xrightarrow{X-(CH₂)ₙCH=CH₂} L-(CH₂)ₙ & \xrightarrow{\text{Hydroboration}} L-(CH₂)ₙOH \\
& \xrightarrow{\text{Oxidative Workup}} L-(CH₂)ₙM \\
& \xrightarrow{U₂} L-U₁-M-U₂ & \xrightarrow{R} L-U₁-M-U₂-R
\end{align*}
\]

\[X, Y = \text{leaving group} \quad n = 1 \text{ or } 2\]

(f) Oxidation of the alcohol intermediate, followed by

i) reductive amination with MU₂; to form LU₁MU₂, wherein U₁ is CH₂CH₂;

ii) reductive amination with R.

\[
\begin{align*}
L & \xrightarrow{[O]} L & \xrightarrow{MU₂} L-U₁-M-U₂ \\
& \xrightarrow{R} L-U₁-M-U₂-R
\end{align*}
\]
# INTERNATIONAL SEARCH REPORT

**International application No.**

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## A. CLASSIFICATION OF SUBJECT MATTER

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According to international Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

- **Classification systems** used
  - C07D

Documentation searched other than minimum documentation in the relevant data base documents not included in the data base searched

Electronic database consulted during the international search (name of data base and, where practical, search terms used)

- EPO-Internal, WPI Data, PAJ, BIOSIS, BIELSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 2006/003148 A (JANSSEN PHARMACEUTICALS N.V.) KENNIS, LUDO; EDMOND, JOSEPHINE; | | MIERENS, J) 12 January 2006 (2006-01-12) | | claim 1 | | tables F-1; compounds 10-12</td>
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<td>X</td>
<td>WO 02/24661 A (BOHRRINGER INSELHEIM PHARMA KG; CERDA, EMILIO; MAIOCCHI, LUCIANO; | | BRABMEN) 28 March 2002 (2002-03-28) | | claim 1 | | examples | 143, 155, 157, 162, 176, 181, 193, 195, 222, 234 | | examples | 236, 251, 273, 275, 278, 292, 312, 324, 326, 329 | | examples | 363, 375, 377, 380, 392, 394</td>
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**Relevant to claim No**

| 1, 4, 5, | 13, 17 |

**From**

**See patent family means**

**Documents considered to be only published after the international filing date of priority and not in conflict with the application but could be relevant to the examination**

**Documents of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is known alone**

**Documents of particular relevance: the claimed inventions cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art**

**Documents of the same patent family**

Date of the actual completion of the international search: 22 September 2006

Date of mailing of the international search report: 05/10/2006

Name and address of the R(A)

European Patent Office, P.B. 6916 Patentlie 2 | European Patent Office, P.B. 6916 Patentlie 2 |
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Authorized officer
### INTERNATIONAL SEARCH REPORT

#### DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>CRISTAU H-J ET AL.: &quot;SYNTHESIS OF DIPHENYLDIALKYLPHOSPHONIUM SALTS&quot; SYNTHESIS, GEORG THIEME VERLAG, STUTTGART, DE, no. 11, 1 November 1988 (1988-11-01), pages 911-912, XP000024950 ISSN: 0039-7881 page 912; figure 2; compound 6b</td>
<td>1.4, 5, 13, 17</td>
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<td>A</td>
<td>WO 2004/002490 A (BLAXO GROUP LIMITED; AXTEN, JEFFREY, MICHAEL; DAINES, ROBERT; A; DAVIE) 8 January 2004 (2004-01-08) the whole document</td>
<td>1-20</td>
</tr>
</tbody>
</table>
INTERNATIONAL SEARCH REPORT

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort, justifying an additional fee, the Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claim 1:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims, it is covered by Claim 1:

Remark on Fees
☐ No additional search fees were accompanied by the applicant's payment.
☐ Additional search fees were accompanied by the applicant's payment.

Form PCT/SA210 (continuation of first sheet (2)) (January 2004)
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<td>WO 2006003148 A</td>
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<td>US 2006958287 A1</td>
<td>16-03-2006</td>
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Abstract. Biocyclic nitrogen containing compounds and their use as antibacterials (Formula I).
Published:

- 'wo/ international search report (Art. 21(3))
This invention relates to novel compounds, compositions containing them and their use as antibacterials including use in the treatment of tuberculosis.


This invention provides a compound of formula (I) or a pharmaceutically acceptable salt or N-oxide thereof:

![Chemical structure](image)

wherein:

Z^1 and Z^2 are independently selected from N and CH;

AB is OCH_2, CH_2O, NR^{11}CH_2 or CH_2NR^{11};

R^{11} is selected from C(1-2)alkyl; formyl; (C_1-2)alkylcarbonyl; and (C_1-2)alkylsulphonyl;

R^{1a} is selected from hydrogen; halogen; cyano; (C_1-6)alkyl; (C_1-6)alkylthio; trifluoromethyl; trifluoromethoxy; carboxy; hydroxy optionally substituted with (C_1-6)alkyl or (C_1-6)alkoxy-substituted(C_1-6)alkyl; (C_1-6)alkoxy-substituted(C_1-6)alkyl;
hydroxy (C_{1-6})alkyl; an amino group optionally N-substituted by one or two (C_{1-6})alkyl, formyl, (C_{1-6})alkylcarbonyl or (C_{1-6})alkylsulphonyl groups; or aminocarbonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl;
R^{1b} is H or F;
R^2 is hydrogen;

R^V and R^W are hydrogen, R^V is absent and R^3 is in the 1-position and R^W is hydrogen or R^V and R^W together are a bond;

R^3 is hydrogen; or
when R^V and R^W are a bond, R^3 is in the 2-, 3- or 4-position and when R^W is hydrogen, R^3 is in the 1-, 2-, 3- or 4-position and R^3 is:
hydroxy optionally substituted by (C_{1-6})alkyl; amino optionally mono- or disubstituted independently by (C_{1-6})alkyl or (C_{1-6})alkylcarbonyl; fluoro; carboxy; cyano; (C_{1-6})alkoxycarbonyl; aminocarbonyl wherein the amino group is optionally substituted by (C_{1-6})alkyl or (C_{1-6})alkylcarbonyl, or (C_{1-4})alkyl optionally substituted with any of the groups listed above for R^3;
provided that when R^3 is in the 4-position it is not optionally substituted hydroxyl or amino;
provided that when R^3 is in the 1-position and AB is CH_2NR^{11} or R^3 is in the 4-position, it is not optionally substituted hydroxyl or amino;
and provided that when R^3 is in the 1-position and AB is CH_2O, it is not optionally substituted amino;

R^4 is UR^5;

U is selected from CO and CH_2 and

R^5 is an optionally substituted bicyclic carbocyclic or heterocyclic ring system (B):

(A)

containing up to four heteroatoms in each ring in which
at least one of rings (a) and (b) is aromatic;
X^1 is C or N when part of an aromatic ring, or CR^{14} when part of a non-aromatic ring;

- 2 -
X^2 is N, NR^{13}, O, S(O)_x, CO or CR^{14} when part of an aromatic or non-aromatic ring or may in addition be CR^{14}R^{15} when part of a non-aromatic ring;

X^3 and X^5 are independently N or C;

Y^1 is a 0 to 4 atom linker group each atom of which is independently selected from N, NR^{13}, O, S(O)_x, CO and CR^{14} when part of an aromatic or non-aromatic ring or may additionally be CR^{14}R^{15} when part of a non-aromatic ring;

Y^2 is a 2 to 6 atom linker group, each atom of Y^2 being independently selected from N, NR^{13}, O, S(O)_x, CO, CR^{14} when part of an aromatic or non-aromatic ring or may additionally be CR^{14}R^{15} when part of a non-aromatic ring;

each of R^{14} and R^{15} is independently selected from: H; (C_{1-2})alkylthio; halo; carboxy(C_{1-2})alkyl; (C_{1-2})alkyl; (C_{1-2})alkoxycarbonyl; (C_{1-2})alkylcarbonyl; (C_{1-2})alkoxy (C_{1-2})alkyl; hydroxy; hydroxy(C_{1-24})alkyl; (C_{1-2})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally mono- or di-substituted by (C_{1-2})alkyl; or

R^{14} and R^{15} may together represent oxo;

each R^{13} is independently H; trifluoromethyl; (C_{1-2})alkyl optionally substituted by hydroxy, (C_{1-2})alkoxy, (C_{1-2})alkylthio, halo or trifluoromethyl; (C_{2})alkenyl; (C_{1-2})alkoxycarbonyl; (C_{1-2})alkylcarbonyl; (C_{1-2})alkylsulphonyl; aminocarbonyl wherein the amino group is optionally mono or disubstituted by (C_{1-2})alkyl;

each x is independently 0, 1 or 2.

This invention also provides a method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt and/or N-oxide thereof.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt and/or N-oxide thereof, in the manufacture of a medicament for use in the treatment of bacterial infections in mammals.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt and/or N-oxide thereof, and a pharmaceutically acceptable carrier.

In one aspect, the invention provides a compound of formula (IA), or a pharmaceutically acceptable salt and/or N-oxide thereof, which is a compound of formula (I) wherein Z^1 is CH; Z^2 is N; AB is OCH_2, CH_2O, NHCH_2 or CH_2NH; and R^3 is hydrogen; or

when R^v and R^w are a bond, R^3 is in the 2-, 3- or 4- position and when R^w is hydrogen, R^3 is in the 1-, 2-, 3- or 4-position and R^3 is:
hydroxy optionally substituted by (C_{1-6})alkyl; amino optionally mono- or disubstituted by (C_{1-6})alkyl; fluoro; carboxy; cyano; or (C_{1-4})alkyl optionally substituted with any of the groups just listed for R^3.

In another aspect the invention provides a compound of formula (I), or a pharmaceutically acceptable salt and/or N-oxide thereof, which is other than a compound of formula (IA).

In particular embodiments:
(1) Z^1 is CH and Z^2 is N;
(2) Z^1 and Z^2 are both CH;
(3) Z^1 is N and Z^2 is CH
(4) Z^1 and Z^2 are both N.

In a particular aspect R^{1a} is hydrogen, (C_{1-4})alkoxy, (C_{1-4})alkylthio, (C_{1-4})alkyl, cyano, carboxy, hydroxymethyl or halogen; more particularly hydrogen, cyano, or halogen.

In some embodiments only one group R^{1a} or R^{1b} is other than hydrogen. In a particular embodiment R^{1a} is halo such as chloro or fluoro or cyano and R^{1b} is hydrogen.

In other embodiments both R^{1a} and R^{1b} are hydrogen.

In a particular aspect R^2 is hydrogen.

Particular examples of R^3 include hydrogen; optionally substituted hydroxy; optionally substituted amino; fluoro (C_{1-4}) alkyl; 1-hydroxy-(C_{1-4}) alkyl. More particular R^3 groups are hydrogen; 1-hydroxyalkyl e.g. CH_2OH; optionally substituted hydroxy e.g. methoxy; optionally substituted amino; and fluoro. Most particularly R^3 is hydrogen or hydroxy, and if hydroxy, most preferably substituted in the 1- or 3-position.

In particular embodiments AB is OCH_2, NHCH_2 or CH_2NH.

In certain embodiments U is CH_2.

In certain embodiments R^5 is an aromatic heterocyclic ring (A) having 8-11 ring atoms including 2-4 heteroatoms of which at least one is N or NR^{13} in which, in particular embodiments, Y^2 contains 2-3 heteroatoms, one of which is S and 1-2 are N, with one N bonded to X^3.

In alternative embodiments the heterocyclic ring (A) has ring (a) aromatic selected from optionally substituted benzo, pyrido, pyridazino and pyrimidino and ring (b) non aromatic and Y^2 has 3-4 atoms including at least one heteroatom, with O, S, CH_2 or NR^{13} bonded to X^5, where R^{13} is other than hydrogen, and either NHCO bonded via N to X^3, or O, S, CH_2, or NH bonded to X^3. In a particular aspect the ring (a) contains aromatic nitrogen, and more particularly ring (a) is pyridine. Examples of rings (A) include optionally substituted:
(a) and (b) aromatic
1H-pyrrolo[2,3-b]-pyridin-2-yl, 1H-pyrrolo[3,2-b]-pyridin-2-yl, 3H-imidazo[4,5-b]-pyrid-2-yl, 3H-quinazolin-4-one-2-yl, benzimidazol-2-yl, benzo[1,2,3]-thiadiazol-5-yl, benzo[1,2,5]-oxadiazol-5-yl, benzosulfur-2-yl, benzothiazol-2-yl, benzo[b]thiophen-2-yl, benzoxazol-2-yl, chromen-4-one-3-yl, imidazo[1,2-a]pyridin-2-yl, imidazo-[1,2-a]-pyrimidin-2-yl, indol-2-yl, indol-6-yl, isoquinolin-3-yl, [1,8]-naphthyridine-3-yl, oxazolo[4,5-b]-pyridin-2-yl, quinolin-2-yl, quinolin-3-yl, quinoxalin-2-yl, naphthalen-2-yl, 1,3-dioxo-isoindol-2-yl, 1H-benzotriazol-5-yl, 1H-indol-5-yl, 3H-benzoxazol-2-one-6-yl, 3H-benzoxazol-2-thione-6-yl, 3H-benzothiazol-2-one-5-yl, 3H-quinazolin-4-one-6-yl, pyrido[1,2-a]pyrimidin-4-one-3-yl, benzo[1,2,3]thiadiazol-6-yl, benzo[1,2,5]thiadiazol-5-yl, benzo[1,4]oxazin-2-one-3-yl, benzothiazol-5-yl, benzothiazol-6-yl, cinnolin-3-yl, imidazo[1,2-a]pyrazin-2-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyrimidin-6-yl, pyrazolo[5,1-c][1,2,4]triazin-3-yl, pyrido[1,2-a]pyrimidin-4-one-2-yl, quinazolin-2-yl, quinoxalin-6-yl, thiazolo[3,2-a]pyrimidin-5-one-7-yl, thiazolo[5,4-b]pyridin-2-yl, thieno[3,2-b]pyridin-6-yl, thiazolo[5,4-b]pyridin-6-yl, thiazolo[4,5-b]pyridin-5-yl, [1,2,3]thiadiazolo[5,4-b]pyridin-6-yl, 2H-isoquinolin-1-one-3-yl
→ is the point of attachment

(a) is non aromatic

(2S)-2,3-dihydro-1H-imol-2-yl, (2S)-2,3-dihydro-benzo[1,4]dioxine-2-yl, 3-(R,S)-3,4-dihydro-2H-benzo[1,4]thiazin-3-yl, 3-(R)-2,3-dihydro-[1,4]dioxino[2,3-h]pyridin-3-yl, 3-
(S)-2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-3-yl, 2,3-dihydro-benzo[1,4]dioxan-2-yl, 3-substituted-3H-quinazolin-4-one-2-yl,

→ is the point of attachment

(b) is non aromatic

1,1,3-trioxo-1,2,3,4-tetrahydro[1,4]thiazin-6-yl, benzo[1,3]dioxol-5-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, 3-substituted-3H-benzooxazol-2-one-6-yl, 3-substituted-3H-benzoxazole-2-thione-6-yl, 3-substituted-3H-benzothiazol-2-one-6-yl, 4H-benzo[1,4]oxazin-3-one-6-yl (3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl), 4H-benzo[1,4]thiazin-3-one-6-yl (3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl), 4H-benzo[1,4]oxazin-3-one-7-yl, 4-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]thiazepine-7-yl, 5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-6-yl, 1H-pyrido[2,3-b][1,4]thiazin-2-one-7-yl (2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl), 2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl, 2-oxo-2,3-dihydro-1H-pyrido[3,4-b]thiazin-7-yl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-6-yl, 2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-7-yl, 3,4-dihydro-2H-benzo[1,4]oxazin-6-yl, 3,4-dihydro-2H-benz[a]thiazin-6-yl, 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl, 3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl, 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl, 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl, 3,4-dihydro-1H-quinolin-2-one-7-yl, 3,4-dihydro-1H-quinolizin-2-one-7-yl, 6,7-dihydro-4H-pyrazolo[1,5-a]pyrimidin-5-one-2-yl, 1,2,3,4-tetrahydro-[1,8]naphthyridin-7-yl, 2-oxo-3,4-dihydro-1H-[1,8]naphthyridin-6-yl, 6-oxo-6,7-dihydro-5H-8-thia-1,2,5-triaza-naphthalen-3-yl, 2-oxo-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yl, 2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-7-yl, 6,7-dihydro-[1,4]dioxino[2,3-d]pyrimidin-2-yl, [1,3]oxathiolo[5,4-c]pyridin-6-yl, 3,4-dihydro-2H-pyran[2,3-c]pyridine-6-yl, 2,3-dihydro[1,4]oxathiino[2,3-c]pyridine-7-yl, 6,7-dihydro[1,4]dioxino[2,3-c]pyridazin-3-yl, 6,7-dihydro[1,4]oxathiino[2,3-c]pyridazin-3-yl, 6,7-dihydro-5H-pyran[2,3-c]pyridazin-3-yl, 5,6-dihydrofuro[2,3-c]pyridazin-3-yl, 2,3-dihydrofuro[2,3-c]pyridin-5-yl, 2-substituted 1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one, 2-substituted 5,6-dihydropyridino[2,3-d]pyrimidin-7(1H)-one, 7-substituted 2H-chromen-2-one, 7-substituted 2H-pyran[2,3-b]pyridin-2-one, 2-substituted 6,7-dihydro-5H-pyran[2,3-d]pyrimidine, 8-substituted 2H-pyridino[1,2-a]pyrimidin-2-one, 2,3-
dihydro-1-benzofuran-5-yl, 7-substituted 3,4-dihydro-1,8-naphthyridin-2(1H)-one, 2- substituted 1H-pyrimido[5,4-b][1,4]thiazin-7(6H)-one.

$\text{\rightarrow is the point of attachment}$

_in some embodiments $R^{13}$ is H if in ring (a) or in addition (C$_{1-4}$)alkyl such as methyl or isopropyl when in ring (b). More particularly, in ring (b) $R^{13}$ is H when NR$^{13}$ is bonded to $X^3$ and (C$_{1-4}$)alkyl when NR$^{13}$ is bonded to $X^5$.\"
In further embodiments R\textsuperscript{14} and R\textsuperscript{15} are independently selected from hydrogen, halo, hydroxy, (C\textsubscript{1-4}) alkyl, (C\textsubscript{1-4}) alkoxy, nitro and cyano. More particularly R\textsuperscript{15} is hydrogen.

More particularly each R\textsuperscript{14} is selected from hydrogen, chloro, fluoro, hydroxy, methyl, methoxy, nitro and cyano. Still more particularly R\textsuperscript{14} is selected from hydrogen, fluorine or nitro.

Most particularly R\textsuperscript{14} and R\textsuperscript{15} are each H.

Particular groups R\textsuperscript{5} include:

- [1,2,3]thiadiazolo[5,4-b]pyridin-6-yl
- 1H-pyrrolo[2,3-b]pyridin-2-yl
- 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-6-yl
- 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-7-yl
- 2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl
- 2,3-dihydro-benzo[1,4]dioxin-6-yl
- 2-oxo-2,3-dihydro-1H-pyrrolo[2,3-b][1,4]oxazin-7-yl
- 2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl
- 3,4-dihydro-2H-benzo[1,4]oxazin-6-yl
- 3-methyl-2-oxo-2,3-dihydro-benzo[1,4]oxazol-6-yl
- 3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl
- 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl (6-substituted 2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one)
- 3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl (4H-benzo[1,4] thiazin-3-one-6-yl)
- 4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl
- 6-nitro-benzo[1,3]dioxol-5-yl
- 7-fluoro-3-oxo-3,4-dihydro-2H-benzo[1,4] oxazin-6-yl
- 8-hydroxy-1-oxo-1,2-dihydro-isoquinolin-3-yl
- 8-hydroxyquinolin-2-yl
- benzo[1,2,3]thiadiazol-5-yl
- benzo[1,2,5]thiadiazol-5-yl
- benzo[1,2,5]thiadiazol-5-yl
- thiazolo-[5,4-b]pyridin-6-yl
- 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl (6-substituted 2H-pyrido[3,2-b][1,4]thiazin-3(4H)-one)
- 7-chloro-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl
- 7-chloro-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl (6-substituted 7-chloro-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one)
- 7-fluoro-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl
2-oxo-2,3-dihydro-1H-pyrido[3,4-b][1,4]thiazin-7-yl
[1,3]oxathiolo[5,4-c]pyridin-6-yl
3,4-dihydro-2H-pyran[2,3-c]pyridine-6-yl
2,3-dihydro-5-carbonitro-1,4-benzodioxin-7-yl (7-substituted 2,3-dihydro-1,4-
benzodioxin-5-carbonitrile)
2,3-dihydro[1,4]oxathiino[2,3-c]pyridine-7-yl
2,3-dihydro-1-benzofuran-5-yl
6,7-dihydro[1,4]dioxino[2,3-c]pyridazin-3-yl
6,7-dihydro[1,4]oxathiino[2,3-c]pyridazin-3-yl
6,7-dihydro-5H-pyrano[2,3-c]pyridazin-3-yl
5,6-dihydropyrolo[2,3-c]pyridazin-3-yl
2-substituted 1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one
2-substituted 4-chloro-1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one
2-substituted 5,6-dihydropyrido[2,3-d]pyrimidin-7(1H)-one
2-substituted 4-chloro-5,6-dihydropyrido[2,3-d]pyrimidin-7(1H)-one
2-substituted 4-methyl-5,6-dihydropyrido[2,3-d]pyrimidin-7(1H)-one
2-substituted 4-methyloxy-5,6-dihydropyrido[2,3-d]pyrimidin-7(1H)-one
7-substituted 2H-chromen-2-one
7-substituted 2H-pyrano[2,3-b]pyridin-2-one
4-chloro-6,7-dihydro-5H-pyran[2,3-c]pyrimidin-2-yl
8-substituted 2H-pyrido[1,2-a]pyrimidin-2-one
6,7-dihydro-5H-pyran[2,3-c]pyrimidin-2-yl)
5-chloro-1-benzothiophen-2-yl
6-chloro-1-benzothiophen-2-yl
1-benzothiophen-5-yl
1-methyl-1H-1,2,3-benzotriazol-6-yl
imidazo[2,1-b][1,3]thiazol-6-yl
4-methyl-3,4-dihydro-2H-1,4-benzoazin-7-yl
1-methyl-1H-indol-2-yl
3-substituted 5H-pyrazidino[3,4-b][1,4]thiazin-6(7H)-one
7-substituted 3,4-dihydro-1,8-naphthyridin-2(1H)-one
2-substituted 1H-pyrimido[5,4-b][1,4]thiazin-7(6H)-one
→ is the point of attachment
especially
2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl
[1,3]oxathiino[5,4-c]pyridin-6-yl
3,4-dihydro-2H-pyrano[2,3-c]pyridine-6-yl
3-substituted 5H-pyrazino[3,4-b][1,4]-thiazin-6-(7H)-one
6-substituted 2H-pyrido[3,2-b][1,4]thiazin-3(4H)-one
6-substituted 7-chloro-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one
6-substituted 2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one
7-substituted 1H-pyrido[2,3-b][1,4]thiazin-2(3H)-one
7-substituted 3,4-dihydro-1,8-naphthyridin-2(1H)-one
5-substituted 2,3-dihydrofuro[3,2-b]pyridine
3-substituted 6,7-dihydro[1,4]dioxino[2,3-c]pyrazine
2-substituted 1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one

When used herein, the term "alkyl" includes groups having straight and branched chains, for instance, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, pentyl and hexyl. The term 'alkenyl' should be interpreted accordingly.

Halo or halogen includes fluoro, chloro, bromo and iodo.

Haloalkyl moieties include 1-3 halogen atoms.

Compounds within the invention contain a heterocyclic group and may occur in two or more tautomeric forms depending on the nature of the heterocyclic group; all such tautomeric forms are included within the scope of the invention.

Some of the compounds of this invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including
hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

Furthermore, it will be understood that phrases such as "a compound of formula (I) or a pharmaceutically acceptable salt or N-oxide thereof" are intended to encompass the compound of formula (I), an N-oxide of formula (I), a pharmaceutically acceptable salt of the compound of formula (I), a solvate of formula (I), or any pharmaceutically acceptable combination of these. Thus by way of non-limiting example used here for illustrative purpose, "a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof" may include a pharmaceutically acceptable salt of a compound of formula (I) that is further present as a solvate.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that in particular embodiments they are provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and particularly at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and more particularly from 10 to 59% of a compound of the formula (I) or pharmaceutically acceptable salt and/or N-oxide thereof.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable N-oxides, salts and solvates.

Pharmaceutically acceptable salts of the above-mentioned compounds of formula (I) include the acid addition or quaternary ammonium salts, for example their salts with mineral acids e.g. hydrochloric, hydrobromic, sulphuric nitric or phosphoric acids, or organic acids, e.g. acetic, fumaric, succinic, maleic, citric, benzoic, p-toluenesulphonic, methanesulphonic, naphthalenesulphonic acid or tartaric acids. Compounds of formula (I) may also be prepared as the N-oxide. The invention extends to all such derivatives.

Certain of the compounds of formula (I) may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention includes all such forms, in particular the pure isomeric forms. For example, the invention includes compounds in which the configuration of the 1,4-substituted cyclohexyl moiety is cis or trans, in particular trans. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses. Certain compounds of formula (I) may also exist in polymorphic forms and the invention includes such polymorphic forms.
In a further aspect of the invention there is provided a process for preparing compounds of formula (I), and pharmaceutically acceptable salts and/or N-oxides thereof, which process comprises reacting a compound of formula (II) with a compound of formula (III):

wherein R°, R°', and R°' are R°, R°, and R° as defined in formula (I) or groups convertible thereto; Z', Z', R', R', and R' are as defined in formula (I);
Q' is NR2R4' or a group convertible thereto wherein R2' and R4' are R2 and R4 as defined in formula (I) or groups convertible thereto and Q' is H or R°' or Q' and Q' together form an optionally protected oxo group;
and X and Y may be the following combinations:
(i) Y is COW and X is NH,R11;
(ii) X is NH,R11 and Y is CH(=O) or X is CH(=O) and Y is NH,R11;
(iii) X is OH and Y is CH2OH;
(iv) one of X and Y is (CH2)p-W and the other is (CH2)q-NH,R11 or (CH2)q-OH, where p+q=1;
(v) X is OH and Y is -CH=N2;
(vi) X is W and Y is CONH2;
(vii) X is OH and Y and R°' together form an epoxide group;
in which W is a leaving group, e.g. halo, methanesulphonyloxy, trifluoromethanesulphonyloxy or imidazolyl;
and thereafter optionally or as necessary converting Q' and Q' to NR2R4'; converting R°, R°', R2', R3', and R4' to R1a, R1b, R2, R3, and R4; converting intermediate linker A'-B' formed by the reaction of X and Y to A-B, converting A-B to other A-B, interconverting R', R', R1a, R1b, R2, R3, and/or R4, and/or forming a pharmaceutically acceptable salt and/or N-oxide thereof.

Process variant (i) initially produces compounds of formula (I) where A-B is NH-CO which may be converted to A-B NH-CH2.

Process variant (ii) produces compounds of formula (I) wherein A-B is NH-CH2, or CH2-NH.
Process variant (iii) produces compounds of formula (I) wherein A-B is O-CH₂.
Process variant (iv) produces compounds of formula (I) wherein one of A and B
is CH₂ and the other is NH or O.
Process variant (v) produces compounds of formula (I) wherein A-B is OCH₂.
Process variant (vi) initially produces compounds of formula (I) where A-B is
NHCO which may be converted to A-B NH-CH₂.
Process variant (vii) produces compounds of formula (I) wherein A-B is OCH₂
and R₃ is OH in the 1-position.
In process variant (i) the reaction is a standard amide formation reaction involving
e.g.:
1. Activation of a carboxylic acid (e.g. to an acid chloride, mixed anhydride, active ester
or other species), and treatment with an amine (Ogliaruso, M.A.; Wolfe, J.F. in The
Chemistry of Functional Groups (Ed. Patat, S.) Suppl. B: The Chemistry of Acid
Derivatives, Pt 1 (John Wiley and Sons, 1979), pp 442-8; Beckwith, A.L.J. in The
Zabricky, J.) (John Wiley and Sons, 1970), p 73 ff. The acid and amine are preferably
reacted in the presence of an activating agent such as 1-(dimethylaminopropyl)-3-
ethylcarbodiimide hydrochloride (EDC) or 1-hydroxybenzotriazole (HOBT) or O-(7-
azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU); or
2. The specific methods of:
a. in situ conversion of an acid into the amine component by a modified Curtius reaction
b. in situ conversion of the acid component into the acid chloride under neutral conditions
In process variant (ii) the reaction is a standard reductive alkylation using, e.g.,
sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride
(Gribble, G. W. in Encyclopedia of Reagents for Organic Synthesis (Ed. Paquette, L. A.)
(John Wiley and Sons, 1995), p 4649).
In process variant (iii) the X=OH and Y=CH₂OH groups can be reacted directly
by activation with 1,3-dicyclohexylcarbodiimide (DCC) (Chem. Berichte 1962, 95, 2997
or Angewante Chemie 1963 75, 377), or the X=OH compound is reacted with a base, for
example sodium hydride, followed by reaction with a methylcyclohexane-derived
alkylating agent, such as a cyclohexylmethyl methanesulphonate. The latter may be
prepared from a hydroxymethyl cyclohexane (prepared from the corresponding acid by
reduction with e.g. borane-dimethylsulphide complex) by treatment with
methanesulphonyl chloride and triethylamine.
The process variant (iv) is a standard alkylation reaction well known to those skilled in the art, for example where an alcohol or amine is treated with an alkyl halide in the presence of a base (for example see March, J; Advanced Organic Chemistry, Edition 3 (John Wiley and Sons, 1985), p364-366 and p342-343). The process is preferably carried out in a polar solvent such as N,N-dimethylformamide.

In process variant (iv) where one of X and Y contains \( \text{NHR}^{11} \) the leaving group W is halogen and the reaction is a standard amine formation reaction such as direct alkylation described in (Malpass, J. R., in Comprehensive Organic Chemistry, Vol. 2 (Ed. Sutherland, I. O.), p 4 ff.) or aromatic nucleophilic displacement reactions (see references cited in Comprehensive Organic Chemistry, Vol. 6, p 946-947 (reaction index); Smith, D. M. in Comprehensive Organic Chemistry, Vol. 4 (Ed. Sammes, P. G.) p 20 ff.). This is analogous to the methods described in GB 1177849.

In process variant (iv) where one of X and Y contains OH, this is preferably converted to an OM group where M is an alkali metal by treatment of an alcohol with a base. The base is preferably inorganic such as NaH, lithium diisopropylamide or sodium, or, metal alkoxide such as sodium methoxide. The leaving group W is a halogen, methanesulphonyloxy, ethanesulphonyloxy or trifluoromethanesulphonyloxy. The reaction may be carried out as described in Chapman et al., J. Chem Soc., (1956), 1563, Gilligan et al., J. Med. Chem., (1992), 35, 4344, Aloup et al., J. Med. Chem. (1987), 30, 24, Gilman et al., J.A.C.S. (1949), 71, 3667 and Clinton et al., J.A.C.S. (1948), 70, 491, Barluenga et al., J. Org. Chem. (1987) 52, 5190. Alternatively where X is OH and Y is CH\(_2\)W, W is a hydroxy group activated under Mitsunobu conditions (Fletcher et al. J Chem Soc. (1995), 623).

In process variant (v) the reaction is as described in den Hertog et. al., Recl.Trav. Chim. Pays-Bas, (1950), 69, 700.

In process variant (vi) the leaving group W is preferably chloro, bromo or trifluoromethylsulphonyl and the reaction is the palladium catalysed process known as the "Buchwald" reaction (J. Yin and S. L. Buchwald, Org.Lett., 2000, 2, 1101). This utilizes a suitable palladium catalyst/ligand combination, for example tris(dibenzyldenediacetone)dipalladium(0) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos), and a base, for example caesium carbonate.

In process variant (vii) the process is the standard epoxide opening of the epoxide (III) with the anion OM where M is an alkali metal, formed by treatment of the alcohol (II) where X=OH with a base. The base is preferably inorganic such as NaH, lithium diisopropylamide or sodium, or, metal alkoxide such as sodium methoxide. The epoxide (III) is obtainable from the corresponding ketone (Y and R\(^3\) together form an oxo group) using the reaction described in Corey et al. Org. Synth. Coll. 5, 755 (1973).
An amide group A'-B' may be reduced to the corresponding amine using a reducing agent such as lithium aluminium hydride.

An example of a group Q¹ convertible to NR² R⁴ is NR²'R⁴' or halogen. Halogen may be displaced by an amine HNR²' R⁴' by a conventional displacement reaction.

When Q¹ Q² together form a protected oxo group this may be an acetal such as ethylenedioxy which can subsequently be removed by acid treatment to give a compound of formula (X):

\[
\begin{align*}
\text{CH}_3 \\
\text{O} & \text{N} \\
R^{1a} & R^{1b} \\
Z^1 & Z^2 \\
R^{4a} & R^{4b} \\
A-B & 1 \ 2 \ 3 \ 4 \ 
\end{align*}
\]

(X)

wherein the variables are as described for formula (I). The ketone of formula (X) is reacted with an amine HNR²' R⁴' by conventional reductive alkylation as described above for process variant (iv).

Other intermediates are of formula (XI):

\[
\begin{align*}
\text{NH}_2 \\
\text{O} & \text{N} \\
R^{1a} & R^{1b} \\
Z^1 & Z^2 \\
R^{4a} & R^{4b} \\
A-B & 1 \ 2 \ 3 \ 4 \ 
\end{align*}
\]

(XI)

Intermediates of formula (X) and (XI) are novel and as such form part of the invention.

Conveniently one of R²' and R⁴' is an N-protecting group, such as such as t-butoxycarbonyl, benzoyloxycarbonyl, 9-fluorenylemethylxycarbonyl or trifluoroacetyl. This may be removed by several methods well known to those skilled in the art (for examples see "Protective Groups in Organic Synthesis", T.W. Greene and P.G.M. Wuts, Wiley-Interscience, 1999), for example conventional acid hydrolysis (e.g. trifluoroacetic acid/dichloromethane, hydrochloric acid/dichloromethane/methanol), or potassium carbonate/methanol, liberation of the aminocyclohexane free base (conveniently using a polymer-bound carbonate base), and the free amine converted to NR²'UR⁵' by conventional means such as amide formation with an acyl derivative R⁵'COW, for compounds where U is CO or, where U is CH₂, by alkylation with an alkyl halide R⁵'CH₂-halide in the presence of base, acylation/reduction with an acyl derivative R⁵'COW or reductive alkylation with an aldehyde R⁵'CHO under conventional conditions.
(see for examples Smith, M.B.; March, J.M. Advanced Organic Chemistry, Wiley-Interscience). Suitable conditions include a borohydride reducing agent such as sodium cyanoborohydride (in methanol/chloroform/acetic acid). If the amine (III) is a hydrochloride salt then sodium acetate may be added to buffer the reaction. Sodium triacetoxyborohydride is an alternative reducing agent.


Interconversions of A-B, R^Y, R^W, R^1a, R^1b, R^2, R^3 and/or R^4, are conventional. For example R^1a halo may be introduced by conventional halogenation reactions eg chlorination with chlorosuccinimide in acetic acid to introduce a chloro group at R^1a. In compounds which contain an optionally protected hydroxy group, suitable conventional hydroxy protecting groups which may be removed without disrupting the remainder of the molecule include acyl and alkylsilyl groups. N-protecting groups are removed by conventional methods.

R^1a methoxy is convertible to R^1a hydroxy by treatment with lithium and diphenylphosphine (general method described in Ireland et al. J. Amer. Chem. Soc., 1973, 7829) or HBr. Alkylation of the hydroxy group with a suitable alkyl derivative bearing a leaving group such as halide, yields R^1a substituted alkoxy. R^1a halogen is convertible to other R^1a by conventional means, for example to hydroxy, alkylthio (via thiol) and amino using metal catalysed coupling reactions, for example using copper as reviewed in Synlett (2003), 15, 2428-2439 and Angewandte Chemie, International Edition, 2003, 42(44), 5400-5449.

R^1a^ and R^1b^ are preferably R^1a and R^1b.

R^3^ is R^3 or more preferably hydrogen or hydroxy. Conversions of R^3^ to R^3^ and interconversions of R^3^ are carried out conventionally, for example as described in WO2004002992 or WO2003087098.
It will be appreciated that under certain circumstances interconversions may interfere, for example, hydroxy groups or amine groups will require protection e.g. as a carboxy- or silyl-ester group for hydroxy and as an acyl derivative for nitrogen, during conversion of R'1a, R'1b, R'2, R'3 and R'4, or during the coupling of the compounds of formulae (II) and (III).

Compounds of formula (II) are known compounds or may be prepared analogously to known compounds. For example compounds of formula (II) in which X is OH, Br or CHO, Z1 is CH and Z2 is N may be prepared from compounds of formula (IV):

\[
\text{CH}_3\text{O} \quad \text{N}^{\text{X}} \quad \text{R}^{\text{1a}} \\
\text{R}^{\text{1b}} \quad \text{Z}^{\text{1}} \quad \text{Z}^{\text{2}}
\]

(IV)

where Z1 is CH, Z2 is N, X' is OH (IVa), see for example WO2008006648.

Compounds of formula (II) where X is NH2 (VII) may be prepared by the following Scheme 1, from a compound of formula (IV) where X' is NH2 (IVc) (itself prepared from the 4-bromo analogue (IVb) by heating with n-propylamine hydrochloride in pyridine):

\[
\text{CH}_3\text{O} \quad \text{N}^{\text{NH}_2} \quad \text{B}^{\text{1a}} \\
\text{R}^{\text{1b}} \quad \text{Z}^{\text{1}} \quad \text{Z}^{\text{2}}
\]

(IVb)

\[
\text{O} \quad \text{C}^{\text{N}^{\text{NH}_2}} \quad \text{R}^{\text{1b}}
\]

(V)

\[
\text{O} \quad \text{N}^{\text{NH}_2} \\
\text{R}^{\text{1b}}
\]

(VI)

Scheme 1

A preparation of compounds of formula (IV) where Z1 is CH, Z2 is N, X is OH and R'1a is fluoro (IVd) is shown below in Scheme 2.
Scheme 2

2-Chloro-6-alkoxy-4-nitropyridine (XIIa) is ethoxyvinylated using 1-
(ethoxyvinyl)tributylstannane in the presence of dichlorobis(diphenylphosphine)
palladium(II). The resulting vinyl ether (XIIb) is fluorinated with a fluorinating agent
such as 1-chloromethyl-4-fluoro-1,4-diazoniumbicyclo[2.2.2]octane bis
(tetrafluoroborate) Selectfluor® and the resulting fluoroketone (XIII) is treated with
dimethylformamide diethylacetal to give dimethylaminovinyl ketone (XIV). This is then
hydrogenated to reduce the nitro group and cyclised by treatment with hydrochloric acid
to give the 3-fluoro-4-hydroxynaphthyridine (IVd).

Compounds of formula (II) in which Z¹ and Z² are N and X=OH may be
prepared by the following Scheme 3:
PMB = para-methoxy benzyl

2,4-pyridinediol 1 is mono-nitrated with, for example nitric acid and converted to the corresponding 2,4-dichloro-3-nitropyridine 3 using standard conditions with a chlorinating agent such as phosphorus oxychloride. Disubstitution by a nucleophilic fluoride source such as potassium fluoride followed by mono-substitution by an alkoxide anion delivers the ether 5. A protected glycine is introduced under thermal conditions followed by selective reduction of the nitro group with a suitable reducing agent such as zinc in acetic acid, to give the amine 7. Standard N-methylation with e.g. methyl iodide followed by acid-mediated cyclisation/deprotection delivers 8-hydroxy-1-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one 9. The final step is oxidation using a mild oxidant such as activated manganese dioxide to deliver 8-hydroxy-1-methyl(pyrido[2,3-b]pyrazin-2(1H)-one 10.

Other compounds of formula (II) may be prepared conventionally. For example a 4-hydroxy derivative of formula (II) can be converted to the 4-methanesulphonyloxy or 4-trifluoromethanesulphonyloxy derivative by reaction with methanesulphonyl chloride or trifluoromethanesulphonic anhydride, respectively, in the presence of an organic base.
The 4-amino derivatives of formula (II) may be prepared as described in Scheme 1, or by conventional procedures from a corresponding 4-halo, 4-methanesulphonyloxy or 4-trifluoromethanesulphonyloxy derivative by treatment with ammonia (O.G. Backeberg et. al., J. Chem Soc., 381, 1942) or propylamine hydrochloride (R. Radinov et. al., Synthesis, 886, 1986).

The compound of formula (II) where X is –CHO may be prepared from a corresponding 4-vinyl derivative-CH₂=CH₂ by ozonolysis followed by decomposition of the ozonide by conventional means, e.g. dimethylsulfide (Me₂S).

4-Vinyl derivatives may be prepared by conventional procedures from a corresponding 4-halogeno derivative of formula (II) by e.g. a Heck synthesis as described in e.g. Organic Reactions, 1982, 27, 345. Alternatively 4-vinyl derivatives may be prepared from the 4-bromo derivative of formula (II) by conventional procedures such as a Suzuki reaction via trivinylcyclotriboroxane (J. Org. Chem. 2002, 67, 4968-4971), see also WO2008006648.

4-Vinyl derivatives may be converted to 4-hydroxymethyl compounds of formula (II) by ozonolysis with sodium borohydride to decompose the ozonide.

4-Carboxaldehyde and 4-hydroxymethyl derivatives of compounds of formula (II) may be prepared by reduction of 4-carboxy derivatives which may themselves be prepared by conventional procedures for preparation of carboxy heteroaromatics well known to those skilled in the art, for example by carbylation of the corresponding 4-bromo or 4-trifluoromethanesulphonyloxy derivative using a palladium catalyst. These 4-carboxy derivatives may be activated by conventional means, e.g. by conversion to an acyl halide or anhydride.

4-Carboxy derivatives such as esters may be reduced to the 4-carboxaldehyde and 4-hydroxymethyl derivatives with for example lithium aluminium hydride or sodium borohydride. Reaction of the 4-hydroxymethyl derivative with mesyl chloride and triethylamine would give the mesylate derivative, while halogenation with phosphorus oxychloride or triphenylphosphine/carbon tetrachloride would give the halomethyl derivative. The 4-carboxaldehyde may be obtained from the acid or 4-alkenyl derivative by standard procedures well known to those skilled in the art.

4-Aminomethyl derivatives of formula (II) may be prepared from a 4-CH₂W derivative by displacement with sodium azide to give 4-CH₂N₃ followed by conventional reduction of the azide, or by displacement of the leaving group W with sodium or potassium succinimide followed by cleavage with eg hydrazine or methylhydrazine to give the amine (Gabriel synthesis).
4-Bromo derivatives may be reacted with sodium malonate in DMF to give the malonate which is decarboxylated with eg lithium chloride in wet DMSO, to give the mono-ester (4-carboxymethyl ester).

Conversions of R₁a', R₁b', R₂', R₃' and/or R₄' may be carried out on the intermediates of formulae (II) and (III) prior to their reaction to produce compounds of formula (I) in the same way as described above for conversions after their reaction.

Compounds of formula (II), (III) and (IV) are known compounds or may be prepared analogously to known compounds, see for example WO2008006648 for compounds of formula (II), WO2003087098 and WO2004002992 for compounds of formula (III) and WO2004058144, WO0021948, WO2002096907, WO2003087098, WO2003010138 and WO2008006648 for compounds of formula (IV).

Further details for the preparation of compounds of formula (I) are found in the examples.

The antibacterial compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibacterials.

The pharmaceutical compositions of the invention may be formulated for administration by any route and include those in a form adapted for oral, topical or parenteral use and may be used for the treatment of bacterial infection in mammals including humans.

The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The
tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-1000 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to about 1.5 to about 50 mg/kg per day. Suitably the dosage is from 5 to 30 mg/kg per day.
The compound of formula (I) may be the sole therapeutic agent in the compositions of the invention or a combination with other antibacterials. If the other antibacterial is a β-lactam then a β-lactamase inhibitor may also be employed.

Compounds of formula (I) may be used in the treatment of bacterial infections caused by a wide range of organisms including both Gram-negative and Gram-positive organisms, such as upper and/or lower respiratory tract infections, skin and soft tissue infections and/or urinary tract infections. Compounds of formula (I) may be also used in the treatment of tuberculosis caused by Mycobacterium tuberculosis. Some compounds of formula (I) may be active against more than one organism. This may be determined by the methods described herein.

The following examples illustrate the preparation of certain compounds of formula (I) and the activity of certain compounds of formula (I) against various bacterial organisms including Mycobacterium tuberculosis.
Examples and Experimental

General

Abbreviations in the examples:
MS = mass spectrum
ES = Electrospray mass spectroscopy
HPLC = High Performance Liquid Chromatography
MDAP or Mass directed autoprep = mass directed preparative HPLC
Psi = pounds per square inch. 1 psi = 0.069 bar or 6.9 kPa
rt = room temperature

Certain reagents are also abbreviated herein. DMF refers to dimethylformamide,
TFA refers to trifluoroacetic acid, THF refers to tetrahydrofuran, Pd/C refers to palladium
on carbon catalyst, DCM refers to dichloromethane, MeOH refers to methanol, Et2O
refers to diethyl ether, EtOAc refers to ethyl acetate. DIAD refers to diisopropyl
azodicarboxylate.

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 400 or
250 MHz, and chemical shifts are reported in parts per million (δ) downfield from the
internal standard tetramethylsilane (TMS). Abbreviations for NMR data are as follows: s =
singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt =
doublet of triplets, app = apparent, br = broad. CDCl₃ is deuteriochloroform, DMSO-d₆
is hexadeuteriodimethylsulfoxide, and CD₃OD is tetadeuteriomethanol. Mass spectra
were obtained using electrospray (ES) ionization techniques. All temperatures are
reported in degrees Celsius.

MP-carbonate refers to macroporous triethylammonium methylpolystyrene
carbonate (Argonaut Technologies).

The SCX (Strong Cation eXchange) column has benzene sulphonic acid
covalently attached to a silica support and as such strongly retains high pKₐ (ie basic)
organic molecules such as amines, which can be subsequently liberated with excess
ammonia in an appropriate solvent.

As will be understood by the skilled chemist, references to preparations carried
out in a similar manner to, or by the general method of, other preparations, may
encompass variations in routine parameters such as time, temperature, workup conditions,
minor changes in reagent amounts etc.

Reactions involving metal hydrides including lithium hydride, lithium aluminium
hydride, di-isobutylaluminium hydride, sodium hydride, sodium borohydride and sodium
triacetoxyborohydride are carried out under argon or other inert gas.
Example 1 6-[(trans-4-[(3-Fluoro-5-methyl)-6-oxo-5,6-dihydro-1,5-naphththyridin-4-yl)oxy]methyl[cyclohexyl]amino]-methyl]-2H-pyrido[3,2-b][1,4]thiazin-3(4H)-one hydrochloride

(a) 2-[1-(Ethoxy)ethenyl]-6-(methylxy)-3-nitropyridine

2-Chloro-6-methoxy-3-nitropyridine (600g, 3.18mol) and dichlorobis(triphenylphosphine)palladium (II) (33.5g, 477mmol) were dissolved in acetonitrile (4200ml). The yellow coloured suspension was heated to 65°C and (1-ethoxyvinyl)-tributyl-stannane (1182ml, 1264g) was added dropwise over 2 hours, maintaining the temperature at ~65°C by the rate of addition. The resulting brown coloured suspension was left to stir at 65°C for 4 hours then left to cool to room temperature, with stirring, overnight.

The reaction mixture was quenched with 10% potassium fluoride aq. solution (3600ml) with vigorous stirring and left to stir for 1 hour. The resulting solid was removed by vacuum filtration and washed with acetonitrile (2 x 3000ml). The layers were separated and the organic layer was evaporated to 3000ml. This was filtered, ethyl acetate (3600ml) was added and the volume reduced by rotary evaporation to 1800ml. Cyclohexane (3600ml) was added and the volume reduced by rotary evaporation to 3000ml. Cyclohexane (2400ml) and silica gel (600g) were added and allowed to stir at r.t. for 1.5 h. The solid was removed by vacuum filtration and washed with ethyl acetate:cyclohexane, 1:8 (4200ml). The filtrate was reduced to 1800 ml. The last four steps were repeated, and finally the solvents were evaporated. Acetonitrile (2000ml) was added and evaporated to give an orange coloured oil (730.3g, 102.4%).

1H NMR confirmed correct structure with ~8% MeCN.

(b) 2-Fluoro-1-[6-(methylxy)-3-nitro-2-pyridinyl]ethanone

1-Chloromethyl-4-fluoro-1,4-diazoniumbicyclo[2.2.2]octane bis(tetrafluoroborate (Selectfluor®)) (1300g, 3.67mol) was dissolved in acetonitrile (2060ml) and water (820ml). A solution of 2-[1-(ethoxy)ethenyl]-6-(methylxy)-3-nitropyridine (730g, 3.18mol) in acetonitrile (1425ml) was added dropwise to the white suspension over 1.5h, maintaining the temperature below 15°C using an ice/water bath. The resulting yellow coloured solution was left to stir at r.t. overnight. The reaction mixture was quenched with sat. aq. sodium bicarbonate (2140ml) and left to stir for 30 minutes. The volume was reduced by rotary evaporation to 3250ml. To the resulting yellow suspension was
added ethyl acetate (4400ml) and water (720 ml) and this was stirred for 15 min. The layers were separated and the aqueous extracted with ethyl acetate (2 x 1000ml). The organic layers were combined and washed with water (1000ml) and sat. brine (1000ml). The organic layer was dried over MgSO₄ (269g), filtered and evaporated. Acetonitrile (1000ml) was added and evaporated to give an orange oil (715.4g, 105.0%)

(c) 3-(Dimethylamino)-2-fluoro-1-[6-(methyloxy)-3-nitro-2-pyridinyl]-2-propen-1-one

To a solution of 2-fluoro-1-[6-(methyloxy)-3-nitro-2-pyridinyl]ethanone (715.4g, 3.18moles maximum) in toluene (2700 ml) was added N,N-dimethylformamide dimethylacetal (1550ml). The solution turned dark brown in colour. The reaction mixture was heated to 50°C and left to stir for 3 hours, under N₂. Product precipitated out after ~1 h. The reaction was stirred for a further 45 min at 50°C. Cyclohexane (2000ml) was added and the reaction mixture left to cool slowly over 1 h, then to 10°C using an ice/water bath. The solid was collected by vacuum filtration and washed with ethyl acetate:cyclohexane, 1:1 (3 x 1000ml), then dried in the oven, under vacuum at 40°C overnight to give a yellow solid (591.5g, 69.0%)

(d) 3-Fluoro-6-(methyloxy)-1,5-naphthyridin-4-ol

3-(Dimethylamino)-2-fluoro-1-[6-(methyloxy)-3-nitro-2-pyridinyl]-2-propen-1-one (591g, 2.20mol) was dissolved in DMF (6100ml) by warming to 40°C and hydrogenated over 5% Pd/C (140g water wet, 59g actual) at 15 psi and 40°C for 2.5h. The reaction mixture was warmed to 60°C and filtered hot to remove the catalyst. Further DMF was added to bring the total volume to 11800ml and the dark yellow solution was cooled to 5°C using an ice/water bath. 6N hydrochloric acid (368ml, 2.20mol) was added dropwise to the reaction mixture over 30 minutes, with temperature maintained below 10°C. The reaction was allowed to warm to room temperature and left to stir overnight. The volume was reduced to ~4000ml by rotary evaporation at 50°C. The yellow suspension was cooled to 10°C using an ice/water bath. Water (5900ml) was added slowly over 30 minutes, temperature maintained below 15°C. The reaction mixture was stirred vigorously for 30 minutes at 7°C. The solid was collected by vacuum filtration and washed with water (2950ml) then ethyl acetate:cyclohexane, 1:1 (3 x 2000ml), then dried in the oven, under vacuum at 50°C for 4 days to give a pale brown solid (339.8g, 79.7%).

MS: m/z 195.0 [MH⁺], 216.9 [MNa⁺].

(e) 10-Fluoro-2,2-dimethyl-2,3-dihydro-5H-[1,4,2]oxazasilino[6,5,4-de]-1,5-naphthyridin-5-one
To a solution of 3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-ol (15g, 77.25mmol) in dry dimethyl formamide (500ml) was added sodium hydride (60% in oil, 6.18g, 154.5mmol) in portions. The mixture was stirred for 1.5h, then chloro(chloromethyl)dimethylsilane (19.5ml, 136.35mmol) was added dropwise by syringe. The mixture was stirred for 1h at room temperature, then heated at 100°C overnight. Solvent was evaporated, toluene was added and evaporated, and the residue was dissolved in dichloromethane/methanol and evaporated onto silica gel. Chromatography on silica, eluting with 5-20% methanol/dichloromethane, gave the title compound (16.0g, 83%). MS (+ve ion electrospray): m/z 251 [MH⁺].

(f) 7-Fluoro-8-hydroxy-1-methyl-1,5-naphthyrid-2(1H)-one
    10-Fluoro-2,2-dimethyl-2,3-dihydro-5H-[1,4,2]oxazasilino[6,5,4-de]-1,5-naphthyridin-5-one (16.03g, 64.1mmol) and caesium fluoride (29.0g, 192mmol) were stirred at 85°C (external temp.) in 1,4-dioxine (700ml) and methanol (350ml) for 4 days. Solvent was evaporated and the residue was dissolved in a minimal volume of water and methanol. The resulting solution was acidified to pH4 with dil. HCl and the solid product was filtered off, washed with a little water and methanol and dried under vacuum at 60°C to give the title compound (12.97g, 100%). MS (+ve ion electrospray): m/z 195 [MH⁺].

(g) 1,1-Dimethylethyl [trans-4-(hydroxymethyl)cyclohexyl]carbamate
    trans-4-[[[1,1-Dimethylethyl]oxy]carbonyl]amino)cyclohexanecarboxylic acid (commercially available or for a preparation see Example 18A(a)) (19.1g) in THF (300ml) was treated dropwise with borane-dimethyl sulphide (2M in THF, 43.2ml, diluted with 200ml THF). The mixture was stirred briefly then left overnight before evaporation. The residue was dissolved in methanol and evaporated again. This was repeated twice before chromatography on silica, eluting with 50-100% ether/hexane, to give the alcohol (12.3g, 68%).

(h) [trans-4-[[[1,1-Dimethylethyl]oxy]carbonyl]amino)cyclohexyl]methyl methanesulfonate
    A solution of 1,1-dimethylethyl [trans-4-(hydroxymethyl)cyclohexyl]carbamate (6.1g, 26.6mmol) and triethylamine (3.66ml) in dichloromethane (240ml) was cooled in ice and methanesulfonyl chloride (2.07ml) was added by syringe. The mixture was stirred for 1h while warming to room temperature, then left overnight. The mixture was washed with aq. sodium bicarbonate, the aqueous phase was extracted twice with
dichloromethane and the organic fractions were dried and evaporated to give the methanesulfonate (8.2 g).

MS (†ve ion electrospray): m/z 330 [MNa⁺], 252 [(MH⁺)-C₄H₈].

(i) 1,1-Dimethylethyl (trans-4-[[3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl]oxy]methyl)cyclohexyl carbamate

A suspension of 7-fluoro-8-hydroxy-1-methyl-1,5-naphthyridin-2(1H)-one (0.30 g) in dry DMF (25 ml) was treated portionwise with sodium hydride (60% suspension in oil; 78 mg) and the mixture was heated at 50°C (with occasional sonication) for 30 minutes. [trans-4-[[1,1-Dimethylethyl]oxy]carbonyl]amino)cyclohexyl)methyl methanesulfonate (0.474 g) was added and the mixture was heated at 110°C for 48 hours, cooled, evaporated, quenched with water, extracted with chloroform and dried (sodium sulphate). The product was chromatographed on silica (methanol-DCM) to afford an oil (0.30 g).

LC/MS (†ve ion electrospray): m/z 406 [MH⁺], 428 [MNa⁺].

Alternative synthesis of intermediate of Example 1(i)

(1) [trans-4-[[1,1-Dimethylethyl]oxy]carbonyl]amino)cyclohexyl)methyl ethanesulfonate

A partial solution of (1,1-dimethylethyl [trans-4-(hydroxymethyl)cyclohexyl]carbamate (for a preparation see Example 1(g)) (3.3905 g, 14.79 mmol) in dry dichloromethane (100 ml) was stirred and cooled in ice and treated with triethylamine (2.081 ml, 14.93 mmol) followed by ethanesulphonyl chloride (1.415 ml, 14.93 mmol) added dropwise. The resulting cloudy solution was stirred for 0.5 hrs then allowed to warm to 21°C and stirred thus for 4 hrs then stood overnight. The reaction was washed with sat aq NaHCO₃ solution and the aqueous phase extracted with DCM (x2). The combined organic fractions were washed with brine, dried (Na₂SO₄) and evaporated in vacuo to give a white solid (4.88 g, 103%). This was used in subsequent reactions without further purification.

MS (ES+) m/z 322 [MH⁺].

(2) 1,1-Dimethylethyl (trans-4-[[3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl]oxy]methyl)cyclohexyl carbamate

A suspension of 7-fluoro-8-hydroxy-1-methyl-1,5-naphthyridin-2(1H)-one (for a preparation see Example 1(f)) (100 mg, 0.515 mmol) in dry N,N-dimethylformamide (15 mL) was stirred at 21°C and treated with potassium carbonate (78 mg, 0.567 mmol). The resulting slight suspension was heated at 60°C (bath temp) for 30 mins then ([trans-4-
(1,1-dimethyl-ethoxy)carbonyl-amino)cyclohexyl)methyl ethanesulfonate (166 mg, 0.515 mmol) added. The resulting mixture was then heated at 120 °C overnight. The reaction was then allowed to cool, evaporated in vacuo, quenched with water and extracted with CHCl₃, then 10% MeOH/CHCl₃ (x2). The combined organic fractions were washed with brine, dried (Na₂SO₄) and evaporated in vacuo to give a brown gum (210 mg) which was purified on a silica column using DCM/MeOH (100/0-90/10) as a gradient eluent which gave a pale yellow oil which crystallised (149 mg, 71%). MS (ES+) m/z 406 [MH⁺].

(j) 8-[(trans-4-aminocyclohexyl)methoxy]-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one hydrochloride

1,1-Dimethyl ethyl (trans-4-[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl)cyclohexyl carbamate (0.40 g) in dry methanol (10 ml) and dry DCM (20 ml) was treated with 4 M HCl in 1,4-dioxane (20 ml), stirred at room temperature for 2 hours and evaporated to give a solid. LC/MS (+ve ion electrospray): m/z 306 [MH⁺].

(k) Title compound

8-[(trans-4-Aminocyclohexyl)methoxy]-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one hydrochloride (60 mg) was dissolved in dry methanol (2 ml), chloroform (2 ml) and acetic acid (6 drops). Anhydrous sodium acetate (115 mg) was added followed by 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-carboxaldehyde (for a synthesis see WO2004058144, Example 7(d)) (45.4 mg) and excess 3A molecular sieves. The mixture was stirred at room temperature for 2.5 hours then sodium cyanoborohydride (50 mg) was added and the mixture was stirred at room temperature for 3.5 hours. Aqueous sodium carbonate was added and the mixture extracted with dichloromethane, dried (sodium sulphate), evaporated and chromatographed on silica gel (0-15% methanol-DCM) to afford the free base. It was treated with 4 M hydrogen chloride in 1,4-dioxane and the solution was evaporated to give the title compound (37 mg), after trituration with ether. ¹H NMR (CD₃OD) δ 1.35 (2H, q), 1.55 (2H, q), 2.00 (1H, br.s) 2.13 (2H, d), 2.31 (2H, d), 3.22 (1H, m), 3.58 (2H, s), 3.94 (3H, s), 4.16 (2H, m), 4.33 (2H, s), 6.86 (1H, d), 7.12 (1H, s), 7.82 (1H, d), 7.90 (1H, d), and 8.48 (1H, s). LC/MS (+ve ion electrospray): m/z 484 [MH⁺].

Example 2. 6-[(trans-4-[[3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl]methyl]amino)cyclohexyl]amino[methyl]-2H-pyrido[3,2-b][1,4]thiazin-3(4H)-one dihydrochloride
(a) 8-Bromo-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one

A suspension 7-fluoro-8-hydroxy-1-methyl-1,5-naphthyridin-2(1H)-one (for a preparation see Example 1(f)) (12.97g, 66.9mmol) in dimethylformamide (500ml) was cooled in ice and phosphorus tribromide (9.98ml, 105mmol) was added dropwise over 5min. The resulting mixture was stirred for 3.75h at room temperature, then evaporated. Toluene was added and evaporated off, then the residue was cooled in ice, treated cautiously with aq. sodium bicarbonate until basic, then extracted four times with dichloromethane. The extracts were dried and evaporated to give the title compound (14.75g, 86%).

MS (+ve ion electrospray): \textit{m/z} 257 & 259 [MH\textsuperscript{+}].

(b) 8-Ethynyl-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one

A solution of 8-bromo-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one (2.0g, 7.81mmol) in 1,2-dimethoxyethane (80ml) was flushed with argon, then tetrakistriphenylphosphine)palladium (0) (0.53g, 0.44mmol), potassium carbonate (1.31g), triethylinboroxin pyridine complex (1.69g, 7.11mmol) and water (20ml) were added. The mixture was heated under reflux for 6h, then water and diethyl ether were added and the phases were separated. The aqueous phase was extracted with ether three times, and the combined organic fractions were dried and evaporated. Chromatography on silica, eluting with 0-100% ethyl acetate/hexane, gave the title compound (1.62g, 100%).

MS (+ve ion electrospray): \textit{m/z} 205 [MH\textsuperscript{+}].

(c) 3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridine-4-carbaldehyde

A solution of 8-ethynyl-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one (0.47g, 2.3mmol) in dichloromethane (100ml) was cooled to -78\textdegree C and ozone in oxygen was passed through the solution for 1h. The mixture was flushed with oxygen and argon, then methyl sulfide (12ml) was added and the mixture was allowed to warm to room temperature overnight. The mixture was diluted with dichloromethane and washed with brine/sodium bicarbonate. The aqueous phase was extracted thoroughly with dichloromethane, and the combined organic fractions were dried and evaporated. Chromatography on silica, eluting with 0-10% methanol/dichloromethane, gave the title compound (90mg, 19%).
MS (+ve ion electrospray): $m/z$ 207 [MH$^+$].

(d) 1,1-Dimethyl ethyl (trans-4-[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)methyl]amino)cyclohexyl) carbamate

3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridine-4-carbaldehyde (90mg, 0.44mmol) and 1,1-dimethyl ethyl (trans-4-aminocyclohexyl) carbamate hydrochloride (165mg, 0.66mmol) were stirred overnight in dry chloroform/methanol (1:1, 6ml) with sodium acetate (270mg), acetic acid (10 drops) and 3A molecular sieves. Sodium cyanoborohydride (82mg) was added and the mixture was stirred for 6h, then basified with aq. sodium bicarbonate and extracted well with dichloromethane. The extracts were dried and evaporated. Chromatography on silica, eluting with 0-2% methanol/dichloromethane, gave the title compound as a solid (120mg, 67%).

MS (+ve ion electrospray): $m/z$ 405 [MH$^+$], 349 [(MH$^+$)-C$_4$H$_8$]

(e) 8-[(trans-4-Aminocyclohexyl)amino]methyl]-7-fluoro-1-methyl-1,5-naphthyridine-2(1H)-one

A solution of 1,1-dimethyl ethyl (trans-4-[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)methyl]amino)cyclohexyl) carbamate (120mg, 0.3mmol) in dichloromethane (2ml) was treated dropwise with trifluoroacetic acid (2ml). After standing at room temperature for 1.75h, the mixture was evaporated. The residue was triturated twice with ether, then dissolved in dichloromethane/methanol (30-40ml) and stirred with MP-carbonate resin (1.2mmol) until the mixture was basic to damp pH indicator paper. The resin was filtered off, washed several times alternately with 10% dichloromethane/methanol and methanol and the liquors evaporated to give the title compound (114mg, approx. 80% pure).

MS (+ve ion electrospray): $m/z$ 305 [MH$^+$], 288 [(MH$^+$)-NH$_3$].

(f) Title compound

8-[(trans-4-Aminocyclohexyl)amino]methyl]-7-fluoro-1-methyl-1,5-naphthyridine-2(1H)-one (0.15mmol) and 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-carboxaldehyde (for a synthesis see WO 2004058144 Example 7(d)) (29mg, 0.15mmol) were stirred for 1.75h in dry chloroform/methanol (1:1, 4ml) with acetic acid (6 drops) and 3A molecular sieves. Sodium cyanoborohydride (34mg) was added and the mixture was stirred for 4.5h, then basified with aq. sodium bicarbonate and extracted well with dichloromethane/methanol. The extracts were dried and evaporated. Chromatography on silica, eluting with 0-20% methanol/dichloromethane, gave the free base of the title compound (31mg, 43%).
$^1$H NMR (250 MHz, CDCl$_3$) δ 8.39 (1H, s), 7.84 (1H, d), 7.58 (1H, d), 6.97 (1H, d), 6.86 (1H, d), 4.08 (3H, s), 4.04 (2H, d), 3.56 (2H, s), 3.49 (2H, s), 2.58 (1H m), 2.51 (1H m), 2.05 (4H, m), 1.23 (4H, m).

MS (+ve ion electrospray): m/z 483 [MH$^+$].

The free base was treated with 2 mole equivalents of 0.4M hydrogen chloride in 1,4-dioxane to give the title dihydrochloride salt (34mg).

**Example 3. 7-Fluoro-1-methyl-8-[[trans-4-[[1,3]oxathiolo[5,4-c]pyridin-6-vlmethyl]aminocyclohexyl]methyl]oxy]-1,5-naphthyridin-2(1H)-one hydrochloride**

The title compound was prepared from 8-[[trans-4-aminocyclohexyl)methyl]oxy]-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one hydrochloride (for a preparation see Example 1(j)) (66mg) and [1,3]oxathiolo[5,4-c]pyridine-6-carbaldehyde (39mg) (for a synthesis see WO2004058144, Example 61) by the general method of Example 1(k). The crude product, after work-up, was chromatographed on a reverse-phase HPLC system with mass-directed collection (eluent acetonitrile/water/formic acid, monitoring for m/z 457) followed by treatment with 4M hydrogen chloride in 1,4-dioxane. The solution was evaporated to give the title compound (31 mg), after trituration with ether.

$^1$H NMR (CD$_3$OD) δ 1.35 (2H, q), 1.55 (2H, q), 2.00 (1H, br.s) 2.13 (2H, d), 2.30 (2H, d), 3.22 (1H, m), 3.58 (2H, s), 3.94 (3H, s), 4.20 (2H, m), 4.32 (2H, s), 5.90 (2H, s), 6.90 (1H, d), 7.48 (1H, s), 7.50 (1H, d), 8.10 (1H, d), and 8.54 (1H, s).

LC/MS (+ve ion electrospray): m/z 457 [MH$^+$].

**Example 4. 7-Fluoro-1-methyl-8-[[trans-4-[[1,3]oxathiolo[5,4-c]pyridin-6-vlmethyl]aminocyclohexyl]amino]methyl]-1,5-naphthyridin-2(1H)-one dihydrochloride**

8-[[trans-4-Aminocyclohexyl]amino]methyl]-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one (for a preparation see Example 2(c)) (0.15mmol) and [1,3]oxathiolo[5,4-c]pyridine-6-carbaldehyde (for a synthesis see WO2004058144.

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Example 61) (25mg, 0.15mmol) were stirred overnight in dry chloroform/methanol (1:1, 4ml) with acetic acid (6 drops) and 3A molecular sieves. Sodium cyanoborohydride (34mg) was added and the mixture was stirred for 6h, then diluted with dichloromethane and basified with aq. sodium bicarbonate. The aqueous phase was extracted a few times with dichloromethane/methanol, and the combined organic fractions were dried and evaporated. Chromatography on silica, eluting with 0-20% methanol/dichloromethane, gave the free base of the title compound (26mg, 38%).

$^1$H NMR (250 MHz, CDCl$_3$) δ 8.38(1H, s), 8.01(1H, s), 7.84(1H, d), 7.19(1H, s), 6.86(1H, d), 5.74(2H, d), 4.08(3H, s), 4.04(2H d), 3.85(2H, s), 2.58(2H m), 2.05(4H, m), 1.23(4H, m).

MS (+ve ion electrospray): m/z 456 [MH$^+$].

The free base was treated with 2 mole equivalents of 0.4M hydrogen chloride in 1,4-dioxane to give the title dihydrochloride salt (30mg).

Example 5 8-[[trans-4-[2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl]amino[cyclohexyl]methyl]oxy]-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one hydrochloride

The title compound was prepared from 8-[[trans-4-aminocyclohexyl)methyl]oxy]-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one hydrochloride (for a preparation see Example 1(j)) (60mg) and 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carboxaldehyde (for a synthesis see WO2004058144 Example 2(c) or WO2003087098 Example 19(d)) (38.5mg), by the general method of Example 1(k). The crude product, after work-up, was chromatographed on a reverse-phase HPLC system with mass-directed collection (MDAP) (eluent acetonitrile/water/formic acid, monitoring for m/z 455) followed by treatment with 4M hydrogen chloride in 1,4-dioxane. The solution was evaporated to give the title compound (41 mg), after trituration with ether.

$^1$H NMR δ(CD$_3$OD) 1.35 (2H, q), 1.55 (2H, q), 2.05 (1H, br.s) 2.13 (2H, d), 2.35 (2H, d), 3.32 (1H, m), 3.96 (3H, s), 4.29 (2H, m), 4.51 (4H, s), 4.64 (2H, m), 6.95 (1H, d), 7.64 (1H, s), 7.91 (1H, d), 8.54 (1H, s), and 8.62 (1H, d).

LC/MS (+ve ion electrospray): m/z 455 [MH$^+$].
Example 6. 3-{{trans-2-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl}oxy[methyl]cyclohexyl}amino[methyl]-5H-pyridazino[3,4-b][1,4]thiazin-6(7H)-one hydrochloride

The title compound was prepared from 8-{{trans-4-aminocyclohexyl)methyl}oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one hydrochloride (for a preparation see Example 1(j)) (80 mg) and 6-oxo-6,7-dihydro-5H-pyridazino[3,4-b][1,4]thiazine-3-carbaldehyde (for a synthesis see WO2004058144, Example 58) (50% pure; 91 mg) by the general method of Example 1(k) (elution with 0-20% methanol-DCM in the silica gel chromatography) to give a yellow solid (31 mg), after conversion to a hydrochloride salt.

$^1$H NMR (400 MHz) (free base) (CDCl$_3$) δ 1.15 (4H, q), 1.87 (1H, br. s) 1.93 (2H, d), 2.10 (2H, d), 2.55 (1H, m), 3.65 (2H, s), 3.92 (3H, s), 4.05 (2H, m), 4.11 (2H, s), 6.87 (1H, d), 7.08 (1H, s), 7.81 (1H, d), and 8.38 (1H, s).

LC/MS (+ve ion electrospray): m/z 485 [MH$^+$].

Example 7. 7-Chloro-6-{{trans-2-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl}oxy[methyl]cyclohexyl}amino[methyl]-2H-pyrido[3,2-b][1,4]oxazine-3(4H)-one hydrochloride

The title compound was prepared from 8-{{trans-4-aminocyclohexyl)methyl}oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one hydrochloride (for a preparation see Example 1(j)) (65 mg) and 7-chloro-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carboxaldehyde (35 mg) (for a synthesis see WO2003064421, Example 15(c)) by the general method of Example 1(k) to give a yellow solid (29 mg), after conversion to the hydrochloride salt.

$^1$H NMR (400 MHz) (free base) (CDCl$_3$) δ 1.15 – 1.35 (4H, m), 1.87 (1H, br.s) 1.93 (2H, d), 2.12 (2H, d), 2.53 (1H, m), 3.92 (3H, s), 3.98 (2H, s), 4.04 (2H, m), 4.65 (2H, s), 6.85 (1H, d), 7.26 (1H, s) (underneath CHCl$_3$ signal), 7.82 (1H, d), and 8.37 (1H, s).

LC/MS (+ve ion electrospray): m/z 502/4 [MH$^+$].
Example 8 6-(((trans-4-[(3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy|methyl|cyclohexyl]amino)methyl)-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one hydrochloride

The title compound was prepared from 8-(((trans-4-aminocyclohexyl)methyl)oxy)-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one hydrochloride (for a preparation see Example 1(j)) (65 mg) and 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carboxaldehyde (29 mg) (for synthesis see WO2004058144, Example 1(h)) by the general method of Example 1(k) to give a yellow solid (56 mg), after conversion to the hydrochloride salt.

1H NMR (400 MHz) (HCl salt) (MeOD) δ 1.32 (2H, q), 1.56 (2H, q), 2.00 (1H, br.s) 2.12 (2H, d), 2.32 (2H, d), 3.22 (1H, m), 3.65 (2H, s), 3.95 (3H, s), 4.25 (2H, m), 4.28 (2H, s), 4.70 (2H, s), 6.92 (1H, d), 7.11 (2H, d), 7.45 (2H, d), 7.90 (1H, d), and 8.59 (1H, s).

LC/MS (+ve ion electrospray): m/z 468 [MH+].

Example 9 7-(((trans-4-[(3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy|methyl|cyclohexyl]amino)methyl)-1H-pyrido[2,3-b][1,4]thiazin-2(3H)-one hydrochloride

The title compound was prepared from 8-(((trans-4-aminocyclohexyl)methyl)oxy)-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one hydrochloride (for a preparation see Example 1(j)) (80 mg) and 2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazine-7-carboxaldehyde (for a synthesis see WO2004058144, Example 48(e)) by the general method of Example 1(k) to give a yellow solid (46 mg) after conversion to the HCl salt.

1H NMR (400 MHz) (free base; CDCl3) δ 1.16 (4H, q), 1.88 (1H, br.s) 1.93 (2H, d), 2.08 (2H, d), 2.50 (1H, m), 3.57 (2H, s), 3.83 (2H, s), 3.92 (3H, s), 4.03 (2H, m), 6.85 (1H, d), 7.20 (1H, s), 7.88 (1H, d), 8.15 (1H, s), and 8.38 (1H, s).

LC/MS (+ve ion electrospray): m/z 484 [MH+].
Example 10 3-[[trans-4-[[3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl]amino[methyl]cyclohexyl]amino[methyl]-5H-pyridazino[3,4-b][1,4]thiazin-6(7H)-one dihydrochloride

(a) 3-Fluoro-6-(methyloxy)-1,5-naphthyridin-4-amine

A mixture of 8-bromo-7-fluoro-2-(methoxy)-1,5-naphthyridine (for a preparation see WO200458144 Ex 53(g)) (25 g), n-propylamine hydrochloride (55 g) in dry pyridine (800 ml) was heated at 115 °C for 4 days, cooled, evaporated and azeotroped (x2) with toluene. Sodium bicarbonate was added and the mixture was extracted with DCM, dried (sodium sulphate), evaporated and chromatographed on silica gel (methanol-DCM) to give the amine (11.0 g) (ca. 75% pure).
LC/MS (+ve ion electrospray): m/z 194 [MH⁺].

(b) 10-Fluoro-2,2-dimethyl-2,3-dihydro-1H,5H-[1,4,2]diazasilino[6,5,4-de]-1,5-naphthyridin-5-one

The title compound was prepared from 3-fluoro-6-(methyloxy)-1,5-naphthyridin-4-amine (1.8 g), sodium hydride (0.58 g), chloro(chloromethyl)dimethylsilane (2.4 ml) in DMF (40 ml) by the general method of Example 1(e) to give a solid.
LC/MS (+ve ion electrospray): m/z 250 [MH⁺].

(c) 8-Amino-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one

The title compound was prepared from crude 10-fluoro-2,2-dimethyl-2,3-dihydro-1H,5H-[1,4,2]diazasilino[6,5,4-de]-1,5-naphthyridin-5-one and caesium fluoride (7.0 g) by the general method of Example 1(f) (heated at 110°C for 24 hours). The crude product was chromatographed on silica gel (methanol-DCM) to give a solid (0.78 g).
LC/MS (+ve ion electrospray): m/z 194 [MH⁺].

(d) 1,1-Dimethylethyl (trans-4-[[3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl]amino[methyl]cyclohexyl]carbamate

The title compound was prepared from 8-amino-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one (0.78 g) and [trans-4-([1,1-dimethylethyl]oxy]carbonyl]amino)cyclohexyl)methyl methanesulfonate (for a preparation see Example 1(h)) (1.365 g) by the general method of Example 1(i) (heated at
110 – 115°C for 48 hours) to give an oil (0.75 g) (after chromatography, and azeotroping with toluene to remove DMF) [contains 20% of mesylate impurity]. LC/MS (+ve ion electrospray): m/z 405 [MH⁺].

(e) 8-[((trans-4-Aminocyclohexyl)methyl]amino]-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one

The title compound was prepared from 1,1-dimethylethyl (trans-4-((3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)amino)methyl)cyclohexylcarbamate (0.8 g) with HCl-1,4-dioxane by the general method of Example 1(j), followed by treatment with MP-carbonate resin (2.8-3.5 mmol/g) (3.0 g) in DCM-methanol (1:1) (50 ml) for 5 hours at room temperature, to give the oily free base. It was chromatographed on silica gel [DCM-methanol-0.88 ammonia (90:9:1)] to give a brown solid (0.34 g). LC/MS (+ve ion electrospray): m/z 305 [MH⁺].

(f) Title compound

The title compound was prepared from 8-[((trans-4-aminocyclohexyl)methyl]amino]-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one (62 mg; 95% purity) and 6-oxo-6,7-dihydro-5H-pyridazino[3,4-b][1,4]thiazine-3-carboxaldehyde (for a synthesis see WO2004058144, Example 58) (50% pure; 76 mg) by the general method of Example 1(k) to give a yellow solid (26 mg) after conversion to the dihydrochloride salt.

\[1H NMR (400 MHz) (free base) (CDCl₃) δ 0.99 (2H, q), 1.10 (2H, q), 1.48 (1H, br. s), 1.82 (2H, d), 2.02 (2H, d), 2.47 (1H, m), 2.95 (2H, m), 3.63 (2H, s), 3.88 (3H, s), 4.05 (2H, m), 4.09 (2H, s), 6.83 (1H, d), 7.10 (1H, s), 7.80 (1H, s), and 8.30 (1H, s).\]

LC/MS (+ve ion electrospray): m/z 484 [MH⁺].

Example 11 8-[((trans-4-((3,4-Dihydro-2H-pyran-2,3-c]pyridin-6-yl)methyl]amino[cyclohexyl]methyl]oxy]-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one hydrochloride

The title compound was prepared from 8-(((trans-4-aminocyclohexyl)methyl]oxy)-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one hydrochloride (for a preparation see Example 1(j)) (65 mg) and 3,4-dihydro-2H-pyran-2,3-c]pyridine-6-carbaldehyde (for a synthesis see WO2004058144, Example 126(e), by the general method of Example 1(k). The chromatographed product was
further purified by chromatography on a reverse-phase HPLC system with mass-directed
collection (eluent acetonitrile/water/formic acid, monitoring for M 452), to give a white
solid (20 mg) after conversion to the title hydrochloride salt.
LC/MS (‘+’ ion electrospray): m/z 453 [MH⁺].

Example 12. 7-Fluoro-1-methyl-8-{[(trans-4-
aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one
hydrochloride

The title compound was prepared from 8-{[(trans-4-
aminocyclohexyl)methyl]oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one
hydrochloride (for a preparation see Example 1(j)) (30 mg) and 7-oxo-5,6,7,8-tetrahydro-
1,8-naphthyridine-2-carboxaldehyde (42 mg) (for a synthesis see WO2003087098,
Example 307(f)) by the general method of Example 1(k). The product was
chromatographed on silica gel (0-15% methanol-DCM) and the second eluted product
was converted to the title hydrochloride salt (16 mg).
LC/MS (‘+’ ion electrospray): m/z 466 [MH⁺].

Example 13. 7-Fluoro-1-methyl-8-{{[(trans-4-[[1,3]oxathiolo[5,4-c]pyridin-6-
ylmethyl]amino)cyclohexyl]methyl}amino}-1,5-naphthyridin-2(1H)-one
dihydrochloride

The title compound was prepared from 8-{{[(trans-4-
aminocyclohexyl)methyl]amino}-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one (for a
preparation see Example 10(e)) (65 mg; 90% purity) and [1,3]oxathiolo[5,4-c]pyridine-6-
carbaldehyde (for a synthesis see WO2004058144, Example 61) (32.5 mg) by the general
method of Example 1(k) (omitting the sodium acetate) to give a pale yellow solid (71 mg)
after conversion to the title dihydrochloride salt.
LC/MS (+‘ve ion electrospray): m/z 456 [MH⁺].
Example 14 8-\{[(cis-4-\{(2,3-Dihydro\{1,4\}dioxino\{2,3-c\}pyridin-7-yl)methyl}amino\}-1-hydroxycyclohexyl\}methyl\}oxy\}-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one dihydrochloride

(a) 1,1-Dimethylmethyl (3s,6s)-1-oxaspiro[2.5]oct-6-ylcarbamate

A solution of trimethylsilphoxonium iodide (7.74g, 35.2 mmol) in dry dimethylsulphoxide (150ml) was treated portionwise with sodium hydride (60% in oil, 1.40g, 35.1 mmol) at 0°C. The mixture was stirred for 30 min. at 0-10°C, then 1,1-dimethylethyl (4-oxocyclohexyl)carbamate (5.0g, 23.5 mmol) was added in portions. The mixture was stirred for 1h at 10-16°C, then refrigerated overnight. After warming to room temperature, water (400ml) was added and the mixture was extracted three times with ether. The extracts were dried and evaporated, and the crude product was recrystallised twice from ethyl acetate/petroleum ether to give a solid (1.93g, 36%). NMR analysis showed <5% other isomer present.

\(^1\text{H NMR} (250 \text{ MHz}, \text{CDCl}_3): 4.47(1\text{H}, \text{br.}), 3.57(1\text{H}, \text{br.m}), 2.66(2\text{H}, \text{s}), 1.94(4\text{H}, \text{br.m}), 1.52(2\text{H}, \text{dd}), 1.45(9\text{H}, \text{s}), 1.35(2\text{H}, \text{m}).

(b) 1,1-Dimethylmethyl (cis-4-\{(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy\}methyl\})-4-hydroxycyclohexylcarbamate

To a suspension of sodium hydride (60% in oil, 0.022g, 0.56 mmol) in dry dimethylformamide (6ml) was added 7-fluoro-8-hydroxy-1-methyl-1,5-naphthyridin-2(1H)-one (for a preparation see Example 1(f)) (0.10g, 0.51 mmol). After stirring at room temperature for 45 min., 1,1-dimethylethyl (3s,6s)-1-oxaspiro[2.5]oct-6-ylcarbamate (0.12g, 0.51 mmol) was added and the mixture was heated at 110°C overnight. Another portion of the epoxide (0.12g) was added and heating continued for 3 days. The mixture was evaporated and the residue was dissolved in dichloromethane/water. The aqueous phase was extracted several times with dichloromethane and the extracts were dried and evaporated. Chromatography on silica gel, eluting with 0-20% methanol/dichloromethane gave the title compound (39mg, 18%).

\text{MS (+ve ion electrospray): } m/z 444 [\text{MNa}^+], 366 [(\text{MH}^+)-\text{C}_4\text{H}_8], 322 [(\text{MH}^+)-\text{C}_5\text{H}_6\text{O}_2].

(c) 8-\{[(cis-4-Amino-1-hydroxycyclohexyl)methyl]oxy\}-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one dihydrochloride
A solution of 1,1-dimethylethyl (cis-4-\{[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl\}-4-hydroxycyclohexyl)carbamate (39 mg, 0.093 mmol) in dichloromethane (1 ml), methanol (0.5 ml) and 4 M hydrogen chloride/1,4-dioxane (1.5 ml) was stirred for 1.5 h, then evaporated to dryness to give a solid (36 mg, 98%).

MS (+ve ion electrospray): m/z 322 [MH\(^+\)].

(d) Title compound

This was prepared from 8-\{[(cis-4-amino-1-hydroxycyclohexyl)methyl]oxy}-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one dihydrochloride (36 mg) and 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carboxaldehyde (for a synthesis see WO2004058144 Example 2(e) or WO2003087098 Example 19(d)) (15 mg), by the general method of Example 1(k) (initial stirring time 1 h, then 5 h after addition of borohydride). The crude product was chromatographed on silica gel, eluting with 0-20% methanol/dichloromethane to give the free base of the title compound (23 mg, 54%).

\(^1\)H NMR (250 MHz, CDCl\(_3\)) \(\delta\) 5.58 (4H, m), 1.85 (m obscured by water signal), 2.60 (1H, m), 3.86 (2H, s), 3.94 (3H, s), 4.01 (2H, d), 4.28 (2H, m), 4.34 (2H, m), 6.84 (1H, s), 6.86 (1H, d), 7.80 (1H, d), 8.10 (1H, s), and 8.39 (1H, d).

LC/MS (+ve ion electrospray): m/z 471 [MH\(^+\)].

The free base was treated with 2 mole equivalents of 0.4 M hydrogen chloride in 1,4-dioxane to give the title dihydrochloride salt (26 mg).

**Example 15** 8-\{[(trans-4-\{(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)amino\}cyclohexyl)methyl]amino\}-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one dihydrochloride

The title compound was prepared from 8-\{[(trans-4-aminocyclohexyl)methyl]amino\}-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one (for a preparation see Example 10(e)) (65 mg; 90% purity) and 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carboxaldehyde (for a synthesis see WO2004058144 Example 2(c) or WO2003087098 Example 19(d)) (32 mg) by the general method of Example 1(k) (omitting the sodium acetate) to give a pale yellow solid (29 mg) after conversion to the title dihydrochloride salt.

LC/MS (+ve ion electrospray): m/z 454 [MH\(^+\)].
Example 16 8-[[trans-4-{(2,3-Dihydrofuro[2,3-c]pyridin-5-ylmethyl)amino}cyclohexyl]methyl]amino]-7-fluoro-1-methyl-1,5-napthyridin-2(1H)-one dihydrochloride

This was prepared from 8-[[trans-4-aminocyclohexyl]methyl]amino]-7-fluoro-1-methyl-1,5-napthyridin-2(1H)-one (for a preparation see Example 10(c)) (62 mg, 95% purity) and 2,3-dihydrofuro[2,3-c]pyridine-5-carbaldehyde (for synthesis see WO2008009700 Example 38(f)) (29 mg) by the general method of Example 1(k) (omitting the sodium acetate) to give a pale yellow solid (56 mg) after conversion to the title dihydrochloride salt.

LC/MS (+ve ion electrospray): m/z 438 [M+H].

Example 17 8-[[trans-4-[(6,7-Dihydro[1,4]dioxino[2,3-c]pyridazin-3-ylmethyl)aminocyclohexyl]methyl]oxy]-7-fluoro-1-methyl-1,5-napthyridin-2(1H)-one hydrochloride

The title compound was prepared from 8-[[trans-4-aminocyclohexyl]methyl]oxy]-7-fluoro-1-methyl-1,5-napthyridin-2(1H)-one hydrochloride (for a preparation see Example 1(j)) (75 mg; assume 50 mg of pure free base) and 6,7-dihydro[1,4]dioxino[2,3-c]pyridazine-3-carbaldehyde (for a synthesis see WO2007081597 Example 10A(c)) (28 mg) by the general method of Example 1(k) to give a solid (22 mg) after conversion to the hydrochloride salt.

MS (+ve ion electrospray) m/z 456 (M+H).

Example 18A 2-[[trans-4-[(3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-napthyridin-4-yl]oxy]methyl]cyclohexyl]amino]-methyl]-1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one hydrochloride

(a) trans-4-[[1,1-Dimethylethoxy]carbonyl]aminocyclohexanecarboxylic acid
To a stirred solution of trans-4-aminocyclohexanecarboxylic acid (1 g, 6.98 mmol) in tert-BuOH (10 mL) and NaOH (0.307 g, 7.68 mmol) in H₂O (10 mL) was added di-tert-butyldicarbonate (1.7 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight. To the reaction mixture hexane (50 mL) was added and the pH was adjusted to pH ~6 with 6N HCl. The mixture was extracted with ethyl acetate (3×50 mL) and washed with brine solution (1×25 mL). Evaporation of the solvent under reduced pressure afforded a white powder (1.4 g, 82.8%). MS (ES-) m/z 242 [MH⁻].

(b) 1,1-Dimethylethyl [trans-4-(hydroxymethyl)cyclohexyl]carbamate

A solution of trans-4-(((1,1-dimethylethyl)oxy)carbonyl)amino)cyclohexanecarboxylic acid (1.45 g, 5.96 mmol) in THF (40 mL) was added to BH₃-DMS (5.2 mL, 17.28 mmol) in THF (40 mL) at 0 °C. The contents were allowed to stir at room temperature for 3 hrs. To the reaction mixture MeOH (10 mL) was added and evaporated to dryness under reduced pressure. The residue was co distilled with MeOH 3 times. The resulting residue was dissolved in DCM and washed with brine solution. Evaporation of the solvent under reduced pressure afforded a white solid (1.3 g, 94%). This crude product was carried over to the next step without further purification.

(c) 1,1-Dimethylethyl (trans-4-(((3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy)methyl) cyclohexyl)carbamate

To a stirred solution of 7-fluoro-1-methyl-1,5-dihydro-1,5-naphthyridine-2,8-dione (7-fluoro-8-hydroxy-1-methyl-1,5-naphthyridin-2(1H)-one, for a preparation see Example 1(f)) (670 mg, 3.48 mmol) in THF (10 mL) was added 1,1-dimethylethyl [trans-4-(hydroxymethyl)cyclohexyl]carbamate (for a preparation see Example 1(g) or 18A(b)) 1 g, 4.36 mmol), PPh₃ (1.42 g, 5.45 mmol) and stirred for 10 minutes. To the mixture DIAD (1.07 mL, 5.45 mmol) in THF (10 mL) was added dropwise. The contents were stirred at 70 °C for 16 hrs. The solvent was removed under reduced pressure and 10% diethyl ether in hexane (10 mL) was added at 0 °C and the reaction mixture was stirred for 30 minutes. The white residue (PPh₃O) thus obtained were filtered and discarded; concentration of the filtrate under reduced pressure afforded the crude compound. The crude compound was purified by silica gel (100-200 mesh) column chromatography using 20%-50% ethyl acetate in petroleum ether. The mixture was then eluted on a preparative HPLC column with 80-20-80% 0.01M ammonium acetate/acetonitrile and the major fraction concentrated to afford a white solid (250 mg, 14.2%). MS (ES+) m/z 406 [MH⁺].
(d) 8-\{[(trans-4-Aminocyclohexyl)methyl]oxy\}-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one

To a solution of CF₃COOH and DCM (1:1) (8 mL) was added 1,1-dimethylethyl (trans-4-\{[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl]oxy\}methyl\}cyclohexyl)carbamate (200 mg, 0.493 mmol) and stirred for 2 hours at room temperature. The reaction mixture was evaporated to dryness, added water (5 mL) and adjusted the pH~ 10 using 1N NaOH solution. Extracted with ethyl acetate (20 mL) and evaporation of the solvent afforded a yellow solid (100 mg, 67%). MS (ES+) m/z 306 [MH⁺]

The isolated yield of 8-\{[(trans-4-aminocyclohexyl)methyl]oxy\}-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one can be improved by and using unpurified 1,1-dimethylethyl (trans-4-\{[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl]oxy\}methyl\}cyclohexyl)carbamate material in the deprotection step.

(e) 2-\{[(trans-4-{[(3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl]oxy}\}methyl\}cyclohexyl]amino\}methyl\}1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one

To a stirred solution of 8-\{[(trans-4-aminocyclohexyl)methyl]oxy\}-7-fluoro-1-methyl-1,5-naphthyridin-2(1H)-one (55 mg, 0.180 mmol) and 7-oxo-6,7-dihydro-1H-pyrimido[5,4-b][1,4]oxazine-2-carbaldehyde (for a synthesis see WO2008009700 Preparation F) (32 mg, 0.180 mmol) in DCM (3 mL) and MeOH (0.25 mL) was added sodiumtriacetoxyborohydride (76 mg, 0.360 mmol) and the contents were allowed to stir for 16 hrs at room temperature. The reaction mixture was filtered and washed with DCM (3 mL) leaving a white inorganic salt. The filtrate was concentrated to obtain the crude compound. The crude compound was washed thoroughly with diethyl ether to obtain the free base of the title compound as a pale yellow solid (30 mg, 36%).

MS (ES+) m/z 469 [MH⁺].

^1H NMR (400 MHz) (free base) (CDCl₃) δ 1.14-1.32 (5H, m), 1.97 (2H, d), 2.10 (2H, d), 2.49-2.56 (1H, m), 3.93 (3H, s), 3.99 (2H, s), 4.05 (2H, dd), 4.73 (2H, s), 6.86 (1H, d), 7.81 (1H, d), 8.26 (1H, s), and 8.38 (1H, d).

(f) Title compound

To a solution of 2-\{[(trans-4-{[(3-fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl]oxy}\}methyl\}cyclohexyl]amino\}methyl\}1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one (42 mg, 0.090 mmol) in methanol (3 mL) at rt was added hydrochloric acid (1 M in diethyl ether) (0.090 mL, 0.090 mmol). The solvent was removed and the solid was dried under high vacuum to deliver the title compound (45 mg).
Example 18B 2-[[trans-4-][(3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-
naphthyridin-4-yl)oxy]methyl]cyclohexyl]amino[methyl]-1H-pyrimido[5,4-
b][1,4]oxazin-7(6H)-one dihydrochloride

2-[[trans-4-][(3-Fluoro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-
yl)oxy]methyl]cyclohexyl]amino[methyl]-1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one (free base) (for a preparation see Example 18A) (380 mg, 0.81 mmol) was dissolved in DCM (6 mL) and MeOH (0.6 mL) and added 3M HCl in diethyl ether (5 mL) at 0 °C. The resulting solution was allowed to stir at 0 °C for 30 minutes. The solvents were evaporated to dryness under reduced pressure. The crude compound was triturated with DCM (20 mL) and filtered. The residue was dried in vacuum to afford the title compound (360 mg) (dihydrochloride salt).

1H (DMSO-d6, 400MHz) δ1.2 (2H, m), δ 1.52-1.6 (2H, m), δ 1.8 (1H, m) δ 1.9-2.0 (2H, d), δ 2.2 (2H, d), δ 3.2 (1H, s), δ 3.8 (3H, s), δ 4.1 (2H, d), δ 4.3 (2H, s) δ 4.8 (2H, s) , δ 6.83 (1H, d), δ 7.83 (1H, d), δ 8.4 (1H, s), δ 8.6 (1H, s), δ 9.2 (1H, s), δ 11.9 (1H,s).

MS (ES+) m/z 469 [MH+].

Example 19 2-[[trans-4-][(7-Fluoro-1-methyl-2-oxo-1,2-dihydro-8-
quinolinyl)oxy]methyl]cyclohexyl]amino[methyl]-1H-pyrimido[5,4-b][1,4]oxazin-
7(6H)-one hydrochloride

(a) 7-Fluoro-8-hydroxy-1-methyl-2(1H)-quinolinone

8-Bromo-7-fluoro-1-methyl-2(1H)-quinolinone (2.06 g, 8.04 mmol) (for a synthesis see WO2008006648 Example 31(h)) was dissolved in THF (200 mL) and cooled to -70°C under nitrogen atmosphere with stirring. 2.5M n-Butyllithium (4 mL, 10 mmol) was added and the mixture stirred at -70°C for 1h. Trimethyl borate (1.35 mL, 12.07 mmol) was then added and the mixture allowed to warm to rt over 1h. Acetic acid (1.38 mL, 24.13 mmol) and hydrogen peroxide (4.23 mL, 24.13 mmol) were then added and the mixture stirred at rt for 48h. Water was added and then the mixture was extracted with EtOAc (x 2). The combined organic layers were dried (Na2SO4), filtered and evaporated. This crude residue was combined with another batch arising from a duplicate reaction on the same scale. The combined residues were purified by silica chromatography, eluting with methanol/DCM (5-10%) to deliver an impure product.

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This was re-purified by silica chromatography, eluting with methanol/DCM (2-12%) to deliver an orange solid which was triturated with Et₂O (30 ml), filtered, washed with more Et₂O (2 x 20 ml) then dried to give the title compound (0.41 g). MS (ES+) m/z 194 [MH+].

(b) 1,1-Dimethylethyl (trans-4-[(7-fluoro-1-methyl-2-oxo-1,2-dihydro-8-quinolinyl)oxy]methyl)cyclohexylcarbamate

To a mixture of 7-fluoro-8-hydroxy-1-methyl-2(1H)-quinolinone (0.25 g, 1.17 mmol), 1,1-dimethylethyl [trans-4-(hydroxymethyl)cyclohexyl]carbamate (0.27 g, 1.17 mmol, for a preparation see Example 1(g)) and triphenylphosphine (0.40 g, 1.51 mmol) in THF (10 ml) was added DIAD (0.294 ml, 1.514 mmol) and the mixture stirred at rt for 1.5h. The mixture was combined with that from a duplicate reaction on trial scale (0.419 mmol of starting material) and evaporated. The residue was purified by silica chromatography, eluting with 0-100% (4% methanol/ethyl acetate) in cyclohexane to deliver the title compound (0.7 g) containing residual triphenylphosphine oxide. This product was carried forward to next step without further purification.

MS (ES+) m/z 405 [MH+].

(c) 8-[(trans-4-Aminocyclohexyl)methyl]oxy]-7-fluoro-1-methyl-2(1H)-quinolinone

Trifluoroacetic acid (5 ml, 64.9 mmol) was added to a solution of 1,1-dimethylethyl (trans-4-[(7-fluoro-1-methyl-2-oxo-1,2-dihydro-8-quinolinyl)oxy]methyl)cyclohexylcarbamate (0.7 g) in DCM (10 ml) and the mixture stirred at rt for 1h. The mixture was evaporated and the residue partitioned between water (20 ml) and DCM (20 ml). The aqueous was then washed with more DCM (30 ml), then CHCl₃ (30 ml) to remove Ph₃PO from previous reaction. The aqueous was then basified with K₂CO₃ and then extracted with 10% methanol/DCM (3 x 30 ml), dried (Na₂SO₄), filtered and evaporated. The residue was purified by silica chromatography eluting with a gradient of 0-12% NH₃/MeOH/DCM to give the title compound (0.12 g). MS (ES+) m/z 305 [MH+].

(d) Title compound

To 8-[(trans-4-aminocyclohexyl)methyl]oxy]-7-fluoro-1-methyl-2(1H)-quinolinone (0.04 g, 0.131 mmol) and 2-(dihydroxymethyl)-1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one (0.023 g, 0.118 mmol) (as a 3:1 mixture of hemiacetal:aldehyde, which may be prepared as for the aldehyde in WO2008009700 Preparation F but the crude residue was further purified by silica column chromatography (x 2), eluting with 0-1% MeOH/DCM) in chloroform (5 ml) and methanol (0.5 ml) was added sodium
triacetoxyborohydride (0.084 g, 0.394 mmol) and the mixture stirred at rt for 18 h. Saturated NaHCO₃ solution (15 ml) was added and the mixture extracted with 10% methanol/DCM (3 x 15 ml), dried over Na₂SO₄, filtered and evaporated. The residue was purified by silica chromatography eluting with a gradient of 2-12% methanol/DCM to give the free base of the title compound (26 mg, 42%). The free base was dissolved in methanol (3 ml) and 1 eq. of 4.0M hydrogen chloride in 1,4-dioxane (0.015 ml) was added. The solvent was evaporated to deliver the title hydrochloride salt (28 mg).

¹H NMR (400 MHz) (free base) (CDCl₃) δ 1.14-1.38 (5H, m), 1.85-1.89 (1H, m), 2.00 (2H, d), 2.11 (2H, d), 2.56-2.63 (1H, m), 3.58 (2H, br s), 3.78 (2H, d), 3.94 (3H, s), 4.03 (2H, s), 4.70 (2H, s), 6.64 (1H, d), 6.99 (1H, dd), 7.22 (1H, dd), and 7.56 (1H, d).
MS (ES+) m/z 468 [MH+].

Example 20. 6-[[trans-4-[[7-Fluoro-1-methyl-2-oxo-1,2-dihydro-8-quinolinyl]oxy][methyl][cyclohexyl]amino][methyl]-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one hydrochloride

(a) Title compound

To 8-[[trans-4-aminocyclohexyl)methyl]oxy]-7-fluoro-1-methyl-2(1H)-quinolinone (0.04 g, 0.131 mmol) (for a preparation see Example 19(c)) and 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (0.021 g, 0.118 mmol, for a synthesis see WO2004058144, Example 1(l)) in chloroform (5 mL) and methanol (0.5 mL) was added sodium triacetoxyborohydride (0.084 g, 0.394 mmol) and the mixture stirred at rt for 18 h. Saturated NaHCO₃ solution (15 ml) was added and the mixture extracted with 10% methanol/DCM (3 x 15 ml), dried over Na₂SO₄, filtered and evaporated. The residue was purified by silica chromatography eluting with a gradient of 2-12% methanol/DCM to give the free base of the title compound (37 mg, 61%). The free base was dissolved in methanol (3 ml) and 1 eq. of 4.0 M hydrogen chloride in 1,4-dioxane (0.021 ml) was added. The solvent was evaporated to deliver the title hydrochloride salt (40 mg).

¹H NMR (400 MHz) (free base) (CDCl₃) δ 1.13-1.34 (5H, m), 1.85-1.89 (1H, m), 1.99 (2H, d), 2.09 (2H, d), 2.50-2.57 (1H, m), 3.79 (2H, d), 3.88 (2H, s), 3.95 (3H, s), 4.64 (2H, s), 6.64 (1H, d), 6.94-7.02 (2H, m), 7.20-7.24 (2H, m), and 7.56 (1H, d).
MS (ES+) m/z 467 [MH+].

To 8-[[trans-4-amino[cyclohexyl]methyl]oxy][7-fluoro-1-methyl-2(1H)-quinolinone (0.04g, 0.131 mmol) (for a synthesis see Example 19 (c)) and 7-chloro-3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1.4]oxazine-6-carbaldehyde (0.025 g, 0.118 mmol) for a synthesis see WO2003064421, Example 15(c)) in chloroform (5 mL) and methanol (0.5 mL) was added sodium triacetoxylborohydride (0.084 g, 0.394 mmol) and the mixture stirred at rt for 18h. Saturated NaHCO₃ solution (15 mL) was added and the mixture extracted with 10% methanol/DCM (3 x 15 mL), dried over Na₂SO₄, filtered and evaporated. The residue was purified by silica chromatography eluting with a gradient of 2-12% methanol/DCM to give the free base of the title compound (43 mg, 66%). The free base was dissolved in methanol (3 mL) and 1 eq. of 4.0 M hydrogen chloride in 1,4-dioxane (0.021 mL) was added. The solvent was evaporated to deliver the title hydrochloride salt (46 mg).

¹H NMR (400 MHz) (free base) (CDCl₃) δ 1.17-1.40 (5H, m), 1.88-1.92 (1H, m), 2.03 (2H, d), 2.15 (2H, d), 2.55-2.62 (1H, m), 3.82 (2H, d), 3.97 (3H, s), 4.02 (2H, s), 4.65 (2H, s), 6.66 (1H, d), 7.02 (1H, dd), 7.2-7.29 (2H, m), and 7.58 (1H, d).
MS (ES+) m/z 501 [MH⁺].

Example 22 5-Methyl-6-oxo-4-[[trans-4-[[[3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl]methyl]amino[cyclohexyl]methyl]oxy]-5,6-dihydro-1,5-naphthylpyridine-3-carbonitrile

(a) Methyl 5-methyl-4-[[4-(methyl[oxy]phenyl)methyl]oxy]-6-oxo-5,6-dihydro-1,5-naphthylpyridine-3-carboxylate

To a suspension of methyl 4-hydroxy-5-methyl-6-oxo-5,6-dihydro-1,5-naphthylpyridine-3-carboxylate (5 g, 21.35 mmol) (for a synthesis see WO2008006648 Example 23(b)) in DMF (200 mL) at rt was added small portions of 60% sodium hydride
(60% in oil) (0.940 g, 39.2 mmol). The green reaction mixture was then heated at 60 °C for 45mins then p-methoxybenzyl chloride (3.18 mL, 23.48 mmol) added dropwise. The solution was then heated at 120°C for 2.5h then allowed to cool and stood at rt overnight. The reaction was then evaporated, quenched with water and extracted with CHCl₃ (x 3). The combined organic layers were washed with brine, dried (Na₂SO₄) and evaporated a solid which was purified by silica chromatography, eluting with MeOH/DCM (0-15%) to give the title compound (3.61g, 48%). MS (ES+) m/z 355 [MH+].

(b) 5-Methyl-4-({4-(methylxylyphenyl)methyl}oxy)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylic acid

A suspension of methyl 5-methyl-4-({4-(methylxylyphenyl)methyl}oxy)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylate (3.59 g, 10.12 mmol) in THF (40 mL and water (40.0 mL) was stirred at rt and 2 M sodium hydroxide (20.23 mL, 40.5 mmol) was added slowly. The resulting mixture was stirred for 1.5 h and then acidified to pH 2 with 2 M HCl. The reaction was evaporated then filtered, washed with water and dried to give the title compound (2.95 g, 86%). MS (ES+) m/z 341 [MH+].

(c) 5-Methyl-4-({4-(methylxylyphenyl)methyl}oxy)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxamide

A suspension of 5-methyl-4-({4-(methylxylyphenyl)methyl}oxy)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylic acid (2.95 g, 8.68 mmol) in DMF (80 ml) was stirred at rt and treated with HATU (O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate) (3.63 g, 9.55 mmol) followed by DIPEA (diisopropylethylamine) (1.68mL, 9.55mmol). The brown solution was at rt for 10 min then treated with ammonium chloride (9.29 g, 174 mmol) and more DIPEA (30.29 ml, 53.49 mmol). The orange reaction mixture was stirred at rt for 2 h then evaporated and the residue dissolved in 10% MeOH/CHCl₃ and washed with water (x 2). The combined aqueous phases were extracted with CHCl₃ and the combined organics washed with brine, dried (Na₂SO₄) and evaporated to give a solid which was treated with DMF and heated, then left to stand at 0 °C overnight, then filtered, washed with Et₂O and dried to give the title compound (2.73 g, 93%). MS (ES+) m/z 340 [MH+].

(d) 5-Methyl-4-({4-(methylxylyphenyl)methyl}oxy)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carbonitrile
A mixture of 5-methyl-4-([4-(methylxy)phenyl)methyl]oxy)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxamide (2.73 g, 8.04 mmol), p-toluenesulphonyl chloride (2.45 g, 12.86 mmol) and pyridine (30 mL) was stirred and heated to 85°C for 2 h. The reaction was allowed to cool, treated with DCM (25 ml) and water (25 ml) then stirred for 10 min. The aqueous phase was separated and extracted with more DCM (x 2) and 10% MeOH/DCM. The combined organic layers were washed with brine, dried (Na₂SO₄) and evaporated to give the title compound (2.56g, 99%).

MS (ES+) m/z 322 [MH⁺].

(e) 4-Hydroxy-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carbonitrile

A suspension of 5-methyl-4-([4-(methylxy)phenyl)methyl]oxy)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carbonitrile (2.56 g, 5.88 mmol) in DCM (10 mL) was stirred and treated dropwise with TFA (10 mL, 130 mmol). The resulting orange solution was heated at reflux overnight. The reaction was heated for a further 24 h, then evaporated and the residue azeotroped with toluene then CHCl₃ (x 3) to give a beige solid (2.43 g). Ca. 1 g of this solid was partitioned between saturated aqueous NaHCO₃ solution and CHCl₃ and the aqueous phase was separated and acidified with 2M HCl solution and extracted with 10% MeOH/CHCl₃ (x 3). The combined organics were evaporated to give the title compound (0.65 g, 55%).

MS (ES+) m/z 202 [MH⁺].

(f) 1,1-Dimethylethyl (trans-4-[(3-cyano-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl)cyclohexylcarbamate

Method 1

A suspension of 4-hydroxy-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carbonitrile (100 mg, 0.50 mmol) in THF (10 mL) was stirred at rt and treated with (1,1-dimethylethyl [trans-4-(hydroxymethyl)cyclohexyl]carbamate (114 mg, 0.50 mmol), triphenyl phosphine (261 mg, 0.99 mmol) and DIAD (0.20 mL, 0.99 mmol) added dropwise. The resulting pale yellow suspension was stirred at rt for 20 min then heated at 80°C overnight. The reaction was then heated at 60°C over the weekend. The reaction was then evaporated to give a yellow gum which was purified by silica chromatography, eluting with MeOH/DCM (0-10%) to give the title compound (0.51 g), containing residual triphenylphosphine oxide. This may be used in the next step without further purification.

MS (ES+) m/z 413 [MH⁺].

Method 2

A suspension of 4-hydroxy-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carbonitrile (0.33g, 1.640 mmol) in DMF (25 mL) was stirred at rt and treated with 60%
sodium hydride in oil (82mg, ~1.91mmol, 1.25eq) added in small portions. The resulting mixture was heated at 60°C for 40 min then trans-4-((1,1-dimethylethyl)oxy)cyclohexylmethyl ethanesulfonate (0.492 g, 1.53 mmol) (for a synthesis see alternative synthesis of Example 1(i)(a) added in small portions and the resulting brown slight suspension heated at 120°C overnight. The reaction was then heated for a further 24 hours, allowed to cool, evaporated, quenched with water and extracted with 10% MeOH/CHCl₃ (x4). The combined organic layers were dried (Na₂SO₄) and evaporated to give a residue which was purified by silica chromatography (x 3), eluting with 0-10% MeOH/DCM to give an impure product which may be used in the next step without further purification.

(g) 4-(((trans-4-Aminocyclohexyl)methyl)oxy)-5-methyl-6-oxo-5,6-dihydro-1,5-naphththyridine-3-carbonitrile

A solution of 1,1-dimethylethyl (trans-4-(((3-cyano-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy)methyl)cyclohexyl)carbamate (0.50 g) (containing triphenylphosphine oxide) in DCM (8 mL) was stirred at rt and treated slowly with trifluoroacetic acid (4 mL, 53.8 mmol). The resulting yellow solution was stirred at rt for 2 h. The reaction was then evaporated and the residue partitioned between DCM and water. The aqueous phase was separated and basified to pH~12 with 1 M NaOH solution and extracted with 10% MeOH/DCM (x 3). The combined organic layers were washed with brine, dried (Na₂SO₄) and evaporated to give a cream solid which was combined with a second batch of crude material (16 mg). The combined residues were purified by silica chromatography, eluting with MeOH/DCM (0-75%) to give the title compound (59 mg).

MS (ES+) m/z 313 [MH+].

(h) Title compound.

A solution of 4-(((trans-4-aminocyclohexyl)methyl)oxy)-5-methyl-6-oxo-5,6-dihydro-1,5-naphththyridine-3-carbonitrile (58 mg, 0.19 mmol) in DCM (5 ml) and methanol (1 ml) was stirred at rt and treated with 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine-6-carbaldehyde (33 mg, 0.19 mmol) (for a synthesis see WO2004058144, Example 1(i)). The resulting orange solution was stirred at rt overnight then sodium triacetoxylborohydride (79 mg, 0.37 mmol) was then added in small portions and the resulting reaction stirred for 3 h. The reaction was then evaporated to give an orange gum which was purified by silica chromatography, eluting with 2M NH₃ in MeOH/DCM (0-15%) to give a pale pink foam which was re-purified by silica chromatography, eluting
with 2M NH₃ in MeOH/DCM (0-10%) to give the title compound as a mixture containing approximately 50 mol% of an unidentified impurity (21 mg, 24%).

\[^1\text{H NMR}\ (600 \text{ MHz}) (\text{CDCl}_3) \delta 1.15-2.02 (9\text{H, m}), 2.43-4.47 (1\text{H, m}), 3.81 (2\text{H, s}), 3.90 (3\text{H, s}), 4.20 (2\text{H, d}), 4.64 (2\text{H, s}), 6.92 (1\text{H, d}), 7.02 (1\text{H, d}), 7.20 (1\text{H, dd}), 7.87 (1\text{H, d}), and 8.59 (1\text{H, s}).

MS (ES+ m/z) 475 [MH+].

Example 23 2-[[trans-4-[[6-Fluoro-4-methyl-3-oxo-3,4-dihydro-5-
quinoxalinyl]oxy]methyl][cyclohexyl]amino]methyl]-1H-pyrimido[5,4-b][1,4]oxazine-
7(6H)-one hydrochloride

(a) (2-Bromo-3-fluoro-6-nitrophenyl)amine

A solution of 2-bromo-1,3-difluoro-4-nitrobenzene (32.14 g, 135.4 mmol) (for a synthesis see EP184384 Example 1 (a)), triethylamine (56.5 ml, 405 mmol) and ammonium carbonate (12.83 g, 135.4 mmol) in DMF (220 mL) were stirred at rt for 24 h then evaporated then the residue was dissolved in DCM/water. The aqueous phase was extracted with DCM (x 2), the organic layers were then dried and evaporated. The crude residue was recrystallised from diethyl ether: petroleum ether (40-60) and the so-obtained product (20.67 g) was combined with the recrystallised mother liquor (3.62 g) (recrystallised from diethyl ether: petroleum ether (40-60) then ethanol) to deliver the title compound (24.29 g, 76%).

\[^1\text{H NMR}\ (250 \text{ MHz}) (\text{CDCl}_3) \delta 6.52-6.60 (1\text{H, m}), 6.82 (2\text{H, br s}), \text{and} 8.19-8.25 (1\text{H, m}).

(b) N-(2-Bromo-3-fluoro-6-nitrophenyl)-2-cyanoacetamide

To a mixture of (2-bromo-3-fluoro-6-nitrophenyl)amine 24.29 g (103.4 mmol) and cyanoacetic acid (17.75 g, 206.3 mmol) in toluene (740 ml) at rt was added PCl₃ (45.15 g, 206.3 mmol) portionwise. The mixture was then heated at 125-130 °C for 2.25 h while passing a slow stream of air over the mixture. Additional cyanoacetic acid (1.8 g, 20.6 mmol) and PCl₃ (5.5 g, 20.6 mmol) were then added and the mixture was heated at 125-130 °C for a further 1.25 h. The mixture was then cooled, evaporated and the residue was dissolved in EtOAc and washed with brine, NaHCO₃, brine then the organics were dried and evaporated. The material as then resuspended in toluene (700 ml) then additional cyanoacetic acid (8.8 g, 105 mmol) and PCl₃ (22.5 g, 105 mmol) were then
added and the mixture was heated at 90 °C for a further 3 h. The mixture was then cooled, evaporated and the residue was dissolved in EtOAc and washed with brine, NaHCO₃, brine then the organics were dried and evaporated to deliver the title compound containing unidentified impurities (32.84 g).

MS (ES-) m/z 301[M-H].

(c) 5-Bromo-6-fluoro-3-oxo-3,4-dihydro-2-quinoxalinecarbonitrile 1-oxide

To a solution of N-(2-bromo-3-fluoro-6-nitrophenyl)-2-cyanoacetamide (32.84 g) in pyridine (120 ml) was added 1 M NaOH (105 ml, 105 mmol) and the mixture was stirred at rt for two nights then water was added and the mixture filtered, washing the precipitate with water. The filtrate was acidified to pH 5 through addition of concentrated HCl and the mixture was filtered, washing the precipitate with water. The precipitate was dried then triturated with diethyl ether (x 2) and dried to deliver the title compound (23.59 g, 81% over 2 steps).

MS (ES-) m/z 282[M-H].

(d) 8-Bromo-7-fluoro-2(1H)-quinoxalinone

A mixture of 5-bromo-6-fluoro-3-oxo-3,4-dihydro-2-quinoxalinecarbonitrile 1-oxide (5.0 g, 17.5 mmol) and sodium sulfate (9 g, 43.9 mmol) in ethanol (50 ml) and water (100 ml) was heated under reflux for 2.5 h then cooled and acidified to pH 1 with 5 M HCl. The reaction was stirred at rt for 30 min then taken to pH 8 with 2 M NaOH and the ethanol was evaporated. The pH of the mixture was then taken to pH13-14 with 8 M NaOH and the mixture was allowed to stand for 4 h. Concentrated HCl was then added to the mixture to acidify to pH 2 and the resulting suspension was filtered and the filtrate was evaporated. The residue was suspended in water (500 ml) and re-acidified with dilute HCl and extracted several times with 10% MeOH/DCM. The combined organic extracts were dried and evaporated to deliver the title compound (2.37 g, 56%).

MS (ES+) m/z 245 [MH+].

(e) 8-Bromo-7-fluoro-2-(methylxyloxy)quinoxaline

A solution of 8-bromo-7-fluoro-2(1H)-quinoxalinone (0.1 g, 0.41 mmol) in DMF (4 ml) was added to a flask containing sodium hydride (60% dispersion in oil) (25 mg, 0.62 mmol) and stirred for 10 min then methyl iodide (0.051 ml, 0.82 mmol) was added and the reaction mixture was stirred for 1.5 h then poured into a mixture of water (5 ml), brine (5 ml) and ethyl acetate (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 ml). The combined organics were washed with water (2 x 10 ml) and brine (2 x 10 ml), dried over MgSO4 and evaporated. The crude
residue was purified by silica chromatography, eluting with EtOAc/hexanes (0-70%) to give the title compound (41 mg, 39%).
MS (ES+) m/z 258 [MH+].

(f) 6-Fluoro-3-(methyloxy)-5-quinoxalinol

8-bromo-7-fluoro-2-(methyloxy)quinoxaline (200 mg, 0.778 mmol), \( \text{Pd}_2(\text{dba})_3 \)
tris(dibenzylideneacetone)dipalladium(0) (3.56 mg, 3.89 \( \mu \)mol), \( \text{bis}(1,1\)-dimethylethyl\)[3,4,5,6-tetramethyl-2',4',6'-tris(1-methylethyl)-2-biphenyl]phosphane
(7.48 mg, 0.016 mmol), KOH (131 mg, 2.334 mmol) were dissolved in degassed 1,4-dioxane (1 mL) and degassed water (1 mL). The reaction was then stirred at 100 °C for 1.5 h (the purple solution turned orange after a few minutes). The reaction was allowed to cool to room temperature and acidified using 1M HCl. The resulting mixture was then extracted with ethyl acetate (3 x 5mL). The organics were combined, dried and evaporated to give the crude product. This was dissolved in DCM (5 mL) and filtered. The filtrate was evaporated to give the title compound (130 mg, 68%).
MS (ES+) m/z 195 [MH+].

(g) 10-Fluoro-2,2-dimethyl-2,3-dihydro-5H-[1,4,2]oxazasilino[4,5,6-de]quinoxalin-5-one

6-Fluoro-3-(methyloxy)-5-quinoxalinol (130 mg, 0.670 mmol) was suspended in DMF (5 mL) and treated with NaH (48.2 mg, 1.205 mmol), chloro(chloromethyl)dimethylsilane (0.176 mL, 1.339 mmol) was then added and the reaction stirred at rt for 1h. The reaction was then heated to 100 °C overnight. The solvent was evaporated and the crude purified using silica chromatography 0-5% MeOH/DCM to deliver the title compound (155 mg, 92%).
MS (ES+) m/z 251 [MH+].

(h) 7-Fluoro-8-hydroxy-1-methyl-2(1H)-quinoxalinone

A solution of 10-fluoro-2,2-dimethyl-2,3-dihydro-5H-[1,4,2]oxazasilino[4,5,6-de]quinoxalin-5-one (155 mg, 0.619 mmol) in 1,4-dioxane (10 mL) and methanol (5.00 mL) was treated with cesium fluoride (282 mg, 1.858 mmol) and stirred at 85 °C overnight. Solvents were evaporated and the residue was dissolved in MeOH/water (1:1, 3mL) and acidified to pH 3 with 5 N HCl. The aqueous was extracted with 20% MeOH/DCM (3 x 50mL). The organic layers were dried (MgSO4), filtered and evaporated to afford the title compound (150 mg) which was used in the next step without further purification.
MS (ES+) m/z 195 [MH+].
(i) 1,1-Dimethylethyl (trans-4-[[6-fluoro-4-methyl-3-oxo-3,4-dihydro-5-
quinoxalinyl]oxy]methyl)cyclohexylcarbamate

To a mixture of 7-fluoro-8-hydroxy-1-methyl-2(1H)-quinoxalinone (150 mg), 1,1-dimethylethyl [trans-4-(hydroxymethyl)cyclohexyl]carbamate (142 mg, 0.618 mmol, for a preparation see Example 1(g)) and triphenylphosphine (195 mg, 0.742 mmol) in THF (10 mL) was added DIAD (0.144 mL, 0.742 mmol) and the mixture was stirred at rt for 1 h then triphenylphosphine (195 mg, 0.742 mmol) and DIAD (0.144 mL, 0.742 mmol) were added and the reaction was stirred at rt overnight. The solvent was evaporated and the residue was purified using silica chromatography (0-20%CH$_3$CN/DCM) to afford the title compound (272 mg) which was used in the next step without further purification. MS (ES+) m/z 423 [MNH$_4$+].

(j) 8-[[trans-4-Aminocyclohexyl]methyl]oxy]-7-fluoro-1-methyl-2(1H)-quinoxalinone

1,1-Dimethylethyl (trans-4-[[6-fluoro-4-methyl-3-oxo-3,4-dihydro-5-
quinoxalinyl]oxy]methyl)cyclohexylcarbamate (272 mg) was dissolved in chloroform (5 mL) and treated with HCl (5 mL, 20.00 mmol) (4M in 1,4-dioxane). The reaction was stirred at rt for 45 min then additional HCl (5 mL, 20.00 mmol) (4M in 1,4-dioxane) was added and the reaction mixture was stirred at rt for 30 min then evaporated. The crude was purified on an SCX cartridge eluting with methanol, then 2 M NH$_3$ in methanol, to deliver the title compound (36 mg, 15% over 3 steps (h,i,j)). MS (ES+) m/z 306 [MH+].

(k) Title compound

8-[[trans-4-Aminocyclohexyl]methyl]oxy]-7-fluoro-1-methyl-2(1H)-quinoxalinone (36 mg, 0.094 mmol) was dissolved in chloroform (5 mL) and methanol (0.5 mL) and then 2-(dihydroxymethyl)-1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one (18.59 mg, 0.094 mmol) (as a 3:1 mixture of hemiacetal:aldehyde, which may be prepared as for the aldehyde in WO2008009700 Preparation F but the crude residue was further purified by silica column chromatography (x 2), eluting with 0-1% MeOH/DCM) was added. The mixture was stirred at rt for 0.5 h and then sodium triacetoxyborohydride (60.0 mg, 0.283 mmol) was added. After 1.5 h additional sodium triacetoxyborohydride (30.0 mg, 0.141 mmol) were added. Sat. aq. NaHCO$_3$ (15 mL) was added and the aqueous was extracted with 20%MeOH/DCM (3 x 25 mL). The organic layers were dried (MgSO$_4$), filtered and evaporated then the residue was purified by silica chromatography eluting with 0-20%MeOH/DCM to afford the free base of the title compound (25 mg, 51%). The free base was dissolved in DCM-MeOH and treated with
one equivalent of 1M HCl in Et₂O. The solvent was evaporated and the salt was dried under high vacuum overnight to deliver the title hydrochloride salt (25 mg).

\(^1\)H NMR (400 MHz) (free base) (CDCl₃) δ 1.15-1.39 (4H, m), 1.89-2.14 (5H, m), 2.58-2.63 (1H, m), 3.83-3.84 (2H, m), 3.94 (3H, s), 4.02-4.04 (2H, m), 4.71-4.76 (3H, m), 7.08-7.13 (1H, m), 7.57-7.61 (1H, m), and 8.21-8.24 (2H, m).

MS (ES+) m/z 469 [MH⁺].

**Example 24 2-[[trans-4-[[5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl]oxy]methyl]cyclohexyl]amino[methyl]-1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one hydrochloride**

(a) 1,1-Dimethylethyl (trans-4-[[5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl]oxy]methyl)cyclohexyl)carbamate

A suspension of 8-hydroxy-1-methyl-1,5-naphthyridin-2(1H)-one (70 mg, 0.397 mmol) (for a synthesis see WO2008006648 Example 19(b)) in THF (7 mL) was stirred at rt and treated with 1,1-dimethylethyl (trans-4-(hydroxymethyl)cyclohexyl)carbamate (91 mg, 0.397 mmol, for a preparation see Example 1(g)), triphenylphosphine (135 mg, 0.517 mmol) and DIAD (0.102 mL, 0.517 mmol). The suspension was placed in a sonic bath for 5 min at rt then removed and heated at 80°C overnight. Additional DIAD (0.117 mL, 0.596 mmol), additional triphenylphosphine (156 mg, 0.596 mmol), additional 1,1-dimethylethyl (trans-4-(hydroxymethyl)cyclohexyl)carbamate (137 mg, 0.596 mmol) were added and the suspension was heated at 80°C for a further 5 h. The reaction was evaporated to dryness. The residue was purified by silica chromatography eluting with 0-50% DCM/MeOH to give the title compound (88 mg, 57%)

MS (ES+) m/z 388 [MH⁺].

(b) 8-[[trans-4-Aminocyclohexyl)methyl]oxy]-1-methyl-1,5-naphthyridin-2(1H)-one

A solution of 1,1-dimethylethyl (trans-4-[[5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl]oxy]methyl)cyclohexyl)carbamate (88 mg, 0.227 mmol) in DCM (2 mL) was stirred at rt and treated with TFA (1.2 mL, 15.58 mmol). The solution was stirred for 2 h then evaporated. This residue was purified on an SCX cartridge eluting with 0-100% 2 M ammonia in MeOH/MeOH to give the title compound (40 mg, 58%).

MS (ES+) m/z 288 [MH⁺].
(c) Title compound

8-{{[(trans-4-Aminocyclohexyl)methyl]oxy}-1-methyl-1,5-naphthyridin-2(1H)-one (40 mg, 0.139 mmol) was dissolved in chloroform (5 mL) and methanol (0.500 mL) at rt and then 2-(dihydroxymethyl)-1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one (27.4 mg, 0.139 mmol) (as a 3:1 mixture of hemiacetal:aldehyde, which may be prepared as for the aldehyde in WO2008009700 Preparation F but the crude residue was further purified by silica column chromatography (x 2), eluting with 0-1% MeOH/DCM) was added. The mixture was stirred at rt for 0.5h and then sodium triacetoxyborohydride (89 mg, 0.418 mmol) was added and stirred overnight at rt. Saturated aq. NaHCO₃ (15 mL) was added and the aqueous was extracted with 20%MeOH/DCM (3 x 25 mL). The combined organic layers were dried (MgSO₄), filtered and evaporated. The residue was purified by silica chromatography (0-20%MeOH/DCM) to deliver the free base of the title compound (12 mg, 19%). The free base was dissolved in DCM-MeOH and treated with one equivalent of 1M HCl in Et₂O. The solvent was evaporated and the salt was dried under high vacuum overnight to deliver the title hydrochloride salt (14 mg).

1H NMR. (400 MHz) (free base) (CDCl₃) δ 1.21-1.35 (4H, m), 1.91-2.01 (3H, m), 2.12 (2H, d), 2.55-2.60 (1H, m), 3.13 (2H, br s), 3.95-3.97 (5H, m), 4.02 (2H, s), 4.72 (2H, s), 6.90 (2H, m), 7.86 (1H, d), 8.24 (1H, s) and 8.38 (1H, d).

MS (ES+) m/z 451 [MH+].

Example 25 2-[[trans-4-{{[(3-Chloro-5-methyl-6-methylidene-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl]amino}methyl]-6H-pyrimido[5,4-b][1,4]oxazin-7(8H)-one hydrochloride

(a) 1,1-Dimethyl(4-{{[(3-chloro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl)oxy]methyl}cyclohexyl}carbamate

A suspension of 7-chloro-8-hydroxy-1-methyl-1,5-naphthyridin-2(1H)-one (1 g, 4.75 mmol) (for a synthesis see WO2008006648 Example 1(c)) in THF (24 ml) was stirred at rt and treated with 1,1-dimethyl (trans-4-(hydroxymethyl)cyclohexyl)carbamate (1.089 g, 4.75 mmol, for a preparation see Example 1(g)), triphenylphosphine (1.619 g, 6.17 mmol) and DIAD (1.215 ml, 6.17 - 58 -
mmol). The resulting yellow suspension was stirred for 30 min then heated at 80°C for 3.5 hours. Additional triphenylphosphine (0.8 g, 3.05 mmol) and DIAD (0.6 ml, 3.05 mmol) were added and the suspension (now orange) was heated to 80°C for 2 hours. The suspension was cooled and stirred at rt overnight. The solvent was evaporated under vacuum and to deliver an orange gum. Chromatography on silica, eluting with 0-50% DCM/CH3CN gave a white solid that contained residual triphenylphosphine oxide. Diethyl ether (50 mL) was added and the resulting suspension was stirred for 30 minutes, filtered under vacuum. The precipitate was dissolved in DCM, filtered and the filtrate was evaporated to give the title compound (1.16 g, 42%).

MS (ES+) m/z 422 [MH+].

(b) 8-[[[(trans-4-Aminocyclohexyl)methyl]oxy]-7-chloro-1-methyl-1,5-naphthyridin-2(1H)-one

1,1-Dimethylethyl (trans-4-[[3-chloro-5-methyl-6-oxo-5,6-dihydro-1,5-naphthyridin-4-yl]oxy]methyl)cyclohexyl carbamate (307 mg, 0.524 mmol) was dissolved in chloroform (10 mL) and treated with HCl in 1,4-dioxane (10 mL, 40.0 mmol). The reaction was stirred at rt for 45 min then further HCl in 1,4-dioxane (10 mL, 40.0 mmol) was added. After 1.5h at rt the reaction was evaporated and the crude was dissolved in MeOH (5 mL) and purified on an SCX cartridge to deliver a yellow gum. This was then further purified by chromatography on silica eluting with 2 M NH3 in methanol/DCM, 0-100% to give the title compound (121 mg, 68%).

MS (ES+) m/z 322 [MH+].

c) Title compound

8-[[[(trans-4-Aminocyclohexyl)methyl]oxy]-7-chloro-1-methyl-1,5-naphthyridin-2(1H)-one (121 mg, 0.376 mmol) was dissolved in chloroform (10 mL) and methanol (1 mL) and then 2-(dihydroxymethyl)-6H-pyririmido[5,4-b][1,4]oxazin-7(8H)-one (78 mg, 0.396 mmol) (as a 3:1 mixture of hemiacetal:aldehyde, which may be prepared as for the aldehyde in WO2008009700 Preparation F but the crude residue was further purified by silica column chromatography (x 2), eluting with 0-1% MeOH/DCM) was added. The reaction mixture was stirred at rt for 0.5 h and then sodium triacetoxyporphorohydride (239 mg, 1.128 mmol) was added. The suspension was stirred at rt for 3 h then additional sodium triacetoxyporphorohydride (239 mg, 1.128 mmol) was added and the suspension was stirred at rt overnight. Additional sodium triacetoxyporphorohydride (398 mg, 1.880 mmol) was added and the suspension was stirred at rt for a further 1.5 h. Saturatedaq. NaHCO3 (50mL) was added to the reaction and the aqueous layer was extracted with 20%MeOH/DCM (3 x 50mL). The combined organics were dried (MgSO4), filtered and evaporated. The residue was purified by silica chromatography (0-50%MeOH/DCM) to
deliver the free base of the title compound (50 mg, 27%). The free base was dissolved in DCM-MeOH (2mL) and treated with one equivalent of 1M HCl in Et₂O (0.103mL). The solvent was evaporated and the salt was dried under high vacuum overnight to deliver the title hydrochloride salt (46 mg).

1H NMR (400 MHz) (free base) (CDCl₃) δ 1.15-1.25 (2H, m), 1.29-1.38 (2H, m) 1.92-2.03 (3H, m), 2.12 (2H, d), 2.56-2.63 (1H, m), 3.78 (2H, d), 3.90 (3H, s), 4.04 (2H, s), 4.69 (2H, s), 5.57 (2H, br s), 6.89 (1H, d), 7.84 (1H, d), 8.22 (1H, s) and 8.46 (1H, s).

MS (ES+) m/z 485 [MH⁺].

**Preparation A 7-Oxo-6,7-dihydro-1H-pyrimido[5,4-b][1,4]thiazine-2-carbaldehyde**

(a) Ethyl [(2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl)thio]acetate

A solution of 5-bromo-2,4(1H,3H)-pyrimidinedione (15 g, 79 mmol) and ethyl mercaptoacetate (8.58 ml, 79 mmol) in DMF (200mL) was treated with tetrabutylammonium hydrogen sulfate (6.67 g, 19.64 mmol) and potassium carbonate (23.88 g, 173 mmol) and stirred at ambient temperature overnight. The solution was filtered and concentrated under reduced pressure to yield crude title compound as a yellow oil which foams up under reduced pressure.

MS (ES+) m/z 231.1 (MH⁺).

(b) Ethyl [(2,4-dichloro-5-pyrimidinyl)thio]acetate

A suspension of ethyl [(2,4-dioxo-1,2,3,4-tetrahydro-5-pyrimidinyl)thio]acetate (crude material) (18.19 g, 79 mmol) in phosphorus oxychloride (100 ml, 1073 mmol) was treated with dimethyl aniline (2.500 ml, 19.72 mmol), and the reaction was heated to reflux and stirred for 2 hours. The solution was allowed to cool to room temperature and poured slowly onto ice to quench the excess phosphorus oxychloride. Once quenched, the aqueous layer was extracted with CH₂Cl₂ (3X). The organic layers were combined, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was chromatographed using a gradient of 0-50% EtOAc/Hexanes. The product was isolated as a dark yellow oil.

1H NMR (400 MHz, chloroform-d) ppm 1.22 (t, J=7.07 Hz, 3 H) 3.71 (s, 2 H) 4.15 (d, J=7.33 Hz, 1 H) 8.53 (s, 1 H)

(c) Ethyl [(4-amino-2-chloro-5-pyrimidinyl)thio]acetate

A solution of ethyl [(2,4-dichloro-5-pyrimidinyl)thio]acetate (2.0 g, 7.49 mmol) in DMF (75ml) was treated with ammonia in isopropanol (7.49 ml, 14.97 mmol) in a pressure tube. The tube was capped, and the reaction was stirred at ambient temperature. Upon completion, the solution was concentrated under reduced pressure and pumped on
to remove any residual DMF. The crude material was chromatographed using a gradient of 0-10% acetone/chloroform. The product contained a small amount of cyclized material (which is the product of the next step). The product was isolated as a light yellow solid. MS (ES+) m/z 248.0 (MH⁺).

(d) 2-Chloro-1H-pyrimido[5,4-b][1,4]thiazin-7(6H)-one

A suspension of ethyl [(4-amino-2-chloro-5-pyrimidinyl)thio]acetate (0.786 g, 3.17 mmol) in ethanol (50 ml) was heated to 70°C. Cesium carbonate (1.034 g, 3.17 mmol) was added and the solution was heated for a further 5 minutes. A white solid precipitated out of solution almost immediately. The solution was concentrated under reduced pressure. The residue was dissolved in water and brought to pH = 5 with 1N HCl. The aqueous layer was extracted with CH₂Cl₂ (2X). The organic layers were combined, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to yield a light yellow solid. MS (ES+) m/z 202.0 (MH⁺).

(e) 2-Ethenyl-1H-pyrimido[5,4-b][1,4]thiazin-7(6H)-one

2-Chloro-1H-pyrimido[5,4-b][1,4]thiazin-7(6H)-one (0.639 g, 3.17 mmol) was treated with tributylvinyl tin (1.388 ml, 4.76 mmol), and tetrakis(triphenylphosphine) palladium(0) (0.293 g, 0.254 mmol) in 1,4-dioxane (4 ml) and toluene (4 ml) in a microwave vial. The reaction was heated in the microwave at 140°C for 20 minutes. The solution was diluted with EtOAc and washed with saturated NaHCO₃ solution. The aqueous layer was extracted with EtOAc (2X). The organic solution were combined, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was chromatographed using a gradient of 0-60% CH₂Cl₂/(CH₂Cl₂/MeOH/NH₄OH) (90:10:1). The product was isolated as a mixture of the desired product and triphenylphosphine. Pure material was obtained by triturating and washing with diethyl ether. The product was isolated as an orange solid. MS (ES+) m/z 194.0 (MH⁺).

(f) Title compound

A solution of 2-ethenyl-1H-pyrimido[5,4-b][1,4]thiazin-7(6H)-one (0.262 g, 1.356 mmol) in methanol/DCM was cooled to -78°C and treated with ozone until the solution turned blue. The solution was stirred at -78°C for an additional 5 minutes. Dimethyl sulfide (5.0 ml, 67.6 mmol) was added and the solution was allowed to warm to room temperature and stir overnight. The solution was concentrated onto silical gel and the crude material was chromatographed using a gradient of 0-100%
CH₂Cl₂/(CH₂Cl₂/MeOH/NH₄OH) (90:10:1). The product was isolated as a light yellow solid.
MS (ES+) m/z 195.9 (MH⁺).

**Biological Activity**

**Antimicrobial Activity Assay:**

Whole-cell antimicrobial activity was determined by broth microdilution using the National Committee for Clinical Laboratory Standards (NCCLS) recommended procedure, Document M7-A7, "Methods for Dilution Susceptibility Tests for Bacteria that Grow Aerobically". The compounds were tested in serial two-fold dilutions ranging from 0.016 to 16 mcg/mL.

The minimum inhibitory concentration (MIC) was determined as the lowest concentration of compound that inhibited visible growth. A mirror reader was used to assist in determining the MIC endpoint.

Compounds were evaluated against Gram-positive organisms, selected from *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Enterococcus faecalis* and *Enterococcus faecium*.

In addition, compounds were evaluated against Gram-negative organisms selected from *Haemophilus influenzae*, *Moraxella catarrhalis*, *Acinetobacter baumannii*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Legionella pneumophila*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Klebsiella pneumoniae* and *Stenotrophomonas maltophilia*.

The *L. pneumophila* isolates were tested using a modified CLSI procedure for broth microdilution. For this assay, compounds were tested in serial doubling dilutions over a concentration range of 0.03 to 32 mcg/mL. An inoculum of each test isolate was prepared in buffered yeast broth and adjusted to a density equivalent to a 0.5 McFarland standard. After inoculation, the microtitre plates were incubated at 37°C for 72 hours.

Each of the listed Examples, as identified in the present application, was tested in at least one exemplified salt or free base form. The tested Examples had a MIC <2µg/ml against a strain of at least one of the organisms listed above. For at least one strain of every organism listed above, at least one Example had a MIC ≤2µg/ml.

*Mycobacterium tuberculosis* H37Rv Inhibition Assay

The measurement of the minimum inhibitory concentration (MIC) for each tested compound was performed in 96 wells flat-bottom, polystyrene microtiter plates. Ten two-fold drug dilutions in neat DMSO starting at 400µM were performed. Five µl of these drug solutions were added to 95 µl of Middlebrook 7H9 medium. (Lines A-H, rows 1-10
of the plate layout). Isoniazid was used as a positive control, 8 two-fold dilution of Isoniazid starting at 160 µg/ml\(^{-1}\) was prepared and 5 µl of this control curve was added to 95µl of Middlebrook 7H9 (Difco catalogue Ref. 271310) + ADC medium (Becton Dickinson Catalogue Ref. 211887). (Row 11, lines A-H). Five µl of neat DMSO were added to row 12 (growth and Blank controls).

The inoculum was standardised to approximately 1x10\(^7\) cfu/ml and diluted 1 in 100 in Middlebrook 7H9+ADC medium and 0.025% Tween 80 (Sigma P4780), to produce the final inoculum of H37Rv strain (ATCC25618). One hundred µl of this inoculum was added to the entire plate but G-12 and H-12 wells (Blank controls). All plates were placed in a sealed box to prevent drying out of the peripheral wells and they were incubated at 37\(^\circ\)C without shaking for six days. A resazurin solution was prepared by dissolving one tablet of resazurin (Resazurin Tablets for Milk Testing; Ref 330884Y VWR International Ltd) in 30 ml sterile PBS (phosphate buffered saline). 25 µl of this solution was added to each well. Fluorescence was measured (Spectramax M5 Molecular Devices, Excitation 530nm, Emission 590nm) after 48 hours to determine the MIC value.

Examples 1, 5, 7-9, 14, 15, 18A and 18B were tested in the Mycobacterium tuberculosis H37Rv inhibition assay. Example 9 showed an MIC value of 1.1 µg/ml or lower. Examples 1, 7, 8, 18A and 18B showed an MIC value of 0.2 µg/ml or lower. Examples 5, 14 and 15 gave MIC values higher than 2.5 µg/ml.
Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt or N-oxide thereof:

   \[
   \begin{align*}
   &\text{wherein:} \\
   &Z^1 \text{ and } Z^2 \text{ are independently selected from } N \text{ and } CH; \\
   &AB \text{ is } OCH_2, \text{ CH}_2O, \text{ NR}^{11}\text{CH}_2 \text{ or CH}_2\text{NR}^{11}; \\
   &R^{11} \text{ is selected from } C(1-2)\text{alkyl;} \text{ formyl;} (C_1-2)\text{alkylcarbonyl;} \text{ and } (C_1-2)\text{alkylsulphonyl;} \\
   &R^{1a} \text{ is selected from hydrogen; halogen; cyano;} (C_1-6)\text{alkyl;} (C_1-6)\text{alkylthio;} \\
   &\text{trifluoromethyl; trifluoromethoxy; carboxy;} \text{ hydroxy optionally substituted with } (C_1-6)\text{alkyl or } (C_1-6)\text{alkoxy-substituted}(C_1-6)\text{alkyl;} (C_1-6)\text{alkoxy-substituted}(C_1-6)\text{alkyl;} \\
   &\text{hydroxy } (C_1-6)\text{alkyl;} \text{ an amino group optionally N-substituted by one or two } (C_1-6)\text{alkyl}, \\
   &\text{formyl; } (C_1-6)\text{alkylcarbonyl or } (C_1-6)\text{alkylsulphonyl groups;} \text{ or aminocarbonyl wherein the amino group is optionally substituted by } (C_1-4)\text{alkyl;} \\
   &R^{1b} \text{ is } H \text{ or } F; \\
   &R^2 \text{ is hydrogen;} \\
   &R^v \text{ and } R^w \text{ are hydrogen, } R^v \text{ is absent and } R^3 \text{ is in the 1-position and } R^w \text{ is hydrogen or } R^v \text{ and } R^w \text{ together are a bond;} \\
   &R^3 \text{ is hydrogen; or} \\
   &\text{when } R^v \text{ and } R^w \text{ are a bond, } R^3 \text{ is in the 2-, 3- or 4- position and when } R^w \text{ is hydrogen, } \\
   &R^3 \text{ is in the 1-, 2-, 3- or 4-position and } R^3 \text{ is:} \\
   &\text{hydroxy optionally substituted by } (C_1-6)\text{alkyl;} \text{ amino optionally mono- or disubstituted independently by } (C_1-6)\text{alkyl or } (C_1-6)\text{alkylcarbonyl;} \text{ fluoro;} \text{ carboxy;} \text{ cyano;} (C_1-6)\text{alkoxycarbonyl;} \text{ aminocarbonyl wherein the amino group is optionally substituted by } (C_1-6)\text{alkyl or } (C_1-6)\text{alkylcarbonyl, or} \\
   &\text{(C}_1-4)\text{alkyl optionally substituted with any of the groups listed above for } R^3;  
   \end{align*}
\]
provided that when \( R^3 \) is in the 4-position it is not optionally substituted hydroxyl or amino;
provided that when \( R^3 \) is in the 1-position and \( AB \) is \( CH_2NR^{11} \) or \( R^3 \) is in the 4-position, it is not optionally substituted hydroxyl or amino;
and provided that when \( R^3 \) is in the 1-position and \( AB \) is \( CH_2O \), it is not optionally substituted amino;

\( R^4 \) is \( UR^5 \);

\( U \) is selected from \( CO \) and \( CH_2 \) and

\( R^5 \) is an optionally substituted bicyclic carbocyclic or heterocyclic ring system (B):

\[
\begin{array}{c}
\text{(a)} \\
X^1 \\
Y^1 \\
X^2 \\
Y^2
\end{array}
\]

containing up to four heteroatoms in each ring in which

- at least one of rings (a) and (b) is aromatic;
- \( X^1 \) is C or N when part of an aromatic ring, or CR\(^{14} \) when part of a non-aromatic ring;
- \( X^2 \) is N, NR\(^{13} \), O, S(O)\(_X\), CO or CR\(^{14} \) when part of an aromatic or non-aromatic ring or may in addition be CR\(^{14}R^{15} \) when part of a non-aromatic ring;
- \( X^3 \) and \( X^5 \) are independently N or C;
- \( Y^1 \) is a 0 to 4 atom linker group each atom of which is independently selected from N, NR\(^{13} \), O, S(O)\(_X\), CO and CR\(^{14} \) when part of an aromatic or non-aromatic ring or may additionally be CR\(^{14}R^{15} \) when part of a non-aromatic ring;
- \( Y^2 \) is a 2 to 6 atom linker group, each atom of \( Y^2 \) being independently selected from N, NR\(^{13} \), O, S(O)\(_X\), CO, CR\(^{14} \) when part of an aromatic or non-aromatic ring or may additionally be CR\(^{14}R^{15} \) when part of a non-aromatic ring;
- each of \( R^{14} \) and \( R^{15} \) is independently selected from: H; (C\(_{1-2}\))alkylthio; halo; carboxy(C\(_{1-2}\))alkyl; (C\(_{1-2}\))alkyl; (C\(_{1-2}\))alkoxycarbonyl; (C\(_{1-2}\))alkylcarbonyl; (C\(_{1-2}\))alkoxy(C\(_{1-2}\))alkyl; hydroxy; hydroxy(C\(_{1-24}\))alkyl; (C\(_{1-2}\))alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally mono- or di-substituted by (C\(_{1-2}\))alkyl; or \( R^{14} \) and \( R^{15} \) may together represent oxo;
- each \( R^{13} \) is independently H; trifluoromethyl; (C\(_{1-2}\))alkyl optionally substituted by hydroxy, (C\(_{1-2}\))alkoxy, (C\(_{1-2}\))alkylthio, halo or trifluoromethyl; (C\(_2\))alkenyl; (C\(_{1-2}\))alkoxycarbonyl; (C\(_{1-2}\))alkylcarbonyl; (C\(_{1-2}\))alkylsulphonyl; aminocarbonyl wherein the amino group is optionally mono or disubstituted by (C\(_{1-2}\))alkyl;
each $x$ is independently 0, 1 or 2.

2. A compound according to claim 1 wherein:
   (1) $Z^1$ is CH and $Z^2$ is N;
   (2) $Z^1$ and $Z^2$ are both CH;
   (3) $Z^1$ is N and $Z^2$ is CH
   (4) $Z^1$ and $Z^2$ are both N.

3. A compound according to claim 1 or 2 wherein $R^{1a}$ is halo or cyano and $R^{1b}$ is hydrogen or both $R^{1a}$ and $R^{1b}$ are hydrogen.

4. A compound according to any preceding claim wherein $R^2$ is hydrogen.

5. A compound according to any preceding claim wherein $R^3$ is hydrogen.

6. A compound according to any preceding claim wherein AB is OCH$_2$, NHCH$_2$ or CH$_2$NH.

7. A compound according to any preceding claim wherein U is CH$_2$.

8. A compound according to any preceding claim wherein $R^5$ is an aromatic heterocyclic ring (A) having 8-11 ring atoms including 2-4 heteroatoms of which at least one is N or NR$_{13}$ in which Y$^2$ contains 2-3 heteroatoms, one of which is S and 1-2 are N, with one N bonded to X$^3$, or the heterocyclic ring (A) has ring (a) aromatic selected from optionally substituted benzo, pyrido, pyridazine and pyrimidino and ring (b) non aromatic and Y$^2$ has 3-4 atoms including at least one heteroatom, with O, S, CH$_2$ or NR$_{13}$ bonded to X$^5$, where R$_{13}$ is other than hydrogen, and either NHCO bonded via N to X$^3$, or O, S, CH$_2$, or NH bonded to X$^3$.

9. A compound according to any of claims 1 to 7 wherein $R^5$ is selected from:
   2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl
   [1,3]oxathiolo[5,4-c]pyridin-6-yl
   3,4-dihydro-2H-pyrano[2,3-c]pyridine-6-yl
   3-substituted 5H-pyridazino[3,4-b][1,4]thiazin-6-(7H)-one
   6-substituted 2H-pyrido[3,2-b][1,4]thiazin-3(4H)-one
   6-substituted 7-chloro-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one
   6-substituted 2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one
7-substituted 1H-pyrido[2,3-b][1,4]thiazin-2(3H)-one
7-substituted 3,4-dihydro-1,8-naphthyridin-2(1H)-one
5-substituted 2,3-dihydrofuro[3,2-b]pyridine
3-substituted 6,7-dihydro[1,4]dioxino[2,3-c]pyridazine
2-substituted 1H-pyrimido[5,4-b][1,4]oxazin-7(6H)-one

10. A compound according to claim 1 which is the free base of the compound of any one of Examples 1 to 25 or a pharmaceutically acceptable salt thereof.

11. A method of treatment of bacterial infections in mammals, particularly in man, which method comprises the administration to a mammal in need of such treatment an effective amount of a compound according to claim 1.

12. The use of a compound according to claim 1 in the manufacture of a medicament for use in the treatment of bacterial infections in mammals.

13. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.
**INTERNATIONAL SEARCH REPORT**

**INTERNATIONAL APPLICATION No.**

PCT/EP2008/065505

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**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D047104 C07D0491048 C07D0491052 C07D0491056 C07D049704

C07D049804 C07D051304 A61K0314704 A61P03104

According to International Patent Classification (IPC) or to both national classification and IPC

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**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation in the fields searched

Electronic data base consulted during the International search stage of this data base and its updates, where substantially filed (100% files)

EPO-Internal, BEILSTEIN Data, WPI Data, CHEMABS Data

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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevance to claim no.</th>
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<tr>
<td>Y</td>
<td>WO 2008/006648 A (GLAXO GROUP LTD [GB]; DAVIES DAVID THOMAS [GB]; JONES GRAHAM ELGIN [GB]) 17 January 2008 (2008-01-17) cited in the application claims 1,9-11 examples 4,10-13</td>
<td>1-13</td>
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**X** Further documents are listed in the continuation of Box G

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**Y** See patent family annex

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* Special categories of class documents:

  * A* Document defining the general state of the art which is not considered to be of particular relevance
  * B* Earlier document but published on or after the international filing date
  * C* Document which may render the patent inadmissible to priority claims or which is cited to establish the publication date of another document or other special reason (if specified)
  * D* Document referring to an essential disclosure, e.g., exhibition or other means
  * E* Document published prior to the international filing date but later than the priority date claimed

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Data of the actual completion of the international search:

4 May 2009

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**Date of mailing of the international search report:**

15/05/2009

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**Name and mailing address of the ISA:**

European Patent Office, P. 9886 Pauwelaar Z
NL-2280 Hl Rijswijk
Tel (+31-70) 540-2040
Fax (+31-70) 940-3016

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**Authorized officer:**

Gutke, Hans-Jürgen
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<td>Y</td>
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The present invention provides a compound represented by the formula (I) wherein X is a hydrogen atom or a fluorine atom, R is a hydrogen atom or alkyl, R' is (1) cyclopropyl optionally substituted by to 3 halogen atoms or (2) phenyl optionally substituted by 1 to 3 halogen atoms, R" is alkyl, alkoxy, haloalkoxy, a halogen atom, cyano, etc., and R' is 7-oxo-7,8-dihydro-1,8- napthyridine, 3-pyridyl, etc., or a salt thereof. The compound of the present invention has excellent antibacterial activity against Clostridium difficile and is useful for the prevention or treatment of intestinal infection such as Clostridium difficile-associated diarrhea.
DESCRIPTION
QUINOLONE COMPOUND

Technical Field

The present invention relates to quinolone compounds and pharmaceutical use thereof.

Background Art

*Clostridium difficile* infection is associated with consumption of antibiotics which disrupt the normal microbial flora of the gut, allowing *Clostridium difficile* to establish itself and produce disease. Currently, only vancomycin or metronidazole is recommended for treatment and many patients suffer from relapse on infection (Expert Opin. Ther. Patents (2010) 20(10), pp. 1389-1399).

EP2177214 A1 describes use of ozenoxacin for *Clostridium difficile*.


Summary of Invention

The object of the present invention is to provide a novel quinolone compound which has excellent antimicrobial activity, particularly excellent antimicrobial activity against *Clostridium difficile*. Another object of the present invention is to provide a pharmaceutical composition containing said quinolone compound, which is useful for the prevention or treatment of various infectious diseases including antibiotics-associated diarrhea (AAD) such as *Clostridium difficile*-associated diarrhea (CDAD). A further object of the present invention is to provide a method for preventing or treating a bacterial infection including AAD such as CDAD, which comprises administering said quinolone compound to a human or an animal.

The present invention provides a quinolone compound, a
pharmaceutical composition comprising said compound, use of said compound, and a method for preventing or treating a bacterial infection, as described in Items 1 to 27 below.

Item 1. A compound represented by the formula (I)

\[ \text{wherein} \]
\[ X \text{ is a hydrogen atom or a fluorine atom;} \]
\[ R \text{ is a hydrogen atom or alkyl;} \]
\[ R^1 \text{ is (1) cyclopropyl optionally substituted by 1 to 3 halogen atoms or (2) phenyl optionally substituted by 1 to 3 halogen atoms;} \]
\[ R^2 \text{ is a hydrogen atom; alkyl optionally substituted by 1 or 2 substituents selected from the group consisting of a halogen atom and hydroxyl; alkoxy; haloalkoxy; a halogen atom; cyano; cyclopropyl; nitro; amino; formyl; alkenyl or alkynyl; or} \]
\[ R^1 \text{ and } R^2 \text{ are bonded to form a 5- or 6-membered ring optionally substituted by alkyl;} \]
\[ R^3 \text{ is} \]
\[ (1) \text{ a fused heterocyclic group of the formula} \]

\[ \text{or} \]

\[ \text{wherein} \]
\[ \text{--- represents a single bond or a double bond,} \]
\[ X^1 \text{ is } C(R^3) \text{ or } N, \]
\[ R^4 \text{ is a hydrogen atom or alkyl, and} \]
\[ R^5 \text{ is (a) a hydrogen atom,} \]
(b) a halogen atom,
(c) cyano,
(d) nitro,
(e) hydroxy,

(f) alkyl optionally substituted by 1 to 3 halogen atoms,
(g) alkenyl or alkynyl,
(h) aryl, or

(i) alkoxy optionally substituted by 1 to 3 halogen atoms,

when X¹ is C(R⁵), R⁷ and R⁸ are optionally bonded to form a 5- or 6-membered ring optionally substituted by oxo, said fused heterocyclic group is optionally substituted by 1 or 2 substituents selected from the group consisting of a halogen atom, cyano, nitro, hydroxy and alkyl,

(2) a group of the formula

![Chemical Structure](image)

wherein

X² is C(R⁶) or N, and

R⁵, R⁷ and R⁸ are each independently,

(a) a hydrogen atom,
(b) a halogen atom,
(c) cyano,
(d) nitro,
(e) amino,

(f) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, alkoxy and amino,

(g) alkenyl,
(h) alkynyl,

(i) aryl,

(j) formyl or CH=N-OH,

(k) carboxy,
(1) carbamoyl,
(m) a 5- to 13-membered aromatic heterocyclic group optionally substituted by alkyl, or
(n) alkenyloxy,

(3) a group of the formula

\[
\begin{align*}
\text{X}^3 & \quad \text{X}^3 \\
\text{R}^6 & \quad \text{R}^6 \\
\end{align*}
\]

or

wherein
\( X^c \) and \( X^{c'} \) are \( N \), or
\( X^c \) is \( N \) and \( X^{c'} \) is \( CR'' \), wherein \( R'' \) is hydrogen atom, amino,
hydroxy, alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of alkoxy and dimethylamino or mercapto, or
\( X^3 \) is \( CH \) and \( X^{c'} \) is \( N \),
\( R' \) is a hydrogen atom or alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of substituted hydroxyl and amino, and
\( R^6 \) is as defined above,
(4) a group of the formula
wherein

— represents a single bond or a double bond and $R^6$ is as
defined above,

(5) 3-pyridyl optionally substituted by 1 or 2 substituents selected from the group consisting of

(a) a halogen atom,
(b) cyano,
(c) nitro,
(d) hydroxy,
(e) amino,

(f) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, alkylamino, dialkylamino and hydroxy,

(g) alkenyl, alkynyl
(h) aryl,

(i) cycloalkyl,
(j) alkoxy,

(k) alkylamino,
(l) dialkylamino,

(m) phenylamino optionally substituted by 1 to 3 halogen atoms,

(n) a cyclic amino group optionally substituted by alkoxy carbonyl,

(o) formyl,

(p) carbamoyl optionally substituted by alkyl optionally substituted by hydroxy, and

(q) a 5- to 10-membered aromatic heterocyclic group optionally substituted by alkyl,

(6) 4-pyridyl optionally substituted by a halogen atom,

(7) 5-pyrimidinyl optionally substituted by 1 or 2 substituents selected from the group consisting of amino, alkylamino, dialkylamino and carboxy,

(8) 2-indolyl, 3-indolyl, 5-indolyl, 6-indolyl, benzofuranyl, benzothiophenyl, benzoazolyl or benzothiazolyl, each optionally substituted by 1 or 2 substituents selected from the group consisting of

(a) a halogen atom,
(b) cyano,
(c) nitro,
(d) hydroxy,
(e) alkyl optionally substituted by 1 to 3 substituents
selected from the group consisting of amino,
alkoxycarbonylamino, alkylamino and dialkylamino,
(f) alkoxy,
(g) formyl,
(h) carboxy, and

(j) amino optionally substituted by 1 or 2 substituents
selected from the group consisting of
(i) alkoxy carbonyl,
(ii) alkyl carbonyl optionally substituted by a
substituent selected from the group consisting of
(A) cycloalkyloxy optionally substituted by 1
to 3 alkyl,
(B) alkylamino,
(C) dialkylamino,
(D) a cyclic amino group optionally substituted
by alkoxy carbonyl, and
(E) a halogen atom,
(iii) phenyl carbonyl optionally substituted by 1 to
3 substituents selected from the group consisting of
alkyl and alkoxy,
(iv) cycloalkyl carbonyl,
(v) a 5- to 10-membered aromatic
heterocyclyl carbonyl group optionally substituted by
alkyl optionally substituted by 1 to 3 halogen
atoms,
(vi) benzyl carbonyl optionally substituted by 1 to 3
substituents selected from the group consisting of a
halogen atom and alkoxy,
(vii) aryl sulfonyl optionally substituted by alkoxy,
(viii) cycloalkyl alkyl sulfonyl optionally
substituted by 1 to 3 substituents selected from the
group consisting of alkyl and c xo, 
(i) a 5- to 10-membered aromatic 
heterocycllylsulfonyl group optionally substituted by 
1 to 3 alkyl, and 

(x) \(-C\left(\text{-N-CN}\right)\)-SR' wherein R' is alkyl, 

(9) a group of the formula 

\[
\begin{align*}
\text{(F)} & \quad \text{or} \\
\text{(G)}
\end{align*}
\]

wherein 
one of \(Y^1, Y^2, Y^3\) and \(Y^4\) is N or \(N\left(-O\right)\), and the remaining three 
are each \(C\left(R^{22}\right), C\left|R^{23}\right|\) and \(C\left(R^{24}\right)\), 
\(W\) is O, S, NE or \(N\left(R^{37}\right)\) 
\(R^{25}\) is a hydrogen atom or alkyl, and 
\(R^{24}, R^{25}, R^{26}\) and \(R^{27}\) are each independently, 
(a) a hydrogen atom, 
(b) cyano, or 
(c) nitro, 

(10) a group of the formula 

\[
\begin{align*}
\text{(H)} & \quad \text{or} \\
\text{(J)}
\end{align*}
\]

wherein 
\(R^{28}\) is a hydrogen atom or hydroxy, and 
\(R^{29}\) is a hydrogen atom or alkyl, 

(11) a group of the formula
wherein

$X^5$ is $C(R^{11})$ or $N$,

$X^6$ is $CH_2$, $C(=O)$, $O$, $S$, $SO_2$ or $N(R^{12})$,

$X^7$ is $CH(R^{13})$, $C(=O)$ or $N(R^{14})$,

$X^8$ is $CH(R^{15})$ or $C(=O)$,

$R^{10}$, $R^{12}$ and $R^{14}$ are each independently,

(a) a hydrogen atom or

(b) alkyl, and

$R^{11}$, $R^{13}$ and $R^{15}$ are each independently,

(a) a hydrogen atom,

(b) a halogen atom,

(c) cyano,

(d) nitro,

(e) amino,

(f) alkylamino,

(g) dialkylamino,

(h) alkyl optionally substituted by hydroxy, or

(i) alkenyl,

when $X^5$ is $C(R^{11})$, $R^{10}$ and $R^{11}$ are optionally bonded to form a 5- or 6-membered ring optionally substituted by alkyl or oxo, and

when $X^6$ is $N(R^{12})$ and $X^7$ is $CH(R^{13})$, $R^{12}$ and $R^{15}$ are optionally bonded to form a 5- or 6-membered ring,

(12) a group of the formula

wherein $R^{16}$ is

(a) a hydrogen atom,
(b) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of cyano, alkylamino and dialkylamino,

c) alkenyl optionally substituted by carboxy,

d) formyl,

e) carboxy,

(f) carbamoyl,

g) \(-\text{C}(\text{R}^{17})=\text{N}=-\text{OH}\) wherein \(\text{R}^{17}\) is a hydrogen atom, cyano or hydroxy,

(h) a 5- to 10-membered aromatic heterocyclic group optionally substituted by alkyl, alkoxy carbonyl, carboxy or phenyl, or

(i) cyano,

(13) a group of the formula

\[
\text{R}^{10}\text{O}_{\text{n}}\text{R}^{19}\text{R}^{20}\text{R}^{33}
\]

wherein

\(\text{R}^{10}\) is a hydrogen atom or alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom and phenyl,

\(\text{n}\) is 0 or 1,

\(\text{R}^{19}, \text{R}^{20}\) and \(\text{R}^{33}\) are each independently,

(a) a hydrogen atom,

(b) a halogen atom,

c) cyano,

d) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of

(i) a halogen atom,

(ii) cyano,

(iii) hydroxy,

(iv) amino,

(v) alkylamino,
(vi) dialkylamino, and
(vii) a cyclic amino group optionally substituted by alkyl,
(e) alkoxy,
(f) amino optionally substituted by 1 or 2 substituents selected from the group consisting of
(i) alkylcarbonyl optionally substituted by a cyclic amino group,
(ii) alkylsulfonyl,
(iii) carbamoyl,
(iv) alkyl, cycloalkyl or cycloalkylalkyl, and
(v) 5- to 10-membered saturated heterocyclic group,
(g) carboxy,
(h) alkoxy carbonyl,
(i) carbamoyl optionally substituted by alkyl optionally substituted by amino, dialkylamino, dialkylamino or alkoxy carbonylamino,
(j) formyl,
(k) a 5- to 10-membered aromatic heterocyclic group optionally substituted by alkyl,
(l) -CH=N−OR\textsuperscript{21} wherein R\textsuperscript{21} is a hydrogen atom or alkyl optionally substituted by alkylamino or dialkylamino,
(m) nitro,
(n) a 5- to 10-membered saturated heterocyclic group optionally substituted by amino,
(o) phenyl, or
(p) -NHC(SMe)−CHCN,
(14) a group of the formula

```
\[
\text{O} \quad \text{O} \\
\quad \text{R}^{30}
\]
```

wherein
R\(^1\) is (a) a hydrogen atom,
(b) a halogen atom,
(c) cyano,
(d) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom and hydroxyl,
(e) alkenyl,
(f) alkynyl,
(g) alkoxy,
(h) formyl,
(i) -CH-N=OH, or
(j) carboxamidyl,
(k) naphthyl or isochroman-1-yl,
(l) quinoyl or isoquinoyl, or their oxide derivatives,
(m) a group of the formula

![Chemical Structure](attachment:image)

(n) a group of the formula

![Chemical Structure](attachment:image)

(wherein

U is O or S, and

R\(^2\) is (a) a hydrogen atom,
(b) a halogen atom,
(c) alkyl optionally substituted by 1 to 3 halogen atoms,
(d) carboxy,
(e) nitrile,
(f) cyano, or

[g]...
(q) amino,

(19) a group of the formula

\[
\begin{align*}
\text{wherein} \\
\text{a} R^{32} \text{ is (a) a halogen atom,} \\
\text{or} \\
\text{a} R^{32} \text{ is (b) phenyl, or} \\
\text{or (c) a group of the formula}
\end{align*}
\]

(20) a group of the formula

\[
\begin{align*}
\text{wherein} \\
R^{34} \text{ and } R^{35} \text{ are each independently,} \\
\text{a) a hydrogen atom, or} \\
\text{or (b) aminocyclyl,}
\end{align*}
\]

(21) a group of the formula

\[
\begin{align*}
\text{wherein } R^{16} \text{ is (a) a hydrogen atom,}
\end{align*}
\]
(b) a halogen atom,
(c) nitro, or
(d) thieryl, or
(22) a group of the formula

\[
\begin{align*}
\text{HN} & \quad \text{HN} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N}
\end{align*}
\]

or a salt thereof.

Item 1A. The compound of item 1, wherein
X is a hydrogen atom or a fluorine atom;
R is a hydrogen atom or alkyl;
\( R^1 \) is (1) cyclopropyl optionally substituted by 1 to 3 halogen atoms or (2) phenyl optionally substituted by 1 to 3 halogen atoms;
R2 is alkyl, alkoxy, haloalkoxy, a chlorine atom or cyano; or
R1 and R2 are bonded to form a 5- or 6-membered ring optionally substituted by alkyl; and
R3 is
(1) a fused heterocyclic group of the formula

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{X} & \quad \text{X}
\end{align*}
\]

or

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O}
\end{align*}
\]

(1) a fused heterocyclic group of the formula

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O}
\end{align*}
\]

wherein

\[
\begin{align*}
\text{X} & \quad \text{X}
\end{align*}
\]

represents a single bond or a double bond,
X¹ is C(R³) or N,
R⁴ is a hydrogen atom or alkyl, and
R⁵ is (a) a hydrogen atom,
(b) a halogen atom,
(c) cyano,
(d) nitro,
(e) hydroxy,
(f) alkyl optionally substituted by 1 to 3 halogen atoms,
(g) alkenyl or alkynyl,
(h) aryl, or
(i) alkoxy optionally substituted by 1 to 3 halogen atoms,
when X¹ is C(R³), R⁴ and R⁵ are optionally bonded to form a 5- or 6-membered ring optionally substituted by oxo,
said fused heterocyclic group is optionally substituted by 1 or 2 substituents selected from the group consisting of a halogen atom, cyano, nitro, hydroxy and alkyl,
(2) a group of the formula
\[
\begin{array}{c}
\text{R}^7 \quad \text{N} \\
\text{X}^2 \\
\text{R}^6 \\
\end{array}
\]
(C)
wherein
X² is C(R⁶) or N, and
R⁶, R⁷ and R⁸ are each independently,
(a) a hydrogen atom,
(b) a halogen atom,
(c) cyano,
(d) nitro,
(e) amino,
(f) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, alkoxy and amino,
(g) alkenyl,
(h) alkynyl,
(i) aryl,
(j) formyl or CH=N-CH,
(k) carboxy,
(l) carbamoyl, or

(m) a 5- to 10-membered aromatic heterocyclic group optionally substituted by alkyl,

(3) a group of the formula

\[ \text{or} \]

wherein

X and X' are N, or

X is H and X' is CR''', wherein R''' is a hydrogen atom, amino, hydroxy, alkyl or mercapto, or

X is CH and X' is N,

R' is a hydrogen atom or alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of substituted hydroxy and amino, and

R is as defined above,

(4) a group of the formula
Wherein

 diversos represents a single bond or a double bond and $R^6$ is as
defined above,

(5) 3-pyridyl optionally substituted by 1 or 2 substituents selected from the group consisting of

(a) a halogen atom,
(b) cyano,
(c) nitro,
(d) hydroxy,
(e) amino,
(f) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, alkylamino, dialkylamino and hydroxy,
(g) alkenyl or alkynyl,
(h) aryl,
(i) cycloalkyl,
(j) alkoxy,
(k) alkylamino,
(l) dialkylamino,
(m) phenylamino optionally substituted by 1 to 3 halogen atoms,
(n) a cyclic amino group optionally substituted by alkoxy carbonyl,
(o) formyl,
(p) carbamoyl optionally substituted by alkyl optionally substituted by hydroxy, and
(q) a 5- to 10-membered aromatic heterocyclic group optionally substituted by alkyl,

(6) 4-pyridyl optionally substituted by a halogen atom,

(7) 5-pyrimidinyl optionally substituted by 1 or 2 substituents selected from the group consisting of amino, alkylamino, dialkylamino and carboxy,

(8) 2-indolyl, 3-indolyl, 5-indolyl, 6-indolyl, benzofuranyl, benzo thiophenyl, benzoazolyl or benzo thi azolyl, each optionally substituted by 1 or 2 substituents selected from the group consisting of

(a) a halogen atom,
(b) cyano,
(c) nitro,
(d) hydroxy,
(e) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of amino, alkoxy carbonylamino, alkylamino and dialkylamino, (f) alkoxy,
(g) formyl,
(h) carboxy, and

(j) amino optionally substituted by 1 or 2 substituents selected from the group consisting of
   (i) alkoxy carbonyl,
   (ii) alkyl carbonyl optionally substituted by a substituent selected from the group consisting of
       (A) cycloalkyloxy optionally substituted by 1 to 3 alkyl,
       (B) alkylamino,
       (C) dialkylamino,
       (D) a cyclic amino group optionally substituted by alkoxy carbonyl, and
       (E) a halogen atom,
   (iii) phenyl carbonyl optionally substituted by 1 to 3 substituents selected from the group consisting of alkyl and alkoxy,
   (iv) cycloalkyl carbonyl,
   (v) a 5- to 10-membered aromatic heterocyclic carbonyl group optionally substituted by alkyl optionally substituted by 1 to 3 halogen atoms,
   (vi) benzyl carbonyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom and alkoxy,
   (vii) aryl sulfonyl optionally substituted by alkoxy,
   (viii) cycloalkylalkyl sulfonyl optionally substituted by 1 to 3 substituents selected from the
group consisting of alkyl and czo.
(ix) a 5- to 10-membered aromatic heterocyclylsulfonyl group optionally substituted by 1 to 3 alkyl, and
(x) \(-C(=\text{N-CN})-\)SR' wherein R' is alkyl,

(a) a group of the formula

\[
\begin{align*}
Y^1 & \equiv Y^2 \equiv Y^3 \equiv Y^4 \\
Y^1 \equiv Y^2 & \equiv Y^3 \equiv Y^4 \\
W & \equiv \text{C}(R^{27})
\end{align*}
\]

wherein

one of Y^1, Y^2, Y^3 and Y^4 is N or N'=(-C'), and the remaining three are each C(R^{28}), C(R^{29}) and C(R^{30}),
W is O, S or N(R^{31})

\(R^{25}\) is a hydrogen atom or alkyl, and
\(R^{24}, R^{25}, R^{26} \text{ and } R^{27}\) are each independently,
(a) a hydrogen atom,
(b) cyano, or
(c) nitro,

(10) a group of the formula

\[
\begin{align*}
R^{28} & \equiv \text{N}
\end{align*}
\]

wherein

\(R^{26}\) is a hydrogen atom or hydroxy, and
\(R^{27}\) is a hydrogen atom or alkyl,

(11) a group of the formula
wherein

$x^5$ is $C(R^{11})$ or $N$,

$x^6$ is $CH_2$, $C(=O)$, $O$, $S$, $SO_2$ or $N(R^{12})$,

$x^7$ is $CH(R^{13})$, $C(=O)$ or $N(R^{14})$,

$x^8$ is $CH(R^{15})$ or $C(=O)$,

$R^{10}$, $R^{12}$ and $R^{14}$ are each independently,

(a) a hydrogen atom or
(b) alkyl, and

$R^{11}$, $R^{13}$ and $R^{15}$ are each independently,

(a) a hydrogen atom,
(b) a halogen atom,
(c) cyano,
(d) nitro,

(e) amino,
(f) alkylamino,
(g) dialkylamino,
(h) alkyl optionally substituted by hydroxy, or
(i) alkenyl,

when $x^5$ is $C(R^{11})$, $R^{10}$ and $R^{11}$ are optionally bonded to form a 5- or 6-membered ring optionally substituted by alkyl or oxo, and when $x^6$ is $N(R^{12})$ and $x^7$ is $CH(R^{13})$, $R^{12}$ and $R^{15}$ are optionally bonded to form a 5- or 6-membered ring,

(12) a group of the formula

wherein $R^{16}$ is

(a) a hydrogen atom,
(b) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of cyano, alkylamino and dialkylamino,
(c) alkenyl optionally substituted by carboxy,
(d) formyl,
(e) carboxy,
(f) carbamoyl,
(g) \(-\text{C}(R^{17})=\text{N}-\text{OH}\) wherein \(R^{17}\) is a hydrogen atom, cyano or hydroxy,
(h) a 5- to 10-membered aromatic heterocyclic group optionally substituted by alkyl, alkoxy carbonyl, carboxy or phenyl, or
(i) cyano,

(13) a group of the formula

\[
\begin{align*}
\text{R}^{19} & \text{R}^{20} \\
\text{R}^{18} & \text{O} \\
\end{align*}
\]

(M)

wherein
\(\text{R}^{18}\) is a hydrogen atom or alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom and phenyl, and
\(\text{R}^{19}\) and \(\text{R}^{20}\) are each independently,
(a) a hydrogen atom,
(b) a halogen atom,
(c) cyano,
(d) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of
(i) a halogen atom,
(ii) cyano,
(iii) hydroxy,
(iv) amino,
(v) alkylamino,
(vi) dialkylamino, and
(vii) a cyclic amino group optionally substituted by alkyl,
(e) alkoxy,
(f) amino optionally substituted by 1 or 2 substituents selected from the group consisting of
(i) alkylcarbonyl optionally substituted by a cyclic amino group,
(ii) alkylsulfonyl,
(iii) carbamoyl, and
(iv) alkyl or cycloalkyl,
(g) carboxy,
(h) alkoxycarbonyl,
(i) carbamoyl optionally substituted by alkyl optionally substituted by amino, alkylamino, dialkylamino or alkoxy carbamoylamino,
(j) formyl,
(k) a 5- to 10-membered aromatic heterocyclic group optionally substituted by alkyl,
(l) -CH=N-OR\(^{21}\) wherein R\(^{21}\) is a hydrogen atom or alkyl optionally substituted by alkylamino or dialkylamino, or
(m) nitro,

(14) a group of the formula
\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{R}^{30} \\
\text{O}
\end{array}
\]

(N)

wherein

R\(^{30}\) is (a) a hydrogen atom,
(b) a halogen atom,
(c) cyano,
(d) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom and hydroxy,
(e) alkenyl,
(f) alkynyl,
(g) alkoxy,
(h) formyl, or
(i) \(-\text{CH}=\text{N}=\text{OH}\),

(15) naphthyl or isochromenyl, or
(16) quinolyl or isoquinolyl, or oxide derivative thereof, or a salt thereof.

Item 2. The compound of item 1 or 1A, wherein X is a fluorine atom, or a salt thereof.

Item 3. The compound of item 1 or 1A, wherein \(R^3\) is a fused heterocyclic group of the formula

\[
\begin{align*}
\text{A} & & \text{or} \\
\text{B} & & \\
\end{align*}
\]

wherein \(X^1\) and \(R^4\) are as defined in item 1, and said fused heterocyclic group is optionally substituted by 1 or 2 substituents selected from the group consisting of a halogen atom, cyano, nitro, hydroxy and alkyl, or a salt thereof.

Item 4. The compound of item 1 or 1A, wherein \(R^3\) is a group of the formula

\[
\begin{align*}
\text{A} & & \text{or} \\
\text{B} & & \\
\end{align*}
\]

wherein \(X^2\), \(R^6\) and \(R^7\) are as defined in item 1, or a salt thereof.

Item 5. The compound of item 1 or 1A, wherein \(R^3\) is a group of the formula
wherein $X'$, $X''$, $R^c$ and $R'$ are as defined in item 1, or a salt thereof.

> Item 6. The compound of item 1 or 1A, wherein $R^3$ is a group of the formula
wherein -- and $R^6$ are as defined in item 1, or a salt thereof.
Item 7. The compound of item 1 or 1A, wherein $R^3$ is a group of the formula

\[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{R}^{22}
\end{array}
\]

wherein $R^{22}$ is

(a) a halogen atom,
(b) cyano,
(c) nitro,
(d) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, alkylamino, dialkylamino and hydroxy,
(e) alkenyl or alkynyl,
(f) aryl,
(g) cycloalkyl,
(h) alkoxy,
(i) formyl, or
(j) carbamoyl optionally substituted by alkyl optionally substituted by hydroxy,

or a salt thereof.

Item 8. The compound of item 1 or 1A, wherein $R^3$ is 5-pyrimidinyl substituted by 1 or 2 substituents selected from the group consisting of amino, alkylamino, dialkylamino and carboxy, or a salt thereof.

Item 9. The compound of item 1 or 1A, wherein $R^3$ is 2-indolyl optionally substituted by 1 or 2 substituents selected from the group consisting of

(a) a halogen atom,
(b) cyano,
(c) nitro,
(d) hydroxy,
(e) alkyl optionally substituted by 1 to 3 substituents 
selected from the group consisting of amino, 
alloxycarbonylamino, alkylamino and dialkylamino, 
(f) alkoxy, 
(g) formyl, 
(h) carboxy, and 
(i) amino optionally substituted by 1 or 2 substituents 
selected from the group consisting of 
(i) alkoxy carbonyl, 
(ii) alkylcarbonyl optionally substituted by a 
substituent selected from the group consisting of 
(A) cycloalkyloxy optionally substituted by 1 
to 3 alkyl, 
(B) alkylamino, 
(C) dialkylamino, 
(D) a cyclic amino group optionally substituted 
by alloxycarbonyl, and 
(E) a halogen atom, 
(iii) phenylcarbonyl optionally substituted by 1 to 
3 substituents selected from the group consisting of 
alkyl and alkoxy, 
(iv) cycloalkylcarbonyl, 
(v) a 5- to 10-membered aromatic 
heterocyclylcarbonyl group optionally substituted by 
alkyl optionally substituted by 1 to 3 halogen 
atoms, 
(vi) benzylcarbonyl optionally substituted by 1 to 3 
substituents selected from the group consisting of a 
halogen atom and alkoxy, 
(vii) arylsulfonyl optionally substituted by alkoxy, 
(viii) cycloalkylalkylsulfonyl optionally 
substituted by 1 to 3 substituents selected from the 
group consisting of alkyl and oxo, 
(ix) a 5- to 10-membered aromatic 
heterocyclylsulfonyl group optionally substituted by
1 to 3 alkyl, and

\((2)\) -C(=N-CN)-SR^2 where in R^2 is alkyl,
or a salt thereof.

Item 10. The compound of item 1 or 1A, wherein R^3 is a
group of the formula

\[
\begin{align*}
&\text{or} \\
&\text{or}
\end{align*}
\]

wherein Y^1, Y^2, Y^3, Y^4, W and R^24 are as defined in item 1, or a
salt thereof.

Item 11. The compound of item 1 or 1A, wherein R^3 is a
group of the formula

\[
\begin{align*}
&\text{or} \\
&\text{or}
\end{align*}
\]

wherein R^28 and R^29 are as defined in item 1, or a salt thereof.

Item 12. The compound of item 1 or 1A, wherein R^3 is a
group of the formula

\[
\begin{align*}
&\text{or} \\
&\text{or}
\end{align*}
\]

wherein X^1, X^2, X^3, X^4 and R^10 are as defined in item 1, or a
salt thereof.
Item 13. The compound of item 1 or 1A, wherein R^3 is a group of the formula

\[
\begin{array}{c}
\text{R}^{16a}
\end{array}
\]

wherein R^{16a} is

(a) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of cyano, alkylamino and dialkylamino,

(b) alkenyl optionally substituted by carboxy,

(c) formyl,

(d) carboxy,

(e) carbamoyl,

(f) -C(R^{17})=N-OH wherein R^{17} is a hydrogen atom, cyano or hydroxy,

(g) a 5- to 10-membered aromatic heterocyclic group optionally substituted by alkyl, alkoxy carbonyl, carboxy or phenyl, or

(h) cyano,

or a salt thereof.

Item 14. The compound of item 1 or 1A, wherein R^3 is a group of the formula

\[
\begin{array}{c}
\text{R}^{19a}
\end{array}
\]

\[
\begin{array}{c}
\text{R}^{18a} \text{O}
\end{array}
\]

wherein

R^{18a} is alkyl, and

R^{19a} is (a) a halogen atom,

(b) cyano,

(c) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of
(i) a halogen atom,
(ii) cyano,
(iii) hydroxy,
(iv) amino,
(v) alkylamino,
(vi) dialkylamino, and
(vii) a cyclic amino group optionally substituted by alkyl,
(d) alkoxy,
(e) amino optionally substituted by 1 or 2 substituents selected from the group consisting of
(i) alkylcarbonyl optionally substituted by a cyclic amino group,
(ii) alkylsulfonyl,
(iii) carbamoyl, and
(iv) alkyl or cycloalkyl,
(f) carboxy,
(g) alkoxy carbonyl,
(h) carbamoyl optionally substituted by alkyl optionally substituted by amino, alkylamino, dialkylamino or alkoxy carbonylamino,
(i) formyl,
(j) a 5- to 10-membered aromatic heterocyclic group optionally substituted by alkyl,
(k) \(-\text{CH} = \text{N} - \text{OR}^{21}\) wherein \(\text{R}^{21}\) is a hydrogen atom or alkyl optionally substituted by alkylamino or dialkylamino, or
(l) nitro,
or a salt thereof.

Item 15. The compound of item 1 or 1A, wherein \(\text{R}^3\) is a group of the formula
wherein $R^{30}$ is as defined in item 1, or a salt thereof.

Item 16. The compound of item 1 or 1A, wherein $R^3$ is naphthyl or isochromenyl, or a salt thereof.

Item 17. The compound of item 1 or 1A, wherein $R^3$ is quinolyl or isoquinolyl, or oxide derivative thereof, or a salt thereof.

Item 18. The compound of item 1 or 1A, wherein $R$ is a hydrogen atom, or a salt thereof.

Item 19. The compound of item 1 or 1A, wherein $R^1$ is cyclopropyl, 2-fluorocyclopropyl or 2,4-difluorophenyl, or a salt thereof.

Item 20. The compound of item 1 or 1A, wherein $R^2$ is methyl, methoxy or a chlorine atom, or a salt thereof.

Item 21. A pharmaceutical composition comprising a compound of item 1 or 1A or a salt thereof and a pharmaceutically acceptable carrier.

Item 22. An antimicrobial agent comprising a compound of item 1 or 1A or a salt thereof.

Item 23. A compound of item 1 or 1A or a salt thereof for use as a medicament.

Item 24. A compound of item 1 or 1A or a salt thereof for
use as an antimicrobial agent.

Item 25. A compound of item 1 or 1A or a salt thereof for use in the prevention or treatment of a bacterial infection.

Item 26. Use of a compound of item 1 or 1A or a salt thereof for the manufacture of a medicament for preventing or treating a bacterial infection.

Item 27. A method for preventing or treating a bacterial infection which comprises administering an effective amount of a compound of item 1 or 1A or a salt thereof to a human or an animal.

The compound of the formula (I) or a salt thereof (hereinafter sometimes to be abbreviated as compound (I)) has excellent antibacterial activity against various gram positive and gram negative bacteria, and is useful for the prevention or treatment of various infectious diseases induced by various bacteria in human, other animals and fish and is also useful as an external antimicrobial or disinfectant agent for medical instruments or the like.

Brief Description of Drawings

Fig. 1 is a graph showing the results of the animals administered with compound 2-18 in Experimental Example 2.

Fig. 2 is a graph showing the results of the animals administered with vancomycin in Experimental Example 2.

Detailed Description of the Invention

Specific examples of groups in the formula (I) are as follows.

Examples of "halogen atom" include fluorine atom, chlorine atom, bromine atom, and iodine atom.

Examples of "alkyl" and "alkyl" moiety in "alkylamino",

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"dialkylamino", "alkylcarbonyl", "cycloalkylalkylsulfonyl", "cycloalkylalkyl", "aminoalkyl" and "alkylsulfonyl" include straight or branched C_{1-6} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 1-ethylpropyl, isopentyl, neopentyl, tert-pentyl, hexyl, 1,2,2-trimethylpropyl, 3,3-dimethylbutyl, 2-ethylbutyl, isoheptyl, 3-methylpentyl, etc.

Examples of "alkenyl" include straight or branched C_{2-6} alkenyl such as vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-methyl-2-propenyl, 2-pentenyl, 2-hexenyl, etc.

Examples of "alkynyl" include straight or branched C_{2-6} alkynyl such as ethynyl, 2-propynyl, 2-butynyl, 3-butynyl, 1-methyl-2-propynyl, 2-pentynyl, 2-hexynyl, etc.

Examples of "alkoxy" and "alkoxy" moiety in "haloalkoxy", "alkoxycarbonyl" and "alkoxycarbonylamino" include straight or branched C_{1-6} alkoxy such as methoxy, ethoxy, propoxy, isopropanyl, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, tert-pentyloxy, hexyloxy, isohexyloxy, 3-methylpentyloxy, etc.

Examples of "haloalkoxy" include straight or branched C_{1-6} alkoxy substituted by 1 to 3 halogen atoms. Examples thereof include fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, bromomethoxy, dibromomethoxy, dichlorofluoromethoxy, 2,2,2-trifluoroethoxy, 2-chloroethoxy, 3,3,3-trifluoropropoxy, 2-chloropropyxy, 3-chloropropoxy, 3-bromopropyxy, 4,4,4-trifluorobutoxy, 2-chlorobutoxy, 4-chlorobutoxy, 4-bromobutoxy, 5,5,5-trifluoropentyloxy, 5-chloropentyloxy, 6,6,6-trifluorohexyloxy, 6-chlorohexyloxy, etc. Preferable examples thereof include difluoromethoxy.

Examples of "alkenyloxy" include straight or branched C_{2-6} alkenyloxy such as vinyloxy, 1-propenyloxy, 2-propenyloxy, 1-butenyloxy, 2-butenyloxy, 3-butenyloxy, 1-methyl-2-propenyloxy, 2-pentenyloxy, 2-hexenyloxy, etc.
Examples of "aryl" and "aryl" moiety in "arylsulfonyl" include C_{6-14} (preferably C_{6-10}) aryl such as phenyl, naphthyl (e.g., 1-naphthyl, 2-naphthyl), etc. Preferable examples thereof include phenyl.

Examples of "5- to 10-membered aromatic heterocyclic group" and "5- to 10-membered aromatic heterocyclyl" moiety in "5- to 10-membered aromatic heterocyclylcarbonyl group" and "5- to 10-membered aromatic heterocyclylsulfonyl group" include 5- to 10-membered (preferably 5- or 6-membered) aromatic heterocyclic group containing 1 to 4 (preferably 1 to 3, more preferably 1 or 2) heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom. Examples thereof include furyl, thiroyl, pyrrolyl, pyrazoly1, imidazoly1, triazolyl (e.g., 1,2,3-triazolyl, 1,2,4-triazolyl), tetrazolyl, isoxazolyl, oxazolyl, furozanyl, isothiazolyl, thiazolyl, pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyridazinyl, pyrimidinyl, pyrazinyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzo[c]thiophenyl, indolyl, isoindolyl, indoliziny1, indazolyl, benzimidazolyl, benzotriazolyl, benzoazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, purinyl, quinolyl, isoquinolyl, quinolizinyl, cinnoliny1, quinazoliny1, quinoxaliny1, phthalazinyl, naphthyridinyl, pteridinyl, etc. Preferable examples thereof include pyrroly1, imidazolyl, oxazolyl, triazolyl (e.g., 1,2,3-triazolyl, 1,2,4-triazolyl), tetrazolyl, pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), benzimidazolyl, etc.

Examples of "alkylamino" include C_{1-6} alkylamino such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, sec-butylamino, tert-butylamino, pentylamino, isopentylamino, neopentylamino, tert-pentylamino, hexylamino, etc.

Examples of "dialkylamino" include di(C_{1-6} alkyl)amino such as dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, diisobutylamino, di(sec-butyl)amino, di(tert-butyl)amino, dipentylamino, di(tert-pentyl)amino, dihexylamino,
ethylethylamino, etc.

Examples of "aminoalkyl" include amino-C_{1-6} alkyl such as aminomethyl, 2-aminooethyl, 3-aminopropyl, 4-aminobutyl, 5-aminopentyl, 6-aminohexyl, etc.

Examples of "cycloalkyl" and "cycloalkyl" moiety in "cycloalkyloxy", "cycloalkylcarbonyl", "cycloalkylalkyl" and "cycloalkylalkylsulfonyl" include C_{3-8} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbornanyl (e.g., 2-norbornanyl), etc.

Examples of "cycloalkylalkyl" include C_{2-8} cycloalkyl-C_{1-6} alkyl such as cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, cyclooctylmethyl, norbornanylethyl (e.g., norbornan-2-ylmethyl), etc.

Examples of "cyclic amino group" includes a 4- to 7-membered (preferably 5- or 6-membered) cyclic amino group containing one nitrogen atom and optionally further containing one heteroatom selected from a nitrogen atom, an oxygen atom and a sulfur atom. Examples thereof include 1-azetidinyl, 1-pyrrolidinyl, 1-imidazolidinyl, 1-pyrrolidinyl, morpholinyl, 1-piperidino, 1-piperazinyl, thiomorpholinyl, 1-azepanyl, 1,4-oxazepan-4-yl, etc. Preferable examples thereof include 1-pyrrolidinyl, piperidino, 1-piperazinyl, morpholinyl, thiomorpholinyl, etc.

Examples of "alkoxy carbonyl" include C_{1-6} alkoxy-carbonyl wherein the alkoxy moiety is C_{1-6} alkoxy. Examples thereof include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxy carbonyl, hexyloxy carbonyl, etc.

Examples of "alkoxy carbonylamino" include C_{1-6} alkoxy-carbonylamino wherein the alkoxy moiety is C_{1-6} alkoxy. Examples thereof include methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, isopropoxycarbonylamino, butoxycarbonylamino, isobutoxycarbonylamino, sec-butoxycarbonylamino, pentyloxy carbonylamino, etc.

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butoxycarbonylamino, tert-butoxycarbonylamino,
pentyloxycarbonylamino, hexyloxycarbonylamino, etc.

Examples of "alkylcarbonyl" include C_{1-6} alkyl-carbonyl
wherein the alkyl moiety is C_{1-6} alkyl. Examples thereof include
acetyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl,
butilcarbonyl, isobutilcarbonyl, sec-butilcarbonyl, tert-
butilcarbonyl, pentyloxy carbonyl, hexyloxy carbonyl, etc.

Examples of "cycloalkylcarbonyl" include C_{3-8} cycloalkylcarbonyl such as
cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl,
cycloheptylcarbonyl, etc.

Examples of "cycloalkylcarbonyl" include C_{3-8} cycloalkyl-
carbonyl such as cyclopropylcarbonyl, cyclobutylcarbonyl,
cyclopentylcarbonyl, cyclohexylcarbonyl, cycloheptylcarbonyl,
cyclooctylcarbonyl, etc.

Examples of "5- to 10-membered aromatic
heterocyclylcarbonyl group" include a 5- to 10-membered
(preferably 5- or 6-membered) aromatic heterocyclylcarbonyl
group wherein the heterocyclyl moiety contains 1 to 4
(preferably 1 to 3, more preferably 1 or 2) heteroatoms selected
from a nitrogen atom, an oxygen atom and a sulfur atom. Examples
of the heterocyclyl moiety are same as the examples of the 5- to
10-membered aromatic heterocyclic group mentioned above.
Preferable examples of "5- to 10-membered aromatic
heterocyclylcarbonyl group" include pyridylcarbonyl (e.g., 2-
3-pyridylcarbonyl, 3-pyridylcarbonyl, 4-pyridylcarbonyl).

Examples of "arylsulfonyl" include C_{6-14} (preferably C_{6-10})
arylsulfonyl such as phenylsulfonyl, naphthylsulfonyl (e.g., 1-
naphthylsulfonyl, 2-naphthylsulfonyl), etc. Preferable examples
thereof include phenylsulfonyl.

Examples of "cycloalkylsulfonyl" include C_{3-8}
cycloalkyl-C_{1-6} alkylsulfonyl such as cyclopropylmethylsulfonyl,
cyclobutylmethylsulfonyl, cyclopentylmethylsulfonyl,
cyclohexylmethylsulfonyl, cycloheptylmethylsulfonyl,
cyclooctylmethylsulfonyl, norbornanyl methylsulfonyl (e.g.,
norbornan-2-ylmethylsulfonyl), etc.
Examples of "5- to 10-membered aromatic heterocyclylsulfonyl group" include a 5- to 10-membered (preferably 5- or 6-membered) aromatic heterocyclylsulfonyl group wherein the heterocyclyl moiety contains 1 to 4 (preferably 1 to 3, more preferably 1 or 2) heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom. Examples of the heterocyclyl moiety are same as the examples of the 5- to 10-membered aromatic heterocyclic group mentioned above. Preferable examples of "5- to 10-membered aromatic heterocyclylsulfonyl group" include imidazolylsulfonyl.

Examples of "alkylsulfonyl" include C_1-6 alkylsulfonyl wherein the alkyl moiety is C_1-6 alkyl. Examples thereof include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, sec-butylsulfonyl, tert-butylsulfonyl, pentylsulfonyl, hexylsulfonyl, etc.

Examples of "cyclopropyl optionally substituted by 1 to 3 halogen atoms" include cyclopropyl optionally substituted by 1 fluorine atom such as cyclopropyl, 2-fluorocyclopropyl, etc.

Examples of "phenyl optionally substituted by 1 to 3 halogen atoms" include phenyl substituted by two fluorine atoms such as 2,4-difluorophenyl, etc.

Examples of "5- to 10-membered saturated heterocyclic group" include a 5- to 10-membered (preferably 5- or 6-membered) saturated heterocyclic group containing 1 to 4 (preferably 1 to 3, more preferably 1 or 2) heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom. Examples thereof include pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, etc.

Examples of "6-membered ring optionally substituted by amino or oxo" formed by R^{34} and R^{35} include a 6-membered ring optionally containing one nitrogen atom, and said ring is optionally substituted by amino or oxo. Examples thereof include cyclohexene and dihydropyrididine, each optionally substituted by amino or oxo.
Examples of "5- or 6-membered ring optionally substituted by alkyl" formed by $R^1$ and $R^2$ include a 5- or 6-membered (preferably 6-membered) ring containing one nitrogen atom and optionally further containing one oxygen atom, and said ring is optionally substituted by alkyl. Preferably, $R^1$ and $R^2$ are optionally bonded to form -O-CH$_2$-CH(CH$_3$)- wherein the oxygen atom is bonded to the phenyl ring of the quinolone ring as shown below.

![Chemical Structure 1](image1.png)

Examples of "5- or 6-membered ring optionally substituted by oxo" formed by $R^4$ and $R^5$ include a 5- or 6-membered (preferably 6-membered) ring containing one nitrogen atom and optionally further containing one oxygen atom, and said ring is optionally substituted by oxo. Preferably, $R^4$ and $R^5$ are optionally bonded to form -CH$_2$-O-(C=O)- wherein the carbonyl is bonded to the phenyl ring of the quinolone ring as shown below.

![Chemical Structure 2](image2.png)

Examples of "5- or 6-membered ring optionally substituted by alkyl or oxo" formed by $R^{10}$ and $R^{11}$ include a 5- or 6-membered (preferably 5-membered) ring containing 2 or 3 nitrogen atoms, and said ring is optionally substituted by alkyl or oxo. Preferably, $R^{10}$ and $R^{11}$ are optionally bonded to form -(C=O)-NH-, -C($R^{31}$)=N- or -N=N- wherein $R^{31}$ is a hydrogen atom or alkyl, and
the nitrogen atom is bonded to the phenyl ring of the fused ring, as shown below.

Examples of "5- or 6-membered ring" formed by $R_{12}^1$ and $R_{13}^1$ include a 5- or 6-membered (preferably 6-membered) ring containing one nitrogen atom. Preferably, $R_{12}^1$ and $R_{13}^1$ are optionally bonded to form $-(\text{CH}_2)_4-$ as shown below.

$X$ is a hydrogen atom or a fluorine atom, preferably, a fluorine atom.

$R$ is a hydrogen atom or alkyl, preferably, a hydrogen atom.

$R^1$ is (1) cyclopropyl optionally substituted by 1 to 3 halogen atoms or (2) phenyl optionally substituted by 1 to 3 halogen atoms, preferably, cyclopropyl, 2-fluorocyclopropyl or 2,4-difluorophenyl.

$R^2$ is a hydrogen atom; alkyl optionally substituted by 1 or 2 substituents selected from the group consisting of a halogen atom and hydroxyl; alkoxy; haloalkoxy; a halogen atom; cyano; cyclopropyl; nitro; amino; formyl; alkenyl or alkynyl,
preferably, alkyl, alkoxy, haloalkoxy, a chlorine atom or cyano, more preferably, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxy substituted by 1 to 3 halogen atoms, a chlorine atom or cyano, still more preferably, methyl, methoxy or a chlorine atom.

Examples of a fused heterocyclic group of the formula (A) or (B) include a fused heterocyclic group of the formula

\[
\text{\begin{align*}
\text{\text{R}}^4 & \quad \text{N} \quad \text{X}^1 \\
\text{\text{R}}^4 & \quad \text{N} \quad \text{X}^1 \\
\text{\text{R}}^4 & \quad \text{N} \quad \text{X}^1 \\
\text{\text{R}}^4 & \quad \text{N} \quad \text{X}^1 \\
\text{\text{R}}^4 & \quad \text{N} \quad \text{X}^1
\end{align*}}
\]

wherein \( X^1 \) and \( R^1 \) are as defined above, and said fused heterocyclic group is optionally substituted by 1 or 2 substituents selected from the group consisting of a halogen atom, cyano, nitro, hydroxy and alkyl.

Preferable examples of a fused heterocyclic group of the formula (A) or (B) include a fused heterocyclic group of the formula
wherein R^4 and R^5 are as defined above, and said fused heterocyclic group is optionally substituted by 1 or 2 substituents selected from the group consisting of a halogen atom, cyano, nitro, hydroxy and alkyl.

Other preferable examples of a fused heterocyclic group of the formula (A) or (B) include a fused heterocyclic group of the formula

wherein X^1 and R^4 are as defined above, and said fused heterocyclic group is optionally substituted by 1 or 2 substituents selected from the group consisting of a halogen atom, cyano, nitro, hydroxy and alkyl.

Examples of a group of the formula (C) include a group of the formula
wherein \( X', R' \) and \( R^7 \) are as defined above.

Preferable examples of a group of the formula (C) include a group of the formula

\[
\begin{align*}
\text{or}
\end{align*}
\]

wherein \( R', R^7 \) and \( R^8 \) are as defined above.

In the above formulas, \( R^6, R^7 \) and \( R^8 \) are each independently,

1. a hydrogen atom,
2. a halogen atom,
3. cyano,
4. nitro,
5. amino,
6. alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom and amino,
7. alkenyl,
8. alkynyl,
9. aryl,
10. formyl,
11. carboxy,
12. carbamoyl, or
(m) a 5- to 10-membered aromatic heterocyclic group
    (e.g., pyridyl, triazolyl) optionally substituted by alkyl.

Examples of a group of the formula (D) or (E) include a

5 group of the formula

\[
\begin{align*}
\text{N} & \text{N} \\
\text{H} & \\
R^6 & \\
\text{N} & \text{N} \\
\text{H} & \\
R^6 & \\
\end{align*}
\]

\[
\begin{align*}
\text{N} & \text{N} \\
\text{H} & \\
R^8 & \\
\end{align*}
\]

or

\[
\begin{align*}
\text{S} & \\
\text{N} & \text{N} \\
\text{H} & \\
R^8 & \\
\end{align*}
\]

wherein \( R^6 \) is as defined above. \( R^6 \) is preferably a hydrogen atom, a halogen atom, nitro or amino.

10 Preferably, \( R^3 \) is 3-pyridyl optionally substituted by 1 or 2 substituents selected from the group consisting of

(a) a halogen atom,
(b) cyano,
(c) nitro,
(d) hydroxy,
(e) amino,
(f) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, alkylamino, dialkylamino and hydroxy,

(g) alkenyl,
(h) aryl,
(i) cycloalkyl,
(j) alkoxy,
(k) alkylamino,

20 (l) dialkylamino,
(m) phenylamino optionally substituted by 1 to 3 halogen
atoms,

(n) a cyclic amino group (e.g., 1-piperazinyl, 
morpholino) optionally substituted by 
alkoxycarbonyl,

(o) formyl,

(p) carbamoyl, and

(q) a 5- to 10-membered aromatic heterocyclic group 
(e.g., triazolyl) optionally substituted by alkyl.

More preferably, \( R^3 \) is a group of the formula

\[
\begin{align*}
\text{N} & \quad \text{R}^{22} \\
\end{align*}
\]

wherein \( R^{22} \) is

(a) a halogen atom,

(b) cyano,

(c) nitro,

(d) alkyl optionally substituted by 1 to 3 substituents 
selected from the group consisting of a halogen 
atom, alkylamino, dialkylamino and hydroxy,

(e) alkenyl,

(f) aryl,

(g) cycloalkyl,

(h) alkoxy,

(i) formyl, or

(j) carbamoyl.

Preferably, \( R^{22} \) is

(a) cyano,

(b) nitro,

(c) aryl,

(d) formyl, or

(e) carbamoyl.

Preferably, \( R^3 \) is 5-pyrimidinyl substituted by 1 or 2 
substituents selected from the group consisting of amino,
alkylamino and dialkylamino.

Preferably, $R^3$ is 2-indolyl, 3-indolyl, 5-indolyl or 6-indolyl, each optionally substituted by 1 or 2 substituents selected from the group consisting of

(a) a halogen atom,
(b) cyano,
(c) nitro,
(d) hydroxy,

(e) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of amino, alkoxy carbonylamino, alkylamino and dialkylamino,

(f) alkoxy,
(g) formyl,

(h) carboxy, and

(j) amino optionally substituted by 1 or 2 substituents selected from the group consisting of

(i) alkoxy carbonyl,
(ii) alkyl carbonyl optionally substituted by a substituent selected from the group consisting of

(A) cycloalkyloxy optionally substituted by 1 to 3 alkyl,
(B) alkylamino,
(C) dialkylamino,

(D) a cyclic amino group (e.g., morpholino, 1-piperazinyl) optionally substituted by alkoxy carbonyl, and

(E) a halogen atom,

(iii) phenyl carbonyl optionally substituted by 1 to 3 substituents selected from the group consisting of alkyl and alkoxy,
(iv) cycloalkyl carbonyl,
(v) a 5- to 10-membered aromatic heterocyclyl carbonyl group (e.g., pyridyl carbonyl) optionally substituted by alkyl optionally
substituted by 1 to 3 halogen atoms,
(vi) benzylcarbonyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom and alkoxy,
(vii) arylsulfonyl optionally substituted by alkoxy,
(viii) cycloalkylalkylsulfonyl optionally substituted by 1 to 3 substituents selected from the group consisting of alkyl and oxo (e.g., camphorsulfonyl),
(ix) a 5- to 10-membered aromatic heterocyclylsulfonyl group (e.g., imidazolylsulfonyl) optionally substituted by 1 to 3 alkyl, and
(x) \(-C(-N-CN)-SR^2\) wherein \(R^2\) is alkyl.

More preferably, \(R^3\) is 2-indolyl optionally substituted by 1 or 2 substituents selected from the group consisting of
(a) a halogen atom,
(b) cyano,
(c) nitro,
(d) hydroxy,
(e) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of amino, alkoxy, carbonylamino, alkylamino and dialkylamino,
(f) alkoxy,
(g) formyl,
(h) carboxy, and
(j) amino optionally substituted by 1 or 2 substituents selected from the group consisting of
(i) alkoxy, carbonyl,
(ii) alkylcarbonyl optionally substituted by a substituent selected from the group consisting of
(A) cycloalkyloxy optionally substituted by 1 to 3 alkyl,
(B) alkylamino,
(C) dialkylamino,
(D) a cyclic amino group (e.g., morpholino, 1-piperazinyl) optionally substituted by alkoxy carbonyl, and
(E) a halogen atom,

(iii) phenyl carbonyl optionally substituted by 1 to 3 substituents selected from the group consisting of alkyl and alkoxy,
(iv) cycloalkyl carbonyl,
(v) a 5- to 10-membered aromatic heterocyclyl carbonyl group (e.g., pyridyl carbonyl) optionally substituted by alkyl optionally substituted by 1 to 3 halogen atoms,
(vi) benzyl carbonyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom and alkoxy,
(vii) aryl sulfonfyl optionally substituted by alkoxy,
(viii) cycloalkyl alkyl sulfonfyl optionally substituted by 1 to 3 substituents selected from the group consisting of alkyl and oxo (e.g., camphorsulfonfyl),
(ix) a 5- to 10-membered aromatic heterocyclyl sulfonfyl group (e.g., imidazolyl sulfonfyl) optionally substituted by 1 to 3 alkyl, and
(x) \(-\text{C}(=\text{N-CN})=\text{SR}^{2}\) wherein \(\text{R}^{2}\) is alkyl.

Examples of a group of the formula (F) or (G) include a group of the formula
wherein

- $R^2$ is a hydrogen atom or alkyl, and
- $R^{24}$, $R^{25}$, $R^{26}$ and $R^{23}$ are each independently,

5  (a) a hydrogen atom,

(b) cyano, or

(c) nitro.

Examples of a group of the formula (K) include a group of

10 the formula

wherein $X^7$, $X^6$, $X^5$, $X^4$ and $R^{10}$ are as defined above.

Preferable examples of a group of the formula (K) include
a group of the formula

\[ R^{10}_1 R^{11}_1 R^{12}_1 R^{13}_1 R^{14}_1 R^{15}_1 \]

wherein \( R^{1}_1, R^{11}_1, R^{12}_1, R^{13}_1, R^{14}_1 \) and \( R^{15}_1 \) are as defined above.

When \( R^{11}_1 \) and \( R^{11}_1 \) are bonded to form a 5- or 6-membered ring optionally substituted by alkyl or \( \text{exo} \), preferable examples of a group of the formula (K) include a group of the formula
wherein Rᵢ is a hydrogen atom or alkyl.

When Rᵢ and Rᵢ' are bonded to form a 5- or 6-membered ring, preferable examples of a group of the formula (K) include a group of the formula

More preferable examples of a group of the formula (K) include a group of the formula

10 wherein Rᵢ is

(a) a hydrogen atom or
(b) alkyl, and
Rᵢ', Rᵢ'' and Rᵢ''' are each independently,

(a) a hydrogen atom,
(b) a halogen atom,
(c) cyano,
(d) nitro,
(e) amino,
(f) alkylamino,
(g) dialkylamino,
(h) alkyl optionally substituted by hydroxy, or
(i) alkenyl,

R\(^{109}\) and R\(^{11a}\) are optionally bonded to form a 5- or 6-membered ring optionally substituted by alkyl or oxo, provided that R\(^{109}\), R\(^{11a}\), R\(^{13a}\) and R\(^{15a}\) are not simultaneously hydrogen atom.

Preferably, R\(^3\) is a group of the formula

![Diagram]

wherein R\(^{16}\) is

(a) a hydrogen atom,
(b) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of cyano, alkylamino and dialkylamino,
(c) alkenyl optionally substituted by carboxy,
(d) formyl,
(e) carboxy,
(f) carbamoyl,
(g) -C(R\(^{17}\))=N-OH wherein R\(^{17}\) is a hydrogen atom, cyano or hydroxy, or
(h) a 5- to 10-membered aromatic heterocyclic group (e.g., tetrazolyl, pyrrolyl, oxazolyl, benzimidazolyl, triazolyl) optionally substituted by alkyl, alkoxy carbonyl, carboxy or phenyl.

More preferably, R\(^3\) is a group of the formula

![Diagram]

wherein R\(^{16\alpha}\) is
(a) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of cyano, alkylamino and dialkylamino,

(b) alkenyl optionally substituted by carboxy,  

(c) formyl,  

(d) carboxy,  

(e) carbamoyl,  

(f) \(-C(R^{17})=N-OH\) wherein \(R^{17}\) is a hydrogen atom, cyano or hydroxy, or

(g) a 5- to 10-membered aromatic heterocyclic group (e.g., tetrazolyl, pyrrolyl, oxazolyl, benzimidazolyl, triazolyl) optionally substituted by alkyl, alkoxy carbonyl, carboxy or phenyl.

Preferably, \(R^3\) is a group of the formula

![Chemical Structure](image)

wherein

\(R^{18}\) is alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom and phenyl, and

\(R^{19}\) and \(R^{20}\) are each independently,

(a) a hydrogen atom,  

(b) a halogen atom,  

(c) cyano,  

(d) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of  

(i) a halogen atom,  

(ii) cyano,  

(iii) hydroxy,  

(iv) amino,  

(v) alkylamino,
(vi) dialkylamino, and
(vii) a cyclic amino group (e.g., 1-piperazinyl)
optitionally substituted by alkyl,

(e) alkoxy,

(f) amino optionally substituted by 1 or 2 substituents
selected from the group consisting of
(i) alkylcarbonyl optionally substituted by a cyclic
amino group (e.g., morpholino),
(ii) alkylsulfonyl, and
(iii) carbamoyl,

(g) carboxy,

(h) alkoxy carbonyl,

(i) carbamoyl optionally substituted by alkyl optionally
substituted by amino, alkylamino, dialkylamino or
alkoxy carbonylamino,

(j) formyl,

(k) a 5- to 10-membered aromatic heterocyclic group
(e.g., oxazolyl, benzimidazolyl), or

(l) -CH=N-OR² wherein R² is a hydrogen atom or alkyl
optionally substituted by alkylamino or dialkylamino.

More preferably, R² is a group of the formula

\[
\begin{array}{c}
\text{R}^{18a} \\
\text{R}^{18a} \\
\end{array}
\]

wherein
R¹⁸a is alkyl, and

R¹⁹a is (a) a halogen atom,
(b) cyano,
(c) alkyl optionally substituted by 1 to 3 substituents
selected from the group consisting of
(i) a halogen atom,
(ii) cyano,
(iii) hydroxy,
(iv) amino,
(v) alkylamino,
(vi) dialkylamino, and
(vii) a cyclic amino group (e.g., 1-piperazinyl)
on Optionally substituted by alkyl,
5 (d) alkoxy,
(e) amino optionally substituted by 1 or 2 substituents
 selected from the group consisting of
 (i) alkylcarboxyl optionally substituted by a
cyclic amino group (e.g., morpholino),
10 (ii) alkylsulfonyl, and
 (iii) carbamoyl,
(f) carboxy,
(g) alkoxy carbonyl,
(h) carbamoyl optionally substituted by alkyl
 optionally substituted by amino, alkylamino,
dialkylamino or alkoxy carbonylamino,
15 (i) formyl,
(j) a 5- to 10-membered aromatic heterocyclic group
 (e.g., oxazolyl, benzimidazolyl), or
20 (k) -CH=N-OR
21 wherein R21 is a hydrogen atom or alkyl
 optionally substituted by alkylamino or
dialkylamino.

Preferable examples of compound (I) are as described
25 below.

[Compound I-1]
A compound of the formula (I) wherein
R is a hydrogen atom;
R1 is cyclopropyl, 2-fluorocyclopropyl or 2,4-difluorophenyl;
30 R2 is C1-6 alkyl (e.g., methyl), C1-6 alkoxy (e.g., methoxy) or a
chlorine atom; or
R1 and R2 are optionally bonded to form -O-CH(CH3)- wherein
the oxygen atom is bonded to the phenyl ring of the quinolone
ring; and
35 R3 is a fused heterocyclic group of the formula
wherein
X$^1$ is C(R$^3$) or N,
R$^2$ is a hydrogen atom or C$_{1-6}$ alkyl, and
R$^5$ is (a) a hydrogen atom,
(b) a halogen atom,
(c) cyano,
(d) nitro,
(e) hydroxy,
(f) C$_{1-6}$ alkyl optionally substituted by 1 to 3 halogen atoms,
(g) C$_{2-5}$ alkynyl,
(h) C$_{6-14}$ aryl, or
(i) C$_{1-6}$ alkoxy optionally substituted by 1 to 3 halogen atoms,
when X$^1$ is C(R$^3$), R$^3$ and R$^5$ are optionally bonded to form -CH$_2$-O-(C=O)- wherein the carbonyl is bonded to the phenyl ring of the quinolone ring,
said fused heterocyclic group is optionally substituted by 1 or 2 substituents selected from the group consisting of a halogen atom, cyano, nitro, hydroxy and C$_{1-6}$ alkyl, or a salt thereof.

[Compound I-2]

A compound of the formula (I) wherein
R is a hydrogen atom;
R$^1$ is cyclopropyl, 2-fluorocyclopropyl or 2,4-difluorophenyl;
R$^2$ is C$_{1-6}$ alkyl (e.g., methyl), C$_{1-6}$ alkoxy (e.g., methoxy) or a chlorine atom; or
R$^1$ and R$^2$ are optionally bonded to form -O-CH$_2$-CH(CH$_3$)$_2$- wherein the oxygen atom is bonded to the phenyl ring of the quinolone
ring; and

R\(^3\) is a group of the formula

![Chemical structure](image)

or

![Chemical structure](image)

wherein

5 \(X^2\) is C\((R^8)\) or N, and

R\(^6\), R\(^7\) and R\(^8\) are each independently,

(a) a hydrogen atom,

(b) a halogen atom,

(c) cyano,

(d) nitro,

(e) amino,

(f) C\(_{1-5}\) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom and amino,

10 (g) C\(_{2-6}\) alkenyl,

(h) C\(_{2-5}\) alkynyl,

(i) C\(_{6-14}\) aryl,

(j) formyl,

(k) carboxy,

15 (l) carbamoyl, or

(m) a 5- to 10-membered aromatic heterocyclic group (e.g., pyridyl, triazolyl) optionally substituted by C\(_{1-6}\) alkyl,

or a salt thereof.

20

[Compound I-3]

A compound of the formula (I) wherein

R is a hydrogen atom;

R\(^1\) is cyclopropyl, 2-fluorocyclopropyl or 2,4-difluorophenyl;

25 R\(^2\) is C\(_{1-6}\) alkyl (e.g., methyl), C\(_{1-6}\) alkoxy (e.g., methoxy) or a chlorine atom; and

R\(^3\) is a group of the formula

57

525
wherein
X' and X' are N, or
X' is N and X' is CH, or
X' is CH and X' is N, and
R' is a hydrogen atom, a halogen atom, nitro or amine,
or a salt thereof.

[Compound 1-4]

10 A compound of the formula (I) wherein
R is a hydrogen atom;
R' is cyclopropyl, 2-fluorocyclopropyl or 2,4-difluorophenyl;
R is C1-C5 alkyl (e.g., methyl), C1-C5 alkoxy (e.g., methoxy) or a
chlorine atom; and
15 R' is a group of the formula
A compound of the formula (I) wherein

R is a hydrogen atom;
R¹ is cyclopropyl, 2-fluorocyclopropyl or 2,4-difluorophenyl;
R² is C₁₋₄ alkyl (e.g., methyl), C₁₋₄ alkoxy (e.g., methoxy) or a chlorine atom; or

R¹ and R² are optionally bonded to form -O-CH₂-CH(CH₃)₂ - wherein the oxygen atom is bonded to the phenyl ring of the quinolone ring; and

R³ is a group of the formula
wherein \( R^{22} \) is

(a) a halogen atom,
(b) cyano,
(c) nitro,
(d) \( C_{1-6} \) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, \( C_{1-6} \) alkylamino, di\((C_{1-6} \) alkyl)amino and hydroxy,
(e) \( C_{2-6} \) alkenyl,
(f) \( C_{6-14} \) aryl,
(g) \( C_{3-9} \) cycloalkyl,
(h) \( C_{1-6} \) alkoxy,
(i) formyl, or
(j) carbamoyl,
or a salt thereof.

[Compound I-6]

A compound of the formula (I) wherein
\[ R \] is a hydrogen atom;
\[ R^1 \] is cyclopropyl, 2-fluorocyclopropyl or 2,4-difluorophenyl;
\[ R^2 \] is \( C_{1-6} \) alkyl (e.g., methyl), \( C_{1-6} \) alkoxy (e.g., methoxy) or a chlorine atom; or
\[ R^1 \] and \[ R^2 \] are optionally bonded to form \(-O-CH_2-CH(CH_3)\) - wherein the oxygen atom is bonded to the phenyl ring of the quinolone ring; and
\[ R^3 \] is a group of the formula

wherein \( R^{22} \) is
(a) cyano,
(b) nitro,
(c) C$_{6-14}$ aryl,
(d) formyl, or
(e) carbamoyl,
or a salt thereof.

[Compound I-7]
A compound of the formula (I) wherein
R is a hydrogen atom;
R$^1$ is cyclopropyl, 2-fluorocyclopropyl or 2,4-difluorophenyl;
R$^2$ is C$_{1-6}$ alkyl (e.g., methyl), C$_{1-6}$ alkoxy (e.g., methoxy) or a
chlorine atom; and
R$^3$ is 5-pyrimidinyl substituted by 1 or 2 substituents selected
from the group consisting of amino, C$_{1-6}$ alkylamino and di(C$_{1-6}$
alkyl)amino,
or a salt thereof.

[Compound I-8]
A compound of the formula (I) wherein
R is a hydrogen atom;
R$^1$ is cyclopropyl, 2-fluorocyclopropyl or 2,4-difluorophenyl;
R$^2$ is C$_{1-6}$ alkyl (e.g., methyl), C$_{1-6}$ alkoxy (e.g., methoxy) or a
chlorine atom; and
R$^3$ is 2-indolyl optionally substituted by 1 or 2 substituents
selected from the group consisting of
(a) a halogen atom,
(b) cyano,
(c) nitro,
(d) hydroxy,
(e) C$_{1-6}$ alkyl optionally substituted by 1 to 3
substituents selected from the group consisting of
amino, C$_{1-6}$ alkoxy-carbonylamino, C$_{1-6}$ alkylamino and
di(C$_{1-6}$ alkyl)amino,
(f) C$_{1-6}$ alkoxy,
(g) formyl,
(h) carboxy, and
(i) amino optionally substituted by 1 or 2 substituents selected from the group consisting of
(i) C₁₋₆ alkoxy-carbonyl,
(ii) C₁₋₆ alkyl-carbonyl optionally substituted by a substituent selected from the group consisting of
(A) C₃₋₈ cycloalkyloxy optionally substituted by 1 to 3 C₁₋₆ alkyl,
(B) C₁₋₆ alkylamino,
(C) di(C₁₋₆ alkyl)amino,
(D) a cyclic amino group (e.g., morpholino, 1-piperazinyl) optionally substituted by C₁₋₆ alkoxy-carbonyl, and
(E) a halogen atom,
(iii) phenylcarbonyl optionally substituted by 1 to 3 substituents selected from the group consisting of C₁₋₆ alkyl and C₁₋₆ alkoxy,
(iv) C₃₋₈ cycloalkyl-carbonyl,
(v) a 5- to 10-membered aromatic heterocyclylcarbonyl group (e.g., pyridylcarbonyl) optionally substituted by C₁₋₆ alkyl optionally substituted by 1 to 3 halogen atoms,
(vi) benzylcarbonyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom and C₁₋₆ alkoxy,
(vii) C₆₋₁₄ arylsulfonyl optionally substituted by C₁₋₆ alkoxy,
(viii) C₅₋₆ cycloalkyl-C₁₋₆ alkylsulfonyl optionally substituted by 1 to 3 substituents selected from the group consisting of C₁₋₆ alkyl and oxo (e.g., camphorsulfonyl),
(ix) a 5- to 10-membered aromatic heterocyclicsulfonyl group (e.g., imidazolylsulfonyl) optionally substituted by 1 to 3
C₁₋₅ alkyl, and
(x) -C(=N-CN)-SR² wherein R² is C₁₋₅ alkyl,
or a salt thereof.

5 [Compound I-9]
A compound of the formula (I) wherein
R is a hydrogen atom;
R¹ is cyclopropyl, 2-fluorocyclopropyl or 2,4-difluorophenyl;
R² is C₁₋₅ alkyl (e.g., methyl), C₁₋₅ alkoxy (e.g., methoxy) or a
chlorino atom; and
R³ is a group of the formula

wherein
R²⁵ is a hydrogen atom or C₁₋₅ alkyl, and
15 R²⁴, R²⁵, R²⁶ and R²⁷ are each independently,
(a) a hydrogen atom,
(b) cyano, or
(c) nitro,
or a salt thereof.

[Compound I-10]
A compound of the formula (I) wherein

5 R is a hydrogen atom;
R¹ is cyclopropyl, 2-fluorocyclopropyl or 2,4-difluorophenyl;
R² is C₁₋₅ alkyl (e.g., methyl), C₁₋₅ alkoxy (e.g., methoxy) or a chlorine atom; and
R³ is a group of the formula

\[
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\]

or

\[
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\]

wherein
R²⁶ is a hydrogen atom or hydroxy, and
R²⁷ is a hydrogen atom or C₁₋₅ alkyl,
or a salt thereof.

25 [Compound I-11]
A compound of the formula (I) wherein
R is a hydrogen atom;
R¹ is cyclopropyl, 2-fluorocyclopropyl or 2,4-difluorophenyl;
R² is C₁₋₅ alkyl (e.g., methyl), C₁₋₅ alkoxy (e.g., methoxy) or a chlorine atom; and
R³ is a group of the formula
wherein

$R_{10}^{10}$, $R_{11}^{11}$ and $R_{12}^{12}$ are each independently,

\(\text{a) a hydrogen atom or}\n\(\text{b) } C_1-, \text{alkyl, and}\n\)

$R_{11}^{11}$, $R_{13}^{13}$ and $R_{15}^{15}$ are each independently,

\(\text{a) a hydrogen atom,}\n\(\text{b) a halogen atom,}\n\(\text{c) cyano,}\n\(\text{d) nitro,}\n
65
(e) amino,
(f) C<sub>1-6</sub> alkylamino,
(g) di(C<sub>1-6</sub> alkyl)amino,
(h) C<sub>1-6</sub> alkyl optionally substituted by hydroxy, or
(i) C<sub>2-6</sub> alkenyl, or

R<sup>R</sup> and R<sup>R</sup> are optionally bonded to form -(C=O)-NH-, -C(R<sup>R</sup>)=N- or -N=N- wherein R<sup>R</sup> is a hydrogen atom or C<sub>1-6</sub> alkyl, and the nitrogen atom is bonded to the phenyl ring of the fused ring, or

R<sup>12</sup> and R<sup>13</sup> are optionally bonded to form -(CH<sub>2</sub>)<sub>6</sub>-, or a salt thereof.

[Compound I-12]

A compound of the formula (I) wherein

R is a hydrogen atom;
R<sup>1</sup> is cyclopropyl, 2-fluorocyclopropyl or 2,4-difluorophenyl;
R<sup>2</sup> is C<sub>1-6</sub> alkyl (e.g., methyl), C<sub>1-6</sub> alkoxy (e.g., methoxy) or a chlorine atom; and
R<sup>3</sup> is a group of the formula

```
\[
\begin{array}{c}
O \\
\end{array}
\]
```

wherein R<sup>10a</sup> is

(a) a hydrogen atom or
(b) C<sub>1-6</sub> alkyl, and
R<sup>11a</sup>, R<sup>15a</sup> and R<sup>15a</sup> are each independently,

(a) a hydrogen atom,
(b) a halogen atom,
(c) cyano,
(d) nitro,
(e) amino,
(f) C<sub>1-6</sub> alkylamino,
(g) di(C$_{1-6}$ alkyl)amino,
(h) C$_{1-6}$ alkyl optionally substituted by hydroxy, or
(i) C$_{2-6}$ alkenyl, and
provided that R$^{103}$, R$^{113}$, R$^{133}$ and R$^{153}$ are not simultaneously
hydrogen atom,
or a salt thereof.

[Compound I-13]
A compound of the formula (I) wherein

R is a hydrogen atom;
R$^1$ is cyclopropyl, 2-fluorocyclopropyl or 2,4-difluorophenyl;
R$^2$ is C$_{1-6}$ alkyl (e.g., methyl), C$_{1-6}$ alkoxy (e.g., methoxy) or a
chlorine atom; and
R$^3$ is a group of the formula

wherein R$^{31}$ is a hydrogen atom or C$_{1-6}$ alkyl,
or a salt thereof.

[Compound I-14]
A compound of the formula (I) wherein

R is a hydrogen atom;
R$^1$ is cyclopropyl, 2-fluorocyclopropyl or 2,4-difluorophenyl;
R$^2$ is C$_{1-6}$ alkyl (e.g., methyl), C$_{1-6}$ alkoxy (e.g., methoxy) or a
chlorine atom; and
R$^3$ is a group of the formula
wherein R^{19a} is

(a) C_{1-6} alkyl optionally substituted by 1 to 3
    substituents selected from the group consisting of cyano, C_{1-6} alkylamino and di(C_{1-6} alkyl)amino,

(b) C_{2-6} alkenyl optionally substituted by carboxy,

(c) formyl,

(d) carboxy,

(e) carbamoyl,

(f) -C(R^{17})=N-OH wherein R^{17} is a hydrogen atom, cyano or hydroxy, or

(g) a 5- to 10-membered aromatic heterocyclic group
    (e.g., tetrazolyl, pyrrolyl, oxazolyl, benzimidazolyl, triazolyl) optionally substituted by C_{1-6} alkyl, C_{1-6} alkoxy-carbonyl, carboxy or phenyl,

or a salt thereof.

[Compound I-15]

A compound of the formula (I) wherein

R is a hydrogen atom;

R^1 is cyclopropyl, 2-fluorocyclopropyl or 2,4-difluorophenyl;

R^2 is C_{1-6} alkyl (e.g., methyl), C_{1-6} alkoxy (e.g., methoxy) or a chlorine atom; and

R^3 is a group of the formula

\[
\begin{align*}
\text{R}^{19a} & \quad \text{R}^{18a}O \\
\end{align*}
\]

wherein

R^{18a} is C_{1-6} alkyl, and

R^{19a} is (a) a halogen atom,

(b) cyano,

(c) C_{1-6} alkyl optionally substituted by 1 to 3
    substituents selected from the group consisting of
    (i) a halogen atom,
    (ii) cyano,
(iii) hydroxy,
(iv) amino,
(v) C₁₋₆ alkylamino,
(vi) di(C₁₋₆ alkyl)amino, and

(vii) a cyclic amino group (e.g., 1-piperazinyl)
optionally substituted by C₁₋₆ alkyl,
(d) C₁₋₆ alkoxy,
(e) amino optionally substituted by 1 or 2 substituents
selected from the group consisting of

(i) C₁₋₆ alkyl-carbonyl optionally substituted by a
cyclic amino group (e.g., morpholino),
(ii) C₁₋₆ alkylsulfonyl, and
(iii) carbamoyl,
(f) carboxy,

(g) C₁₋₆ alkoxy-carbonyl,
(h) carbamoyl optionally substituted by C₁₋₆ alkyl
optionally substituted by amino, C₁₋₆ alkylamino,
di(C₁₋₆ alkyl)amino or C₁₋₆ alkoxy-carbonylamino,
(i) formyl,

(j) a 5- to 10-membered aromatic heterocyclic group
(e.g., oxazolyl, benzimidazolyl), or
(k) -CH=N-OR²¹ wherein R²¹ is a hydrogen atom or C₁₋₆
alkyl optionally substituted by C₁₋₆ alkylamino or
di(C₁₋₆ alkyl)amino,

or a salt thereof.

[Compound I-16]

A compound of the formula (I) wherein
R is a hydrogen atom;
R¹ is cyclopropyl, 2-fluorocyclopropyl or 2,4-difluorophenyl;
R² is C₁₋₆ alkyl (e.g., methyl), C₁₋₆ alkoxy (e.g., methoxy) or a
chlorine atom; and
R³ is a group of the formula
wherein

R³⁰ is (a) a hydrogen atom,
(b) a halogen atom,
(c) cyano,
(d) C₁₋₆ alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom and hydroxy,
(e) C₂₋₆ alkenyl,
(f) C₂₋₆ alkynyl,
(g) C₁₋₆ alkoxy,
(h) formyl, or
(i) -CH=N-OH,
or a salt thereof.

Examples of salts of the compound of the formula (I) include pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compound of the formula (I) are conventional non-toxic salts and include, for example, a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylene diamine salt, etc.); an inorganic acid addition salt (e.g., hydrochloride, hydrobromide, sulfate, hydrogensulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, citrate, fumarate,
methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); and a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

Compound (I) can be produced, for example, by a method according to the following reaction schemes.

Reaction Scheme I

\[
\begin{align*}
\text{(1)} & \xrightarrow{\text{a}} \text{(2)} & \xrightarrow{\text{b}} \text{(3)} \\
\text{(1)} & \xrightarrow{\text{c}} \text{(4)} & \xrightarrow{\text{d}} \text{(5)}
\end{align*}
\]

wherein \( X, R^1 \) and \( R^2 \) are as defined above, \( R^{32} \) is alkyl and \( R^{35} \) is alkyl.

**Step a**

Compound (1) can be converted to acid halide by reacting compound (1) with a halogenating agent in the presence or absence of a solvent. The solvent includes aromatic hydrocarbons such as benzene, toluene and xylene; halogenated hydrocarbons such as dichloromethane, chloroform and carbon tetrachloride; ethers such as dioxane, tetrahydrofuran and diethyl ether; \( N,N \)-dimethylformamide (DMF); dimethyl sulfoxide (DMSO); and the like. The halogenating agent may be any conventional halogenating agents which can convert hydroxy in carboxy group into a halogen atom, and includes, for example, thionyl chloride, phosphorus oxychloride, phosphorus oxybromide, phosphorus pentachloride, phosphorus pentabromide, and the like. The amounts of compound (1) and the halogenating agent are not particularly limited, but, in case of using no solvent, the
halogenating agent is usually used in a large excess amount, and in case of using a solvent, the halogenating agent is usually used in an amount of at least 1 mole, preferably 2 to 4 moles, per 1 mole of compound (1). The reaction temperature and the reaction period of time are not particularly limited, but the reaction is usually carried out at a temperature of from room temperature to about 100°C for about 30 minutes to about 6 hours.

The obtained acid halide is reacted with magnesium salt of malonic acid monoalkyl ester to give compound (2). Magnesium salt of malonic acid monoalkyl ester can be prepared in situ from potassium salt of malonic acid monoalkyl ester such as potassium ethyl malonate in the presence of magnesium chloride and a basic compound such as triethylamine. The reaction can be carried out in a suitable solvent. The solvent used in the reaction may be any conventional solvents unless they give any undesirable effect on the reaction, and includes, for example, esters such as ethyl acetate; ethers such as diethyl ether, dioxane, tetrahydrofuran, monoglyme and diglyme; alcohols such as methanol, ethanol and isopropanol; aromatic hydrocarbons such as benzene, toluene and xylene; aliphatic hydrocarbons such as n-hexane, heptane, cyclohexane and ligroin; amines such as pyridine and N,N-dimethylaniline; halogenated hydrocarbons such as chloroform, dichloromethane and carbon tetrachloride; aprotic polar solvents such as DMF, DMSO and hexamethylphosphoric triamide (HMPA); and a mixture of these solvents. The reaction is usually carried out at a temperature of from about 0°C to about 150°C, preferably from about 0°C to about 120°C, for about 0.5 to about 20 hours. Potassium salt of malonic acid monoalkyl ester is usually used in an amount of at least 1 mole, preferably 1 to 2 moles, per 1 mole of compound (1). Magnesium chloride and the basic compound are usually used in an amount of at least 1 mole, preferably 1 to 2 moles, per 1 mole of compound (1).

Step b

Compound (3) can be prepared by reacting compound (2) with
triaxyl orthoformate such as trimethyl orthoformate and triethyl orthoformate in acetic anhydride. The reaction is usually carried out at a temperature of from about 0°C to about 200°C, preferably from about 0°C to about 150°C, for about 0.5 to about 20 hours. Trialkyl orthoformate is usually used in an amount of at least 1 mole, preferably 1 to 10 moles, per 1 mole of compound (2).

**Step c**

Compound (4) can be prepared by reacting compound (3) with compound (6).

The reaction between compound (3) and compound (6) can be carried out in a suitable solvent. The solvent employed in the reaction may be any conventional solvents unless they give any undesirable effect on the reaction, and includes, for example, alcohols such as methanol, ethanol and propanol; ethers such as diethyl ether, dioxane, tetrahydrofuran, monoglyme and diglyme; aromatic hydrocarbons such as benzene, toluene and xylene; aliphatic hydrocarbons such as n-hexane, heptane, cyclohexane and ligroin; halogenated hydrocarbons such as chloroform, methylene chloride and carbon tetrachloride; aprotic polar solvents such as DMF, DMSO and HMPA; and the like. The reaction is usually carried out at a temperature of from about 0°C to about 150°C, preferably from room temperature to about 100°C, for about 0.1 to about 15 hours. Compound (6) is usually used in an amount of at least 1 mole, preferably 1 to 2 moles, per 1 mole of compound (3).

**Step d**

Compound (5) can be prepared by cyclization of compound (4).

The cyclization of compound (4) can be carried out in a suitable solvent in the presence of a basic compound. The solvent employed in the reaction may be any conventional solvents unless they give any undesirable effect on the reaction, and includes, for example, ethers such as diethyl ether, dioxane, tetrahydrofuran, monoglyme and diglyme;
aliphatic hydrocarbons such as n-hexane, heptane and ligroin; halogenated hydrocarbons such as chloroform, methylene chloride and carbon tetrachloride; aprotic polar solvents such as DMF, DMSO and HMPA; and the like. The basic compound employed in the reaction includes inorganic bases such as metallic sodium, metallic potassium, sodium hydride, sodium amide, sodium hydroxide, potassium hydroxide, sodium carbonate and potassium carbonate, metal alcoholates such as sodium methylate and sodium ethylate, organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), N-benzyltrimethylammonium hydroxide and tetrabutylammonium hydroxide, and the like. The reaction is usually carried out at a temperature of from about 0°C to about 200°C, preferably from room temperature to about 150°C, for about 0.5 to about 15 hours. The basic compound is usually used in an amount of at least 1 mole, preferably 1 to 2 moles, per 1 mole of the compound (4).

Reaction Scheme II

wherein X, R¹, R², R³ and R³² are as defined above.

Step a

Compound (Ia) can be prepared by reacting compound (5) and compound (7) or compound (8) in an inert solvent or without using any solvents, in the presence or absence of a basic compound, in the presence of a palladium catalyst.

Examples of inert solvents include water; ethers such as dioxane, tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, diethylene glycol dimethyl ether and ethylene glycol dimethyl ether; aromatic hydrocarbons such as benzene, toluene and
xylene; alcohols such as methanol, ethanol and isopropanol; ketones such as acetone and methyl ethyl ketone; and aprotic polar solvents such as DMF, DMSO, HMPA and acetonitrile. These inert solvents can be used singly or in combinations of two or more.

The palladium catalyst used in the reaction is not particularly limited, but include, for example, tetravalent palladium catalysts such as sodium hexachloropalladate(IV) tetrahydrate and potassium hexachloropalladate(IV); divalent palladium catalysts such as palladium(II) chloride, palladium(II) bromide, palladium(II) acetate, palladium(II) acetylacetonate, dichlorobis(benzonitrile)palladium(II), dichlorobis(acetonitrile)palladium(II), dichlorobis(triphenylphosphine)palladium(II), dichlorotetramine palladium(II), dichloro(cycloocta-1,5-diene)palladium(II), palladium(II) trifluoroacetate, and 1,1'bis(diphenylphosphino)ferrocene dichloropalladium(II) dichloromethane complex (Pd(dppf)Cl₂CH₂Cl₂); zerovalent palladium catalysts such as tris(dibenzylideneacetone)dipalladium(0), tris(dibenzylideneacetone)dipalladium(0) chloroform complex and tetrakis(triphenylphosphine)palladium(0), etc. These palladium catalysts are used singly or in combinations of two or more.

In the reaction, the amount of the palladium catalyst is not particularly limited, but is typically in the range from 0.000001 to 20 moles in terms of palladium relative to 1 mole of compound (5). The amount of the palladium catalyst is preferably in the range from 0.0001 to 5 moles in terms of palladium relative to 1 mole of compound (5).

This reaction advantageously proceeds in the presence of a suitable ligand. Examples of ligands of the palladium catalyst include, for example, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), tri-o-tolylphosphine, bis(diphenylphosphino)ferrocene, triphenylphosphine, tri-t-butylphosphine and 4,5-bis(diphenylphosphino)-9,9-
dimethylxanthene (Xantphos). These ligands are used singly or in combinations of two or more.

The proportion of the palladium catalyst and ligand is not particularly limited. The amount of the ligand is about 0.1 to about 100 moles per 1 mole of the palladium catalyst, and preferably about 0.5 to about 15 moles per 1 mole of the palladium catalyst.

Various known inorganic and organic bases can be used as basic compounds.

Inorganic bases include, for example, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, cesium hydroxide and lithium hydroxide; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and lithium carbonate; alkali metal hydrogen carbonates such as lithium hydrogen carbonate, sodium hydrogen carbonate and potassium hydrogen carbonate; alkali metals such as sodium and potassium; phosphates such as sodium phosphate and potassium phosphate; amides such as sodium amide; and alkali metal hydrides such as sodium hydride and potassium hydride.

Organic bases include, for example, alkali metal lower alkoxides such as sodium methoxide, sodium ethoxide, sodium t-butoxide, potassium methoxide, potassium ethoxide and potassium t-butoxide, and amines such as triethylamine, tripropylamine, pyridine, quinoline, piperidine, imidazole, N-ethylidiisopropylamine, dimethylaminopyridine, trimethylamine, dimethylaniline, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diaza-bicyclo[2.2.2]octane (DABCO), etc.

Such basic compounds can be used singly or in combinations of two or more. More preferable basic compounds used in the reaction include alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and lithium carbonate.

The basic compound is usually used in an amount of 0.5 to 10 moles per 1 mole of compound (5), and preferably 0.5 to 6
moles per 1 mole of compound (5).

Compound (7) or compound (8) is usually used in an amount of at least 1 mole per 1 mole of compound (5), and preferably about 1 to about 5 moles per 1 mole of compound (5).

The reaction can be conducted under normal pressure, under inert gas atmosphere including nitrogen, argon, etc., or under increased pressure.

The reaction proceeds usually from room temperature to about 200°C, and preferably from room temperature to about 150°C, and is usually completed in about 1 to about 30 hours. The reaction is also achieved by heating at about 100°C to about 200°C for about 5 minutes to about 1 hour using a microwave reactor.

Step b

Compound (Ib) can be prepared by hydrolysis of compound (Ia).

The hydrolysis of compound (Ia) can be carried out under the conditions of conventional hydrolysis, for example, in the presence of a basic compound such as sodium hydroxide, potassium hydroxide, barium hydroxide or potassium carbonate; a mineral acid such as sulfuric acid, hydrochloric acid or nitric acid; or an organic acid such as acetic acid or an aromatic sulfonic acid, in a solvent including water, alcohols such as methanol, ethanol and isopropanol; ketones such as acetone and methyl ethyl ketone; ethers such as dioxane and ethylene glycol diethyl ether; acetic acid; or a mixture thereof. The reaction is usually carried out at a temperature of from room temperature to about 200°C, preferably from room temperature to about 150°C, for about 0.1 to about 30 hours.
Reaction Scheme III

Preparation of boronate and boronic acid

\[ \text{R}^3\text{-Z} + \begin{array}{c}
\text{O} \\
\text{O} \\
\text{B} \quad \text{B} \\
\text{O} \\
\text{O}
\end{array} \rightarrow \begin{array}{c}
\text{O} \\
\text{O} \\
\text{B} \quad \text{R}^3 \\
\text{O} \\
\text{O}
\end{array} \quad \text{a} \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{B} \quad \text{OH} \\
\text{OH}
\end{array} \quad \text{b} \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{B} \quad \text{OH} \\
\text{OH}
\end{array} \]

\begin{align*}
(9) & \quad (10) & \quad (7) & \quad (9) & \quad (8)
\end{align*}

wherein \( \text{R}^3 \) is as defined above, and \( \text{Z} \) is a bromine atom or an iodine atom.

**Step a**

Compound (7) can be prepared by reacting compound (9) with bis(pinacolato)diboron (10) in an inert solvent in the presence of a palladium catalyst and a basic compound.

Examples of inert solvents and palladium catalyst are same as those described in Step a in Reaction Scheme II.

The basic compound employed in the reaction includes potassium acetate, triethylamine, N-methylmorpholin, sodium carbonate, potassium carbonate, cesium carbonate, lithium carbonate, potassium phosphate and sodium hydrogen carbonate.

In the reaction, the amount of the palladium catalyst is not particularly limited, but is typically in the range from 0.000001 to 20 moles in terms of palladium relative to 1 mole of compound (9). The amount of the palladium catalyst is preferably in the range from 0.0001 to 5 moles in terms of palladium relative to 1 mole of compound (9).

The basic compound is usually used in an amount of 0.5 to 10 moles per 1 mole of compound (9), and preferably 0.5 to 6 moles per 1 mole of compound (9).

Bis(pinacolato)diboron (10) is usually used in an amount of at least 1 mole per 1 mole of compound (9), and preferably about 1 to about 5 moles per 1 mole of compound (9).

The reaction can be conducted under normal pressure, under inert gas atmosphere including nitrogen, argon, etc., or under increased pressure.

The reaction proceeds usually from room temperature to about 200°C, and preferably from room temperature to about 150°C.
and is usually completed in about 1 to about 30 hours.

**Step b**

Compound (8) can be prepared by reacting compound (9) with trialkyl borate such as trimethyl borate, triethyl borate, tri(isopropyl) borate and tri(n-butyl) borate in an inert solvent in the presence of n-butyllithium or lithium diisopropylamide.

Examples of inert solvents are same as those described in Step a in Reaction Scheme II.

The trialkyl borate is usually used in an amount of at least 1 mole per 1 mole of compound (9), and preferably about 1 to about 5 moles per 1 mole of compound (9).

n-Butyllithium or lithium diisopropylamide is usually used in an amount of at least 1 mole per 1 mole of compound (9), and preferably about 1 to about 5 moles per 1 mole of compound (9).

The reaction is usually carried out at a temperature of from about -70°C to about 0°C for about 0.1 to about 15 hours.

Compound (I) of the present invention can easily be converted into a salt thereof by treating with a pharmaceutically acceptable acid or base. The acid includes inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid and hydrobromic acid and organic acids such as oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, benzoic acid, lactic acid, methanesulfonic acid and propionic acid. The base includes sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium hydrogen carbonate, and the like.

The compound thus obtained can easily be isolated and purified by conventional methods, such as, for example, extraction with solvents, dilution method, recrystallization, column chromatography and preparative thin layer chromatography.

Compound (I) shows an excellent antimicrobial activity against mycoplasma, *Pseudomonas aeruginosa*, anaerobic bacteria, resistant cells against various antimicrobials, clinically
isolated bacteria, and gram negative and gram positive bacteria such as Clostridium difficile, Enterococcus faecalis and Staphylococcus pyogenes and hence is useful as an antimicrobial agent for the treatment of diseases induced by these microorganisms. Compound (I) also shows low toxicity and less side effects and is characteristic in good absorbability and in sustained activity.

Since compound (I) shows an excellent antimicrobial activity against Clostridium difficile, it is useful for the prevention or treatment of intestinal infections including antibiotics-associated diarrhea (AAD) such as Clostridium difficile-associated diarrhea (CDAD).

The compounds of the present invention are usually used in the form of a usual pharmaceutical preparation. The pharmaceutical preparation can be prepared in admixture with conventional pharmaceutically acceptable diluents or carriers, such as fillers, bulking agents, binding agents, wetting agents, disintegrators, surfactants and lubricating agents. The pharmaceutical preparation includes various preparations suitable for treatment of the diseases, for example, tablets, pills, powders, solutions, suspensions, emulsions, granules, capsules, suppositories, injections such as solutions and suspensions, and the like. In the preparation of tablets, there may be used any conventional carriers, for example, excipients such as lactose, white sugar, sodium chloride, glucose, urea, starches, calcium carbonate, kaolin, crystalline cellulose and silicate, binding agents such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate and polyvinylpyrrolidone, disintegrators such as dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogen carbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, stearic monoglyceride, starches and lactose,
disintegration inhibitors such as white sugar, stearin, cacao butter and hydrogenated oils, absorption promoters such as quaternary ammonium salts and sodium lauryl sulfate, wetting agents such as glycerin and starches, adsorbents such as starches, lactose, kaolin, bentonite and colloidal silicates, lubricants such as purified talc, stearates, boric acid powder and polyethylene glycol, and the like. The tablets may also be coated with conventional coating agents, for example, may be in the form of a sugar coated tablet, a gelatin-coated tablets, an enteric coating tablet, a film coating tablet, or a double or multiple layers tablet. In the preparation of pills, there may be used conventional carriers, including excipients such as glucose, lactose, starches, cacao butter, hydrogenated vegetable oils, kaolin and talc, binding agents such as gum arabic powder, tragacanth powder, gelatin and ethanol, disintegrators such as laminaran and agar, and the like. In the preparation of suppositories, there may be used conventional carriers, such as, for example, polyethylene glycol, cacao butter, higher alcohols, higher alcohol esters, gelatin and semi-synthesized glycerides.

In the preparation of injections, the solutions, emulsions or suspensions of the compounds are sterilized and are preferably made isotonic with the body liquid. These solutions, emulsions and suspensions are prepared by admixing the active compound with a conventional diluent, such as water, aqueous lactic acid solution, ethyl alcohol, propylene glycol, ethoxylated isostearyl alcohol, polyoxyated isostearyl alcohol or polyoxyethylene sorbitan fatty acid esters. The preparations may also be incorporated with sodium chloride, glucose or glycerin in an amount sufficient to make them isotonic with the body liquid. The preparations may also be incorporated with conventional solubilizers, buffering agents, anesthetizing agents, and further, with coloring agents, preservatives, perfumes, flavors, sweetening agents, and other medicaments. The preparations in the form of a paste, cream or gel may be prepared by using as a diluent such as white petrolatum,
paraffin, glycerin, cellulose derivatives, polyethylene glycol, silicone, bentonite, or the like. When the compound of the active ingredient precipitates in the injection, an acid such as, for example, methanesulfonic acid, propionic acid, hydrochloric acid, succinic acid or lactic acid may be added to the injection as required to preserve the injection in a stable solution.

Compound (I) may be contained in any amount in the preparations, and are usually contained in an amount of from 1 to 70% by weight based on the whole weight of the preparations.

The pharmaceutical preparations of the present invention can be administered in any methods. Suitable method for administration may be selected in accordance with the preparation form, age and sex of patients, severity of the diseases, and the like. For instance, tablets, pills, solutions, suspensions, emulsions, granules and capsules are administered in oral route. In case of injection, it is administered intravenously in a single form or together with an auxiliary liquid such as glucose or amino solution. The injections may also be administered in intramuscular, intracutaneous, subcutaneous, or intraperitoneal route. Suppositories are administered in intrarectal route.

The dosage of the pharmaceutical preparations of the present invention may vary according to administration methods, age and sex of patients, severity of the diseases, and the like, usually in the range of about 0.1 to about 100 mg, more preferably in the range of about 0.1 to about 50 mg, of compound (I) per 1 kg body weight of the patient per day. The preparation is usually administered by dividing into 2 to 4 times per day.

The present invention is illustrated by the following Examples, Experimental Examples and Preparation Examples. It is to be understood that the present invention is not limited to these Examples, Experimental Examples or Preparation Examples and various changes and modifications can be made without departing from the scope and spirit of the present invention.
Examples

General Scheme I. Synthesis of intermediates

Reaction reagents and conditions: a. KO$_2$CCH$_2$CO$_2$Et, MgCl$_2$, Et$_3$N, 80°C;
b. HC(ETO)$_3$, 150°C; c. Cyclopropylamine; d. K$_2$CO$_3$, DMSO, 100°C

In our work, Suzuki coupling was employed as key reaction to construct our final products. For the coupling, the corresponding iodo-intermediates could be prepared through well-known methods that were wildly used to synthesis of quinolones before (General Scheme I).

Example 1: Synthesis of Intermediate 5a (R$^2$ = Me)

1.1. Compound 2: A mixture of compound 1 (2 g, 6.71 mmol) and thionyl chloride (9.8 mL) was refluxed for 3 hr, and then concentrated to give acid chloride. To the residue was added dry EtOAc (10 mL) and then the mixture was concentrated.

A mixture of potassium ethyl malonate (1.6 g, 9.40 mmol) and MgCl$_2$ (1.91 g, 20.13 mmol) in dry EtOAc was stirred for 30 min below 50°C. To the mixture was added Et$_3$N (2.83 mL, 20.13 mmol) below 50°C. Then, the mixture was refluxed for 1 hr. To the mixture was added dropwise a solution of the acid chloride in dry EtOAc (10 mL) at 50-70°C and then the mixture was refluxed for 1.5 hr. Water (30 mL) and 5 N HCl (30 mL) were
added to the reaction mixture under ice-cooling. The EtOAc solution was washed with water, dried and concentrated to give compound 2 as a yellow oil, which was used in the next step without purification.

1.2. Compound 3: A mixture of compound 2 (11 g, 29.88 mmol), triethyl orthoformate (7.47 mL, 44.82 mmol) and acetic anhydride (6.77 mL, 71.72 mmol) was heated at 150°C for 1 hr, and then concentrated to give compound 3, which was used in the next step without purification.

1.3. Compound 4: To compound 3 (obtained above) were added EtOH (50 mL) and cyclopropylamine (2.48 mL, 35.86 mmol). The mixture was stirred for 30 min and concentrated to give compound 4, which was used in the next step without purification.

1.4. Intermediate 5a: Compound 4 (obtained above) was dissolved in dry DMSO (100 mL). K₂CO₃ (16.52 g, 119.53 mmol) was added to the solution. The reaction mixture was stirred at 100°C for 1 hr. When TLC (EtOAc/diisopropyl ether=1/1) indicated the reaction was completed, the mixture was cooled to room temperature, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried and concentrated to give a yellow solid which was recrystallized from EtOAc. Intermediate 5a was obtained as a white solid in 75% overall yield. $^1$H NMR (400 MHz, DMSO) δ 8.60 (s, 1H), 7.70 (d, J = 7.8 Hz, 1H), 4.29 - 4.14 (m, 3H), 2.96 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.14 (q, J = 7.0 Hz, 2H), 0.87 - 0.76 (m, 2H).

The following compounds were synthesized according to General Scheme I.

Example 2: Intermediate 5b (R² = OMe): $^1$H NMR (400 MHz, DMSO) δ 8.51 (s, 1H), 7.69 (d, J = 7.7 Hz, 1H), 4.23 (dd, J = 14.0, 6.9 Hz, 2H), 4.03 (s, 1H), 3.80 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.09 (d, J = 6.2 Hz, 2H), 0.97 (m, 2H).
Example 3: Intermediate 5c (R^2 = Cl): ^1H NMR (400 MHz, DMSO) δ 8.61 (s, 1H), 7.81 (d, J = 7.6 Hz, 1H), 4.23 (m, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.21 - 1.08 (dd, J = 7.1, 2.2 Hz, 2H), 0.99 - 0.92 (m, 2H).

Example 4: Intermediate 5d: ^1H NMR (400 MHz, CDCl$_3$) δ 8.59 - 8.51 (d, J = 3.1 Hz, 1H), 8.03 - 7.92 (d, J = 7.5 Hz, 1H), 4.98 - 4.73 (dddd, J = 62.9, 6.3, 4.9, 3.4 Hz, 1H), 4.44 - 4.34 (q, J = 7.1 Hz, 2H), 3.91 - 3.83 (dt, J = 8.6, 5.4 Hz, 1H), 2.95 - 2.88 (s, 3H), 1.59 - 1.48 (m, 1H), 1.45 - 1.38 (t, J = 7.1 Hz, 3H), 1.35 - 1.18 (m, 1H).

Example 5: Intermediate 5e: ^1H NMR (400 MHz, CDCl$_3$) δ 8.51 - 8.43 (d, J = 2.0 Hz, 1H), 7.94 - 7.86 (d, J = 7.6 Hz, 1H), 4.90 - 4.65 (dddd, J = 62.7, 6.0, 5.1, 3.3 Hz, 1H), 4.37 - 4.28 (q, J = 7.1 Hz, 2H), 3.80 - 3.76 (s, 3H), 3.75 - 3.69 (dt, J = 8.7, 5.5 Hz, 1H), 1.61 - 1.47 (m, 2H), 1.46 - 1.30 (m, 4H).

Example 6: Intermediate 5f: ^1H NMR (400 MHz, DMSO) δ 8.65 (s, 1H), 7.48 (d, J = 8.16 Hz, 1H), 4.79 (q, J = 6.65 Hz, 1H), 4.62 (dd, J = 1.82, 11.36 Hz, 1H), 4.44 (dd, J = 2.20, 11.36 Hz, 1H), 4.23 (qd, J = 2.95, 7.09 Hz, 2H), 1.40 (d, J = 6.65 Hz, 3H), 1.28 (t, J = 7.09 Hz, 3H).
General Scheme II. Preparation of boronate and boronic acid

\[ \text{R}^3\text{-Z} + \begin{array}{c}
\text{O} \\
\text{B} - \text{B} - \text{O}
\end{array} \xrightarrow{a} \begin{array}{c}
\text{R}^3\text{-B}
\end{array} \]
\[ \text{Z} = \text{Br, I} \]

\[ \begin{array}{c}
\text{R}^3\text{-Z} \\
\xrightarrow{b} \begin{array}{c}
\text{R}^3\text{-O}
\end{array}
\end{array} \]
\[ \text{Z} = \text{Br, I} \]

Reaction reagents and conditions: a. Pd(dppf)Cl₂·CH₂Cl₂ (5% mol), KOAc, dioxane, 80°C; b. nBuLi (or LDA), B(OiPr)₃, THF

General Scheme II outlined the preparation of required boronic acids and boronates. They are readily prepared through general methods.

Example 7 Synthesis of boronic acid 7

![Synthesis of boronic acid 7](image)

Reaction reagents and conditions: a. 1) NaH, THF, r.t.; 2) nBuLi, B(OiPr)₃, -70°C to 0°C

7.1 Boronic acid 7: To a solution of compound 6 (10 g, 44.44 mmol) in dry tetrahydrofuran (350 mL) was added sodium hydride (2 g, 66.66 mmol, 80% dispersion) at 0°C. After the mixture was stirred at room temperature for 30 min, the mixture was cooled below -60°C in a dry ice/acetone bath, and n-butyllithium (70 mL, 112 mmol, 1.6 M in hexane) was added over 30 min. The mixture was kept stirring for another 30 min, then triisopropyl borate (40 mL, 177 mmol) was added dropwise. The reaction mixture was stirred for 10 min, and then warmed to 0°C slowly in an ice bath. HCl (5 N) was added to the mixture to adjust pH = 3-4, and the mixture was stirred for 20 min. Aq. NaOH was added to the mixture to adjust pH = 10. After filtration, the organic layer was separated. The aqueous layer was extracted with a mixture of ethyl acetate/THF (4/1; 2 x 120 mL) and EtOAc (100 mL). The aqueous layer was adjusted to pH = 5-6 with HCl. The precipitate thus formed was collected
by filtration and dried to give boronic acid 7 (3.5 g, 41%) as a white solid.

Example 8 Synthesis of boronate 10

8.1 Compound 9: 2-Aminonicotinonitrile 8 (100 g, 0.839 mol) was dissolved in HOOAc (600 mL). To the solution was added Na₂CO₃ (88.97 g, 0.839 mol). Then, Br₂ (46.4 mL, 0.923 mol) was added dropwise. The reaction mixture was stirred at room temperature for 50 min. To the mixture was added water (600 mL). The mixture was cooled to about 5°C. The precipitate thus formed was collected by filtration and dried to give compound 9 (207 g, 96%).

8.2 Boronate 10: Compound 9 (50 g, 0.224 mol), bis(pinacolato)diboron (85.6 g, 0.337 mol), KOAc (44.1 g, 0.449 mol) and Pd(dppf)Cl₂·CH₂Cl₂ (2.77 g, 3.4 mmol) were charged into a flask. Dioxane (400 mL) was added. The reaction mixture was stirred at 100°C for 2 hr under Ar. When LC-MS indicated that the reaction was completed, the mixture was cooled to room temperature. The mixture was filtered through diatomite, concentrated, diluted with a mixture of ethyl acetate and hexane in 3/1 ratio (1000 mL), filtered through silica gel (300-400 mesh), concentrated, crystallized and dried to give boronate 10 (32 g, 66%) as a white solid.

Example 9 Synthesis of boronate 13
9.1 Compound 12: 3-Chloropyridin-2-amine (100 g, 0.778 mol) was dissolved in acetic acid (1200 mL). To the solution was added Na₂CO₃ (82.4 g, 0.778 mol). Then, Br₂ (39.1 mL, 0.856 mmol) was added dropwise. After addition, the reaction mixture was stirred at room temperature for 30 min. To the mixture was added water (800 mL). The mixture was cooled to about 5°C. The resulting solid was collected by filtration and dried to give compound 12 (147 g, 91%) as a white solid.

9.2 Boronate 13: Compound 12 (4 g, 17.2 mmol), bis(pinacolato)diboron (4.79 g, 18.8 mmol), KOAc (3.37 g, 34.2 mmol) and Pd(dppf)Cl₂·CH₂Cl₂ (0.210 g, 0.25 mmol) were charged into a flask. Dioxane (80 mL) was added. The mixture was stirred at 85°C for 2 hr under Ar. When LC-MS indicated that the reaction was completed, the mixture was cooled to room temperature. The mixture was filtered through diatomite and concentrated. The residue was diluted with ethyl acetate and hexane (3/1, 100 mL), filtered through silica gel (300-400 mesh), concentrated and crystallized by n-hexane to give boronate 13 (3.4 g, 78%) as a white solid.

General Scheme III

![Diagram](image)

Reaction reagents and conditions: a. Pd(dppf)Cl₂·CH₂Cl₂(5% mol), K₂CO₃, dioxane, 80°C; b. NaOH, EtOH

Example 10 Synthesis of compound 1-2

![Diagram](image)

10.1 Compound 16: Intermediate 5a (30 g, 65 mmol), boronic
acid 7 (17 g, 71.6 mmol) and K₂CO₃ (27, 195 mmol) were charged into a flask. Dioxane (600 mL) and water (60 mL) were added. The solution was deoxygenated with N₂ for 15 min. Pd(dppf)Cl₂.CH₂Cl₂ (2.8 g, 3.24 mmol) was added to the mixture. The reaction mixture was stirred at 85°C overnight. When the reaction was completed, the reaction mixture was cooled to room temperature. The precipitate was filtered, dissolved in water, filtered, triturated with EtOH, filtered and dried to give compound 16 (16 g, 57%) as an off-white solid. The obtained compound was pure enough for use.

The organic filtrate was concentrated. To the residue were added water, dichloromethane and EtOAc. The precipitate thus formed was collected by filtration and dissolved in HCl (5 N). After filtration to remove Pd residue, the filtrate was basified with aq. NaOH (pH = 7-8). The precipitate was collected by filtration and dried to give compound 16 (3 g, 11%) as an off-white solid.

10.2 Compound 1-2: Compound 16 (33 g, 76.1 mmol) was suspended in EtOH (300 mL). Aq. NaOH (4 N, 100 mL) was added to the suspension, and the mixture was stirred at 60°C for 2 hr. 200 mL of EtOH was evaporated under reduced pressure. To the residue was added HCl (5 N) to adjust pH = 4. The resulting precipitate was filtered, triturated with EtOH, filtered and dried to give compound 1-2 (30 g, 97%) as an off-white solid.

m.p. > 300°C. ¹H NMR (400 MHz, DMSO) δ 14.64 (s, 1H), 12.39 (s, 1H), 8.92 (s, 1H), 8.58 (s, 1H), 8.28 (s, 1H), 8.01 (m, 2H), 6.67 (d, J = 9.4 Hz, 1H), 4.42 (s, 1H), 2.68 (s, 3H), 1.27 (d, J = 6.4 Hz, 2H), 1.12 - 1.03 (m, 2H). ¹³C NMR (101 MHz, DMSO) δ 176.92, 165.25, 162.85, 158.16, 155.72, 152.71, 150.92, 149.62, 139.29, 138.79, 137.62, 133.70, 133.52, 131.80, 127.47, 127.38, 123.75, 123.42, 113.89, 108.05, 107.81, 107.29, 41.29, 20.64, 20.62, 10.62. HPLC-MS m/z 406 (MH⁺).

Example 11 Synthesis of compound 2-18

11.1 Compound 17: Boronate 10 (14 g, 56.1 mmol), intermediate 5a (20 g, 46.7 mmol), Cs$_2$CO$_3$ (15.22 g, 46.7 mmol) and Pd(dppf)Cl$_2$.CH$_2$Cl$_2$ (0.98 g, 1.2 mmol) were charged into a flask. Dioxane (500 mL) and water (5 mL) were added. The mixture was stirred at 110°C overnight under Ar. The mixture was cooled to room temperature. The mixture was filtered, and the solid was washed with dioxane and ethyl acetate. The solid was dissolved in hot CH$_2$Cl$_2$ (1200 mL), and the solution was filtered through diatomite. The operation was repeated twice. The organic layers were combined and concentrated. To the residue was added ethyl acetate (200 mL). The solid was collected by filtration, washed with ethyl acetate (60 mL) and dried to give compound 17 (17.6 g, 90%) as a white solid.

11.2 Compound 2-18: Compound 17 (43 g, 0.101 mol) was dissolved in THF and EtOH (1/1, 500 mL). To the solution was added NaOH (60 mL, 4 N). The mixture was stirred at room temperature for 2 hr. HCl (63 mL, 4 N) was added to acidify the mixture (pH = 3-4). The solid was collected by filtration, washed with EtOH (100 mL) and dried to give compound 2-18 (35.7 g, 99%) as a white solid. m.p. > 300°C. $^1$H NMR (400 MHz, DMSO) δ 14.65 (s, 1H), 8.89 (s, 1H), 8.32 - 8.23 (m, 1H), 8.08 (d, J = 2.09 Hz, 1H), 7.94 (d, J = 8.87 Hz, 1H), 7.28 (s, 2H), 4.40 (tt, J = 3.74, 7.17 Hz, 1H), 2.67 (s, 3H), 1.31 - 1.19 (m, 2H), 1.10 - 0.99 (m, 2H). $^{13}$C NMR (101 MHz, DMSO) δ 176.95, 176.92, 165.32, 159.60, 158.29, 155.86, 154.07, 152.67, 143.59, 139.32, 133.39, 133.22, 131.73, 127.13, 127.05, 116.93, 116.52, 107.96, 107.71, 107.27, 89.15, 41.32, 20.64, 20.62, 10.65. HPLC-MS m/z 379 (MH$^+$). Anal. Calcd for C$_{20}$H$_{25}$F$_{14}$N$_4$O$_6$: C, 63.49, H, 4.00, N, 14.81. Found: C, 62.04, H, 4.20, N, 13.97.
Example 12 Synthesis of compound 3-11

12.1 Compound 18: Boronate 13 (20 g, 75.4 mmol), intermediate 5a (24.1 g, 58.03 mmol), Cs₂CO₃ (26.5 g, 81.2 mmol) and Pd(dppf)Cl₂.CH₂Cl₂ (1.42 g, 1.7 mmol) were charged into a flask. Dioxane (400 mL) and water (4 mL) were added. The mixture was stirred at 100°C overnight under Ar. The mixture was cooled to room temperature. The mixture was filtered, and the solid was washed with dioxane and ethyl acetate. The solid was dissolved in hot CH₂Cl₂ (1200 mL), and the solution was filtered through diatomite. The operation was repeated twice. The organic layers were combined and concentrated. To the residue was added ethyl acetate (200 mL). The solid was collected by filtration, washed with ethyl acetate (60 mL) and dried to give compound 18 (21 g, 85%) as a white solid.

12.2 Compound 19: Compound 18 (39 g, 91.91 mmol) was dissolved in THF and EtOH (1/1, 600 mL). To the mixture was added NaOH (4 N, 60 mL). The mixture was stirred at room temperature for 2 hr. HCl (4 N, 62 mL) was added to acidify the solution (pH = 3-4). The solid was collected by filtration, washed with EtOH (100 mL) and dried to give compound 19 (34 g, 98%) as a white solid.

12.3 Compound 3-11: Chloroacetaldehyde (40% in water, 80 mL)
was added to a solution of compound 19 (34 g, 91.9 mmol) in EtOH (600 mL). The mixture was refluxed for 3 hr. When LC-MS indicated that the reaction was completed, the mixture was cooled to 5°C and filtered. The solid was dried to give compound 3-11 (21 g). The mother liquid was basified (pH=7-8) with aq. NaOH. The precipitate was collected by filtration, washed with EtOH and dried to give compound 3-11 (11.5 g) as a white solid. In total, 32.5 g of compound 3-11 was obtained in 93% yield. m.p.: 307 - 311°C. 1H NMR (400 MHz, DMSO) δ 14.53 (s, 1H), 8.98 - 8.84 (m, 2H), 8.28 (d, J = 1.16 Hz, 1H), 7.98 (d, J = 8.83 Hz, 1H), 7.90 (d, J = 0.89 Hz, 1H), 7.77 (s, 1H), 4.43 (tt, J = 3.70, 7.10 Hz, 1H), 3.50 - 3.36 (m, 1H), 2.72 (s, 3H), 1.26 (d, J = 6.80 Hz, 2H), 1.07 (d, J = 10.24 Hz, 2H). 13C NMR (101 MHz, DMSO) δ 176.91, 176.88, 165.23, 158.22, 155.77, 152.84, 139.98, 139.17, 139.16, 132.44, 132.15, 131.98, 131.54, 127.86, 127.78, 127.38, 120.72, 118.97, 116.37, 108.15, 107.91, 107.37, 41.38, 20.54, 20.52, 10.72. HPLC-MS: m/z 412 (MH^+). Anal. Calcd for C_{21}H_{15}ClF_{1}N_{1}O_{3}: C, 61.25, H, 3.67, N, 10.20. Found: C, 58.59, H, 3.86, N, 9.76.

Compounds listed in the following Tables were synthesized according to General Scheme III.
<table>
<thead>
<tr>
<th>Compound No.</th>
<th>( R^3 = )</th>
<th>( R^2 = )</th>
<th>( R^1 = )</th>
<th>NMR</th>
<th>MS (M^+</th>
<th>HPLC</th>
</tr>
</thead>
<tbody>
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<td><img src="image1.png" alt="Structure" /></td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>( ^1H ) NMR (400 MHz, DMSO) δ 14.63 (s, 1H), 12.41 (s, 1H), 8.82 (s, 1H), 8.69 (s, 1H), 8.38 (s, 1H), 8.05 (d, J = 9.6 Hz, 1H), 7.99 (d, J = 9.1 Hz, 1H), 6.66 (dd, J = 9.5, 1.6 Hz, 1H), 4.24 (s, 1H), 3.42 (s, 3H), 1.19 (d, J = 7.2 Hz, 4H).</td>
<td>422</td>
<td>98%</td>
</tr>
<tr>
<td>1-2</td>
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<td>Me</td>
<td>Cyclopropyl</td>
<td>( ^1H ) NMR (400 MHz, DMSO) δ 14.64 (s, 1H), 12.39 (s, 1H), 8.92 (s, 1H), 8.58 (s, 1H), 8.28 (s, 1H), 8.01 (m, 2H), 6.67 (d, J = 9.4 Hz, 1H), 4.42 (s, 1H), 2.68 (s, 3H), 1.27 (d, J = 6.4 Hz, 2H), 1.12 – 1.03 (m, 2H).</td>
<td>406</td>
<td>98%</td>
</tr>
<tr>
<td>1-3</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>OMe</td>
<td></td>
<td>( ^1H ) NMR (400 MHz, DMSO) δ 14.49 (s, 1H), 12.41 (s, 1H), 8.85 (d, J = 1.3 Hz, 1H), 8.67 (s, 1H), 8.36 (s, 1H), 8.05 (d, J = 9.6 Hz, 1H), 8.00 (d, J = 9.1 Hz, 1H), 6.77 – 6.54 (m, 1H), 5.24 – 4.97 (m, 1H), 4.29 – 4.10 (m, 1H), 3.44 (s, 3H), 1.89 – 1.59 (m, 2H).</td>
<td>440</td>
<td>98%</td>
</tr>
<tr>
<td>1-4</td>
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<td>Me</td>
<td></td>
<td>( ^1H ) NMR (400 MHz, DMSO) δ 14.50 (s, 1H), 12.39 (s, 1H), 8.90 (d, J = 3.0 Hz, 1H), 8.58 (s, 1H), 8.27 (s, 1H), 8.02 (m, 2H), 6.74 – 6.61 (m, 1H), 5.17 (dd, J = 64.3, 3.1 Hz, 1H), 4.39 (s, 1H), 2.60 (s, 3H), 1.84 – 1.50 (m, 2H).</td>
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<td>439</td>
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</tr>
<tr>
<td>1-8</td>
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<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.66 (s, 1H), 11.99 (s, 1H), 8.91 (s, 1H), 8.03 (d, J = 9.1 Hz, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.60 (s, 1H), 7.57 (d, J = 11.5 Hz, 1H), 6.66 (d, J = 9.6 Hz, 1H), 4.51 – 4.29 (m, 1H), 1.25 (d, J = 6.3 Hz, 2H), 1.15 – 0.94 (m, 2H).</td>
<td>423</td>
<td>98%</td>
</tr>
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<td>1-9</td>
<td><img src="image" alt="Structure" /></td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.64 (s, 1H), 11.30 (s, 1H), 8.82 (s, 1H), 8.15 – 8.03 (m, 1H), 8.00 – 7.93 (d, J = 9.1 Hz, 1H), 7.93 – 7.80 (d, J = 12.9 Hz, 2H), 6.79 – 6.51 (d, J = 9.4 Hz, 1H), 4.28 – 4.15 (m, 1H), 3.51 – 3.38 (s, 3H), 1.31 – 1.09 (m, 4H).</td>
<td>455</td>
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<td>1-10</td>
<td><img src="image" alt="Structure" /></td>
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<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.69 – 14.59 (s, 1H), 12.08 – 11.94 (s, 1H), 8.90 – 8.74 (s, 1H), 8.13 – 8.01 (d, J = 1.8 Hz, 1H), 7.99 – 7.91 (d, J = 9.1 Hz, 1H), 7.77 – 7.71 (s, 1H), 7.68 – 7.59 (d, J = 11.6 Hz, 1H), 6.71 – 6.62 (d, J = 9.6 Hz, 1H), 4.30 – 4.17 (ddd, J = 11.2, 7.5, 4.7 Hz, 1H), 3.47 – 3.39 (s, 3H), 1.22 – 1.11 (m, 4H).</td>
<td>439</td>
<td>95%</td>
</tr>
<tr>
<td>1-11</td>
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<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.68 (s, 1H), 9.92 (s, 1H), 8.91 (s, 1H), 8.09 (d, J = 9.6 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.81 (s, 1H), 7.62 – 7.53 (m, 4H), 7.52 – 7.47 (m, 1H), 7.46 (s, 1H), 6.65 (d, J = 9.5 Hz, 1H), 4.65 – 4.23 (m, 1H), 2.70 (s, 3H), 1.24 (d, J = 7.0 Hz, 2H), 1.07 (s, 2H).</td>
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<td>1-13</td>
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<td>$^1$H NMR (400 MHz, DMSO) δ 14.66 (s, 1H), 10.55 (s, 1H), 8.91 (s, 1H), 8.04 (d, J = 9.5 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.84 (s, 1H), 7.74 (s, 1H), 6.68 (d, J = 9.4 Hz, 1H), 4.75 (s, 1H), 4.40 (m, 1H), 2.64 (s, 3H), 1.25 (d, J = 6.9 Hz, 2H), 1.08 (s, 2H).</td>
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<td>Cyclopropyl</td>
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<td>90%</td>
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<td>No.</td>
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<td>1-15</td>
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<td>δ 14.65 (s, 1H), 10.97 (s, 1H), 8.92 (s, 1H), 8.28 - 8.06 (m, 2H), 8.01 (d, J = 8.8 Hz, 1H), 7.95 (s, 1H), 6.74 (d, J = 8.5 Hz, 1H), 4.49 - 4.33 (m, 1H), 2.64 (s, 3H), 1.25 (d, J = 6.8 Hz, 2H), 1.10 (s, 2H).</td>
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<td><img src="image2" alt="Cyclopropyl" /></td>
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<td>δ 14.63 (s, 1H), 11.86 (s, 1H), 8.92 (s, 1H), 8.16 (m, 3H), 8.00 (d, J = 8.7 Hz, 1H), 6.80 (s, 1H), 4.42 (s, 1H), 2.65 (s, 3H), 1.26 (m, 2H), 1.09 (m, 2H).</td>
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<tr>
<td>1-19</td>
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<td>1-20</td>
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<tr>
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<td>Cyclopropyl</td>
<td>δ 14.75 (s, 1H), 12.18 (s, 1H), 8.91 (s, 1H), 8.14 (s, 1H), 7.96 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 7.9 Hz, 1H), 7.28 (d, J = 7.4 Hz, 1H), 4.43 (s, 1H), 2.71 (s, 3H), 1.24 (s, 2H), 1.05 (s, 2H).</td>
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<td>1-22</td>
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<td>Cyclopropyl</td>
<td>δ 14.75 (s, 1H), 8.91 (s, 1H), 8.16 (s, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.90 (s, 1H), 7.85 (d, J = 7.3 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.38 (d, J = 6.7 Hz, 1H), 4.42 (s, 1H), 3.74 (s, 3H), 2.69 (s, 3H), 1.23 (s, 2H), 1.05 (s, 2H).</td>
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<tr>
<td>1-23</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>(^1)H NMR (400 MHz, DMSO) (\delta) 14.72 (s, 1H), 12.04 (s, 1H), 8.93 (s, 1H), 8.04 (d, J = 8.2 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 9.7 Hz, 1H), 7.17 (d, J = 7.1 Hz, 1H), 6.49 (d, J = 9.7 Hz, 1H), 4.39 (s, 1H), 2.50 (s, 3H), 1.16 (m, 4H).</td>
<td>405</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>1-24</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>(^1)H NMR (400 MHz, DMSO) (\delta) 14.82 (s, 1H), 10.88 (s, 1H), 8.95 (s, 1H), 8.20 – 7.94 (m, 2H), 7.86 (d, J = 30.6 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.36 (s, 1H), 6.57 (s, 1H), 4.41 (s, 1H), 2.67 (s, 3H), 1.47 – 0.92 (m, 4H).</td>
<td>405</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>1-25</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>(^1)H NMR (400 MHz, DMSO) (\delta) 14.66 (s, 1H), 12.12 (s, 1H), 8.94 (s, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.58 (s, 1H), 7.45 (d, J = 7.0 Hz, 1H), 7.13 (s, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.65 (s, 1H), 4.40 (m, 1H), 2.62 (s, 3H), 1.28 – 1.04 (m, 4H).</td>
<td>405</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>1-26</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>(^1)H NMR (400 MHz, DMSO) (\delta) 14.70 (s, 1H), 11.88 (s, 1H), 8.92 (s, 1H), 8.01 (d, J = 8.8 Hz, 2H), 7.86 (d, J = 7.8 Hz, 1H), 7.29 (s, 1H), 7.22 (d, J = 7.6 Hz, 1H), 6.60 (d, J = 9.6 Hz, 1H), 4.40 (s, 1H), 2.62 (s, 3H), 1.24 (d, J = 5.6 Hz, 2H), 1.07 (s, 2H).</td>
<td>405</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>1-27</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>(^1)H NMR (400 MHz, DMSO) (\delta) 14.80 (s, 1H), 11.57 (s, 1H), 11.48 (s, 1H), 8.97 (s, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.82 (s, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.49 (d, J = 8.2 Hz, 1H), 5.86 (s, 1H), 4.45 (s, 1H), 2.68 (s, 3H), 1.30 (d, J = 5.7 Hz, 2H), 1.13 (s, 2H).</td>
<td>421</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>1-28</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>(^1)H NMR (400 MHz, DMSO) (\delta) 14.75 (s, 1H), 10.73 (s, 1H), 8.90 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.89 (s, 1H), 7.43 (s, 1H), 7.28 (d, J = 7.6 Hz, 1H), 4.40 (s, 1H), 2.62 (s, 3H), 1.24 (s, 2H), 1.06 (s, 2H).</td>
<td>466</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>1-29</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>(^1)H NMR (400 MHz, DMSO) (\delta) 14.69 (s, 1H), 11.96 (s, 1H), 8.81 (s, 1H), 8.01 (d, J = 9.6 Hz, 1H), 7.95 (d, J = 9.1 Hz, 1H), 7.87 (s, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 6.57 (dd, J = 9.5, 1.7 Hz, 1H), 4.32 – 4.10 (m, 1H), 3.38 (s, 3H), 1.18 (m, 4H).</td>
<td>421</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>1-30</td>
<td>Cl</td>
<td>Cyclopropyl</td>
<td>(^1)H NMR (400 MHz, DMSO) (\delta) 14.41 (s, 1H), 11.96 (s, 1H), 8.91 (s, 1H), 8.20 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 9.1 Hz, 1H), 7.80 (s, 1H), 7.68 (d, J = 8.6 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 6.62 (dd, J = 9.5, 1.7 Hz, 1H), 4.32 – 4.10 (m, 1H), 1.30 (m, 2H), 1.18 (m, 2H).</td>
<td>425</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>1-31</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.67 (s, 1H), 11.89 (s, 1H), 8.82 (s, 1H), 8.17 – 7.90 (m, 2H), 7.85 (d, J = 8.0 Hz, 1H), 7.48 (s, 1H), 7.35 (d, J = 7.9 Hz, 1H), 6.60 (d, J = 11.2 Hz, 1H), 4.28 – 4.14 (m, 1H), 3.41 (s, 4H), 1.18 (m, 4H).</td>
<td>421</td>
<td>90%</td>
</tr>
<tr>
<td>1-32</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.69 (s, 1H), 11.78 (s, 1H), 8.91 (s, 1H), 7.98 (d, J = 8.77 Hz, 1H), 7.72 (s, 1H), 7.54 (s, 1H), 7.50 – 7.44 (m, 1H), 6.48 (s, 1H), 2.63 (s, 3H), 2.44 (s, 3H), 1.28 – 1.21 (m, 2H), 1.12 – 1.02 (m, 2H).</td>
<td>419</td>
<td>96%</td>
</tr>
<tr>
<td>1-33</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.62 (s, 1H), 13.15 (s, 1H), 8.92 (s, 1H), 8.87 (s, 1H), 8.77 (d, J = 1.74 Hz, 1H), 8.38 (d, J = 1.97 Hz, 1H), 8.02 (d, J = 8.86 Hz, 1H), 4.42 (tt, J = 3.74, 7.15 Hz, 1H), 2.66 (s, 3H), 1.25 (q, J = 6.85 Hz, 2H), 1.08 (s, 2H).</td>
<td>431</td>
<td>96%</td>
</tr>
<tr>
<td>1-34</td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 9.11 (s, 1H), 8.92 (s, 1H), 8.31 (d, J = 8.86 Hz, 1H), 8.16 (d, J = 8.54 Hz, 1H), 8.03 (d, J = 8.91 Hz, 1H), 6.51 (s, 1H), 4.44 (tt, J = 3.64, 7.02 Hz, 2H), 2.69 (s, 3H), 2.51 (s, 3H), 1.24 (d, J = 6.83 Hz, 2H), 1.10 (s, 2H).</td>
<td>420</td>
<td>95%</td>
</tr>
<tr>
<td>1-35</td>
<td><img src="image5.png" alt="Chemical Structure" /></td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.75 – 14.55 (m, 1H), 9.83 – 9.67 (d, J = 3.2 Hz, 1H), 8.89 – 8.73 (s, 1H), 7.96 – 7.86 (d, J = 9.1 Hz, 1H), 7.58 – 7.47 (s, 1H), 7.42 – 7.34 (s, 1H), 4.30 – 4.14 (tt, J = 7.3, 4.5 Hz, 1H), 3.52 – 3.39 (s, 3H), 3.11 – 2.95 (t, J = 7.5 Hz, 2H), 2.62 – 2.56 (dd, J = 8.5, 6.3 Hz, 2H), 1.21 – 1.12 (m, 4H).</td>
<td>457</td>
<td>99%</td>
</tr>
<tr>
<td>1-36</td>
<td><img src="image6.png" alt="Chemical Structure" /></td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, CDCl₃) δ 14.52 – 14.39 (s, 1H), 8.87 – 8.82 (s, 1H), 8.01 – 7.92 (m, 1H), 7.75 – 7.69 (s, 1H), 7.39 – 7.34 (t, J = 1.7 Hz, 1H), 7.21 – 7.18 (s, 1H), 6.79 – 6.69 (dd, J = 17.3, 11.0 Hz, 1H), 5.70 – 5.62 (d, J = 17.3 Hz, 1H), 5.54 – 5.44 (d, J = 11.0 Hz, 1H), 4.09 – 3.99 (d, J = 3.7 Hz, 1H), 3.45 – 3.36 (s, 3H), 3.03 – 2.95 (dd, J = 8.5, 6.5 Hz, 2H), 2.68 – 2.59 (dd, J = 8.7, 6.5 Hz, 2H), 1.26 – 1.21 (dd, J = 5.2, 1.8 Hz, 2H), 1.11 – 1.03 (dt, J = 4.0, 1.9 Hz, 2H).</td>
<td>449</td>
<td>85%</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>R</td>
<td>Functional Group</td>
<td>Spectroscopy Details</td>
<td>Chemical Shifts</td>
<td>References</td>
</tr>
<tr>
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<tr>
<td>1-37</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>$^1\text{H NMR (400 MHz, DMSO)}$ $\delta$ 14.73 - 14.60 (s, 1H), 10.38 - 10.26 (s, 1H), 8.84 - 8.76 (s, 1H), 7.96 - 7.88 (d, $J = 9.1$ Hz, 1H), 7.36 - 7.28 (d, $J = 11.2$ Hz, 1H), 7.25 - 7.19 (s, 1H), 4.29 - 4.18 (ddd, $J = 11.3, 7.3, 4.4$ Hz, 1H), 3.47 - 3.43 (s, 3H), 3.07 - 2.99 (t, $J = 7.4$ Hz, 2H), 2.60 - 2.53 (dd, $J = 8.5, 6.5$ Hz, 2H), 1.21 - 1.08 (d, $J = 5.3$ Hz, 4H).</td>
<td>441</td>
<td>85%</td>
</tr>
<tr>
<td>1-38</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>$^1\text{H NMR (400 MHz, DMSO)}$ $\delta$ 14.70 (s, 1H), 9.62 (s, 1H), 8.79 (d, $J = 9.2$ Hz, 1H), 7.20 (d, $J = 8.5$ Hz, 2H), 4.39 - 4.16 (m, 1H), 3.42 (s, 3H), 3.03 - 2.88 (m, 2H), 2.54 (m, 5H), 1.16 (m, 4H).</td>
<td>436</td>
<td>99%</td>
</tr>
<tr>
<td>1-39</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>$^1\text{H NMR (400 MHz, DMSO)}$ $\delta$ 15.13 - 14.27 (m, 1H), 10.76 - 10.64 (s, 5H), 8.98 - 8.88 (s, 1H), 8.19 - 8.14 (d, $J = 2.2$ Hz, 1H), 8.00 - 7.94 (d, $J = 8.7$ Hz, 1H), 7.75 - 7.70 (d, $J = 2.1$ Hz, 1H), 4.49 - 4.32 (tt, $J = 7.3, 3.8$ Hz, 1H), 3.03 - 2.95 (m, 2H), 2.69 - 2.64 (s, 3H), 2.62 - 2.56 (t, $J = 7.5$ Hz, 2H), 1.28 - 1.22 (m, 2H), 1.09 - 1.03 (m, 2H).</td>
<td>408</td>
<td>90%</td>
</tr>
<tr>
<td>1-40</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1\text{H NMR (400 MHz, DMSO)}$ $\delta$ 14.60 (s, 1H), 12.01 (s, 1H), 8.92 (s, 1H), 8.53 (s, 1H), 8.08 - 7.98 (m, 2H), 7.72 (s, 1H), 6.85 (d, $J = 9.75$ Hz, 1H), 4.41 (s, 1H), 3.34 (s, 1H), 2.65 (s, 3H), 2.54 (s, 3H), 1.24 (d, $J = 6.54$ Hz, 2H), 1.09 (s, 2H).</td>
<td>406</td>
<td>96%</td>
</tr>
<tr>
<td>1-41</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1\text{H NMR (400 MHz, DMSO)}$ $\delta$ 14.85 - 14.51 (s, 1H), 9.00 - 8.91 (m, 2H), 8.60 - 8.53 (s, 1H), 8.18 - 8.09 (t, $J = 8.4$ Hz, 2H), 8.09 - 8.02 (m, 1H), 7.95 - 7.84 (s, 1H), 7.79 - 7.68 (s, 1H), 4.51 - 4.31 (s, 1H), 2.79 - 2.61 (s, 3H), 1.36 - 1.20 (d, $J = 6.9$ Hz, 2H), 1.16 - 1.04 (s, 2H).</td>
<td>389</td>
<td>100%</td>
</tr>
<tr>
<td>1-42</td>
<td><img src="image6.png" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1\text{H NMR (400 MHz, DMSO)}$ $\delta$ 15.01 - 14.88 (d, $J = 2.6$ Hz, 1H), 8.95 - 8.82 (d, $J = 2.5$ Hz, 1H), 8.05 - 7.94 (d, $J = 6.7$ Hz, 1H), 7.89 - 7.77 (d, $J = 9.4$ Hz, 1H), 7.62 - 7.40 (m, 3H), 6.33 - 6.21 (s, 1H), 5.59 - 5.49 (s, 2H), 4.48 - 4.35 (s, 1H), 2.86 - 2.76 (s, 3H), 1.30 - 1.15 (d, $J = 7.0$ Hz, 2H), 1.00 - 0.88 (s, 2H).</td>
<td>392</td>
<td>100%</td>
</tr>
<tr>
<td>1-43</td>
<td><img src="image7.png" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1\text{H NMR (400 MHz, MeOD)}$ $\delta$ 9.05 - 8.91 (s, 1H), 8.87 - 8.77 (s, 1H), 8.43 - 8.36 (s, 1H), 8.14 - 8.06 (d, $J = 7.3$ Hz, 1H), 8.02 - 7.88 (d, $J = 21.7$ Hz, 2H), 7.74 - 7.62 (d, $J = 8.7$ Hz, 1H), 7.59 - 7.51 (s, 1H), 4.35 - 4.15 (s, 1H), 2.73 - 2.53 (m, 3H), 1.05 - 0.93 (s, 2H), 0.85 - 0.71 (d, $J = 8.0$ Hz, 2H).</td>
<td>389</td>
<td>97%</td>
</tr>
<tr>
<td>1-44</td>
<td>![Structure Image]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.72 – 14.59 (s, 1H), 9.01 – 8.91 (s, 1H), 8.88 – 8.80 (s, 1H), 8.66 – 8.56 (d, J = 8.8 Hz, 1H), 8.25 – 8.16 (d, J = 8.0 Hz, 1H), 8.14 – 8.09 (s, 1H), 8.08 – 8.01 (d, J = 8.6 Hz, 1H), 7.95 – 7.89 (d, J = 8.7 Hz, 1H), 7.88 – 7.79 (d, J = 7.7 Hz, 1H), 4.51 – 4.35 (s, 1H), 2.75 – 2.67 (s, 3H), 1.30 – 1.19 (d, J = 6.8 Hz, 2H), 1.16 – 1.07 (s, 2H).</td>
<td>405</td>
<td>97.5%</td>
</tr>
<tr>
<td>1-45</td>
<td>![Structure Image]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.85 – 14.58 (s, 1H), 9.00 – 8.88 (s, 1H), 8.19 – 8.07 (d, J = 8.3 Hz, 1H), 8.07 – 7.94 (m, 4H), 7.68 – 7.58 (d, J = 6.0 Hz, 2H), 7.57 – 7.48 (d, J = 8.2 Hz, 1H), 4.49 – 4.33 (s, 1H), 2.72 – 2.59 (s, 3H), 1.33 – 1.19 (d, J = 7.4 Hz, 2H), 1.16 – 1.00 (s, 2H).</td>
<td>388</td>
<td>98%</td>
</tr>
<tr>
<td>1-46</td>
<td>![Structure Image]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 9.69 – 9.59 (s, 1H), 9.01 – 8.92 (d, J = 2.5 Hz, 1H), 8.69 – 8.58 (d, J = 2.4 Hz, 1H), 8.47 – 8.34 (d, J = 7.6 Hz, 1H), 8.14 – 8.04 (d, J = 8.1 Hz, 1H), 7.95 – 7.80 (t, J = 8.7 Hz, 2H), 7.57 – 7.46 (d, J = 7.9 Hz, 1H), 4.48 – 4.34 (s, 1H), 2.32 – 2.50 (s, 3H), 1.29 – 1.01 (m, 4H).</td>
<td>389</td>
<td>98%</td>
</tr>
<tr>
<td>1-47</td>
<td>![Structure Image]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.96 – 14.46 (s, 1H), 12.04 – 11.50 (s, 1H), 8.98 – 8.89 (s, 1H), 8.34 – 8.17 (d, J = 12.3 Hz, 1H), 8.17 – 8.01 (m, 2H), 7.97 – 7.90 (d, J = 8.1 Hz, 1H), 4.48 – 4.36 (dd, J = 7.3, 4.1 Hz, 1H), 2.66 – 2.56 (s, 3H), 1.31 – 1.17 (d, J = 7.1 Hz, 2H), 1.15 – 1.03 (d, 2H).</td>
<td>422</td>
<td>99%</td>
</tr>
<tr>
<td>1-48</td>
<td>![Structure Image]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 9.19 – 9.11 (s, 1H), 8.98 – 8.92 (s, 1H), 8.45 – 8.39 (s, 1H), 8.13 – 8.00 (dd, J = 16.7, 8.4 Hz, 2H), 7.80 – 7.69 (t, J = 7.7 Hz, 1H), 7.66 – 7.55 (t, J = 7.7 Hz, 1H), 7.38 – 7.29 (d, J = 8.3 Hz, 1H), 4.47 – 4.34 (s, 1H), 2.65 – 2.54 (s, 3H), 1.28 – 1.07 (m, 4H).</td>
<td>405</td>
<td>98%</td>
</tr>
<tr>
<td>1-49</td>
<td>![Structure Image]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.69 – 14.45 (s, 1H), 10.31 – 10.19 (s, 1H), 9.06 – 8.94 (d, J = 3.6 Hz, 2H), 8.73 – 8.62 (d, J = 8.2 Hz, 1H), 8.61 – 8.43 (m, 2H), 8.32 – 8.21 (t, J = 7.5 Hz, 1H), 8.21 – 8.11 (m, 2H), 7.83 – 7.71 (d, J = 8.3 Hz, 1H), 4.67 – 4.52 (s, 3H), 4.50 – 4.39 (d, J = 7.6 Hz, 1H), 2.52 – 2.50 (m, 3H), 1.32 – 1.03 (m, 4H).</td>
<td>404</td>
<td>100%</td>
</tr>
<tr>
<td>1-50</td>
<td>1-51</td>
<td>1-52</td>
<td>1-53</td>
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<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
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<tr>
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<td>Cyclopropyl</td>
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<td>Cyclopropyl</td>
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<tr>
<td><strong>^1^H NMR (400 MHz, DMSO)</strong> δ 14.72 – 14.45 (s, 1H), 9.88 – 9.78 (s, 1H), 9.58 – 9.48 (s, 1H), 9.02 – 8.92 (s, 1H), 8.70 – 8.60 (d, J = 9.0 Hz, 1H), 8.69 – 8.51 (d, J = 8.2 Hz, 1H), 8.46 – 8.36 (t, J = 7.9 Hz, 1H), 8.24 – 8.06 (t, J = 9.7 Hz, 2H), 4.78 – 4.67 (s, 2H), 4.53 – 4.40 (s, 1H), 2.82 – 2.71 (s, 3H), 1.37 – 1.18 (d, J = 6.4 Hz, 2H), 1.16 – 1.07 (m, 2H).</td>
<td><strong>^1^H NMR (400 MHz, DMSO)</strong> δ 9.10 – 9.01 (d, J = 4.0 Hz, 1H), 8.98 – 8.91 (d, J = 2.6 Hz, 1H), 8.30 – 8.19 (d, J = 8.4 Hz, 1H), 8.14 – 8.07 (s, 1H), 8.05 – 7.97 (t, J = 7.7 Hz, 1H), 7.96 – 7.89 (d, J = 8.4 Hz, 1H), 7.78 – 7.68 (d, J = 6.8 Hz, 1H), 7.65 – 7.57 (m, 1H), 4.45 – 4.33 (s, 1H), 2.48 – 2.40 (d, J = 2.8 Hz, 3H), 1.28 – 1.03 (m, 4H).</td>
<td><strong>^1^H NMR (400 MHz, DMSO)</strong> δ 14.78 – 14.66 (s, 1H), 9.06 – 8.97 (s, 1H), 8.96 – 8.88 (s, 1H), 8.54 – 8.46 (d, J = 8.1 Hz, 1H), 8.26 – 8.14 (d, J = 8.3 Hz, 1H), 8.14 – 8.06 (s, 1H), 8.06 – 7.98 (d, J = 8.6 Hz, 1H), 7.74 – 7.58 (d, J = 8.3 Hz, 1H), 4.51 – 4.29 (s, 1H), 2.73 – 2.60 (s, 3H), 1.29 – 1.18 (d, J = 7.0 Hz, 2H), 1.15 – 1.07 (s, 2H).</td>
<td><strong>^1^H NMR (400 MHz, DMSO)</strong> δ 8.96 – 8.88 (d, J = 2.4 Hz, 1H), 8.85 – 8.78 (s, 1H), 8.57 – 8.47 (d, J = 8.2 Hz, 1H), 8.25 – 8.13 (d, J = 8.3 Hz, 1H), 8.03 – 7.95 (d, J = 8.3 Hz, 1H), 7.86 – 7.77 (m, 2H), 7.69 – 7.54 (d, J = 8.7 Hz, 1H), 4.44 – 4.31 (s, 1H), 2.48 – 2.42 (s, 3H), 1.29 – 1.16 (d, J = 7.6 Hz, 2H), 1.15 – 1.02 (s, 2H).</td>
<td><strong>^1^H NMR (400 MHz, DMSO)</strong> δ 9.17 – 9.09 (s, 1H), 9.01 – 8.91 (d, J = 2.7 Hz, 1H), 8.26 – 8.17 (d, J = 8.5 Hz, 1H), 8.15 – 8.06 (d, J = 8.5 Hz, 1H), 7.94 – 7.84 (s, 1H), 2.48 – 2.42 (m, 2H), 7.72 – 7.59 (d, J = 9.2 Hz, 2H), 7.56 – 7.45 (d, J = 8.3 Hz, 1H), 4.45 – 4.35 (s, 1H), 2.52 – 2.45 (s, 3H), 1.29 – 1.03 (dd, J = 16.6, 7.5 Hz, 4H).</td>
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<td></td>
</tr>
<tr>
<td>1-55</td>
<td><img src="image" alt="Molecule" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 15.08 – 14.78 (s, 1H), 8.95 – 8.83 (s, 2H), 8.48 – 8.37 (d, $J = 6.0$ Hz, 1H), 8.33 – 8.19 (d, $J = 8.2$ Hz, 1H), 8.14 – 8.02 (d, $J = 8.5$ Hz, 1H), 7.94 – 7.76 (m, 2H), 7.68 – 7.59 (d, $J = 7.1$ Hz, 1H), 7.58 – 7.49 (t, $J = 7.2$ Hz, 1H), 4.47 – 4.34 (s, 1H), 2.73 – 2.56 (s, 3H), 1.31 – 0.99 (m, 4H).</td>
<td>405</td>
<td>95%</td>
</tr>
<tr>
<td>1-56</td>
<td><img src="image" alt="Molecule" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 9.00 – 8.91 (s, 1H), 8.85 – 8.75 (d, $J = 6.1$ Hz, 1H), 8.73 – 8.64 (d, $J = 8.6$ Hz, 1H), 8.13 – 8.05 (d, $J = 8.4$ Hz, 1H), 7.97 – 7.86 (d, $J = 8.1$ Hz, 1H), 7.80 – 7.71 (s, 1H), 7.65 – 7.58 (d, $J = 5.8$ Hz, 1H), 7.57 – 7.48 (d, $J = 8.4$ Hz, 1H), 4.46 – 4.35 (s, 1H), 2.57 – 2.52 (s, 3H), 1.28 – 1.04 (m, 4H).</td>
<td>405</td>
<td>96%</td>
</tr>
<tr>
<td>1-57</td>
<td><img src="image" alt="Molecule" /></td>
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<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.95 – 14.35 (m, 1H), 9.01 – 8.90 (t, $J = 2.0$ Hz, 1H), 8.80 – 8.63 (m, 2H), 8.13 – 8.06 (m, 1H), 8.04 – 7.95 (t, $J = 7.8$ Hz, 1H), 7.84 – 7.75 (d, $J = 6.5$ Hz, 1H), 7.52 – 7.41 (ddd, $J = 10.0$, 5.1, 2.5 Hz, 1H), 7.38 – 7.29 (d, $J = 8.4$ Hz, 1H), 4.46 – 4.32 (d, $J = 6.9$ Hz, 1H), 2.49 – 2.44 (s, 3H), 1.29 – 0.99 (m, 4H).</td>
<td>405</td>
<td>93.3%</td>
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<td>1-58</td>
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<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 8.98 – 8.89 (s, 1H), 8.73 – 8.64 (d, $J = 6.6$ Hz, 1H), 8.58 – 8.52 (s, 1H), 8.35 – 8.26 (d, $J = 8.2$ Hz, 1H), 8.12 – 7.99 (t, $J = 10.7$ Hz, 2H), 7.83 – 7.75 (d, $J = 8.3$ Hz, 1H), 7.65 – 7.53 (s, 1H), 4.46 – 4.36 (s, 1H), 2.65 – 2.59 (s, 3H), 1.29 – 1.19 (d, $J = 7.8$ Hz, 2H), 1.14 – 1.07 (s, 2H).</td>
<td>405</td>
<td>96.2%</td>
</tr>
<tr>
<td>1-59</td>
<td><img src="image" alt="Molecule" /></td>
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<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 8.96 – 8.87 (s, 1H), 8.75 – 8.64 (d, $J = 7.2$ Hz, 2H), 8.28 – 8.19 (s, 1H), 8.10 – 7.99 (d, $J = 8.5$ Hz, 2H), 7.90 – 7.80 (d, $J = 9.0$ Hz, 1H), 7.63 – 7.52 (s, 1H), 4.48 – 4.34 (s, 1H), 2.65 – 2.57 (s, 3H), 1.30 – 1.18 (d, $J = 7.1$ Hz, 2H), 1.14 – 1.02 (s, 2H).</td>
<td>405</td>
<td>99%</td>
</tr>
<tr>
<td>1-60</td>
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<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 9.77 – 9.61 (s, 1H), 9.00 – 8.90 (d, $J = 3.1$ Hz, 1H), 8.75 – 8.62 (d, $J = 5.8$ Hz, 1H), 8.57 – 8.42 (d, $J = 8.2$ Hz, 1H), 8.31 – 8.21 (s, 1H), 8.22 – 8.13 (d, $J = 5.3$ Hz, 1H), 8.11 – 8.01 (d, $J = 8.7$ Hz, 1H), 7.94 – 7.81 (d, $J = 8.4$ Hz, 1H), 4.49 – 4.34 (s, 1H), 2.68 – 2.59 (s, 3H), 1.34 – 1.18 (d, $J = 7.6$ Hz, 2H), 1.15 – 1.00 (s, 2H).</td>
<td>389</td>
<td>93.6%</td>
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<tr>
<td>1-61</td>
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<td>Me</td>
<td>Cyclopropyl</td>
<td>¹H NMR (400 MHz, DMSO) δ 9.19 – 9.10 (s, 1H), 9.03 – 8.95 (s, 1H), 8.37 – 8.27 (d, J = 6.9 Hz, 1H), 8.18 – 8.05 (m, 4H), 7.81 – 7.73 (d, J = 8.4 Hz, 1H), 4.52 – 4.42 (t, J = 5.2 Hz, 1H), 2.74 – 2.65 (s, 3H), 1.36 – 1.27 (d, J = 7.1 Hz, 2H), 1.19 – 1.10 (s, 2H).</td>
<td>405</td>
<td>1005</td>
</tr>
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<td>1-62</td>
<td><img src="image" alt="Molecule" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>¹H NMR (400 MHz, DMSO) δ 14.82 – 14.70 (s, 1H), 11.54 – 11.41 (s, 1H), 9.03 – 8.93 (s, 1H), 8.44 – 8.33 (d, J = 8.2 Hz, 1H), 8.14 – 8.01 (d, J = 8.0 Hz, 1H), 7.84 – 7.75 (s, 1H), 7.58 – 7.51 (d, J = 7.6 Hz, 1H), 7.39 – 7.26 (s, 1H), 6.76 – 6.64 (d, J = 6.6 Hz, 1H), 4.52 – 4.40 (s, 1H), 2.70 – 2.61 (s, 3H), 1.37 – 1.22 (d, J = 6.8 Hz, 2H), 1.19 – 1.04 (s, 2H).</td>
<td>405</td>
<td>100%</td>
</tr>
<tr>
<td>1-63</td>
<td><img src="image" alt="Molecule" /></td>
<td>³H NMR (400 MHz, DMSO) δ 15.18 (s, 1H), 12.31 (s, 1H), 9.09 (s, 1H), 8.82 (d, J = 2.0 Hz, 1H), 8.45 (d, J = 1.7 Hz, 1H), 8.03 (t, J = 9.3 Hz, 2H), 7.76 (d, J = 8.4 Hz, 1H), 6.63 (d, J = 9.4 Hz, 1H), 5.00 (d, J = 6.7 Hz, 1H), 4.58 (d, J = 10.8 Hz, 1H), 4.45 (d, J = 10.0 Hz, 1H), 2.54 (s, 1H), 1.52 (d, J = 6.7 Hz, 3H).</td>
<td>390</td>
<td>98%</td>
<td></td>
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</tr>
<tr>
<td>1-64</td>
<td><img src="image" alt="Molecule" /></td>
<td>³H NMR (400 MHz, DMSO) δ 14.96 (s, 1H), 12.35 (s, 1H), 9.10 (s, 1H), 8.68 (s, 1H), 8.34 (s, 1H), 8.01 (d, J = 9.53 Hz, 1H), 7.79 (d, J = 9.70 Hz, 1H), 6.64 (d, J = 9.45 Hz, 1H), 5.01 (d, J = 6.68 Hz, 1H), 4.60 – 4.54 (m, 1H), 4.46 (d, J = 9.78 Hz, 1H), 1.49 (d, J = 6.71 Hz, 3H).</td>
<td>408</td>
<td>96%</td>
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<td></td>
</tr>
<tr>
<td>1-65</td>
<td><img src="image" alt="Molecule" /></td>
<td>³H NMR (400 MHz, DMSO) δ 9.27 (s, 1H), 8.95 (s, 1H), 8.87 (d, J = 15.4 Hz, 1H), 8.41 – 8.22 (m, 3H), 8.01 (t, J = 7.3 Hz, 1H), 7.85 (t, J = 7.3 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 4.45 (m, 1H), 2.77 (s, 3H), 1.31 (d, J = 6.2 Hz, 2H), 1.11 (s, 2H).</td>
<td>371</td>
<td>97%</td>
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Table 2

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<th>Compound No.</th>
<th>R^3</th>
<th>R^2</th>
<th>R^1</th>
<th>NMR</th>
<th>MS (MH^+)</th>
<th>HPLC</th>
</tr>
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<td>2-1</td>
<td><img src="image1.png" alt="Image" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>^1H NMR (400 MHz, DMSO) δ 8.28 (s, 1H), 7.98 (s, 1H), 7.80 (s, 1H), 7.33 (d, J = 8.90 Hz, 1H), 7.16 (d, J = 9.30 Hz, 1H), 3.66 (d, J = 3.58 Hz, 1H), 1.96 (s, 3H), 0.58 (d, J = 5.78 Hz, 2H), 0.37 (d, J = 1.61 Hz, 2H).</td>
<td>357</td>
<td>94%</td>
</tr>
<tr>
<td>2-2</td>
<td><img src="image2.png" alt="Image" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>^1H NMR (400 MHz, DMSO) δ 8.93 (s, 1H), 8.48 (d, J = 2.77 Hz, 1H), 8.13 (s, 1H), 8.01 (d, J = 8.72 Hz, 1H), 7.61 (s, 1H), 4.50 – 4.30 (m, 1H), 3.49 (d, J = 5.30 Hz, 5H), 3.36 – 3.29 (m, 5H), 2.66 (d, J = 15.95 Hz, 3H), 1.43 (s, 9H), 1.28 – 1.21 (m, 2H), 1.08 (s, 2H).</td>
<td>523</td>
<td>98%</td>
</tr>
<tr>
<td>2-3</td>
<td><img src="image3.png" alt="Image" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>^1H NMR (400 MHz, DMSO) δ 8.92 (s, 1H), 8.79 (d, J = 5.61 Hz, 2H), 8.01 (d, J = 9.93 Hz, 1H), 7.50 (d, J = 5.50 Hz, 2H), 4.40 (s, 1H), 2.61 (s, 3H), 1.24 (d, J = 5.97 Hz, 2H), 1.07 (s, 2H).</td>
<td>339</td>
<td>98%</td>
</tr>
<tr>
<td>2-4</td>
<td><img src="image4.png" alt="Image" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>^1H NMR (400 MHz, DMSO) δ 9.00 (s, 2H), 8.92 (s, 1H), 8.49 (d, J = 2.73 Hz, 1H), 8.12 (s, 1H), 7.98 (d, J = 11.57 Hz, 1H), 7.56 (d, J = 1H), 4.44 – 4.34 (m, 1H), 3.64 (s, 5H), 3.26 (s, 4H), 2.62 (s, 3H), 1.23 (d, J = 6.27 Hz, 2H), 1.07 (s, 2H).</td>
<td>423</td>
<td>95%</td>
</tr>
<tr>
<td>2-5</td>
<td><img src="image5.png" alt="Image" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>^1H NMR (400 MHz, DMSO) δ 8.93 (s, 1H), 8.71 (d, J = 28.47 Hz, 1H), 8.04 (d, J = 8.68 Hz, 2H), 7.61 (d, J = 45.28 Hz, 1H), 4.44 – 4.38 (m, 1H), 2.55 (s, 2H), 2.34 (d, J = 9.33 Hz, 3H), 1.23 (s, 2H), 1.06 (dd, J = 4.45, 8.57 Hz, 2H).</td>
<td>353</td>
<td>95%</td>
</tr>
<tr>
<td>2-6</td>
<td><img src="image6.png" alt="Image" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>^1H NMR (400 MHz, DMSO) δ 14.55 (s, 1H), 8.92 (s, 1H), 8.83 (d, J = 8.69 Hz, 1H), 8.65 (dt, J = 8.70, 17.42 Hz, 1H), 8.05 (d, J = 8.87 Hz, 1H), 7.73 – 7.52 (m, 1H), 4.41 (tt, J = 3.77, 7.16 Hz, 1H), 2.64 (s, 3H), 1.31 – 1.16 (m, 2H), 1.10 – 0.97 (m, 2H).</td>
<td>357</td>
<td>98%</td>
</tr>
<tr>
<td>No.</td>
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<td>R</td>
<td>Functional Group</td>
<td>NMR Data</td>
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<td>98%</td>
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<td><img src="image1.png" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 8.93 (s, 1H), 8.85 – 8.61 (m, 2H), 8.03 (d, J = 6.60 Hz, 1H), 7.96 (s, 2H), 7.69 (dd, J = 6.19, 7.64 Hz, 1H), 4.41 (ddd, J = 3.87, 7.26, 10.97 Hz, 2H), 2.75 – 2.72 (m, 5H), 1.33 – 1.20 (m, 3H), 1.13 – 1.03 (m, 2H).</td>
<td>339</td>
<td>98%</td>
</tr>
<tr>
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<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, MeOD) δ 8.79 (s, 1H), 7.92 – 7.71 (m, 2H), 7.55 (t, J = 17.62 Hz, 1H), 6.84 (t, J = 36.31 Hz, 1H), 4.16 – 4.04 (m, 1H), 3.02 (s, 5H), 1.09 – 1.01 (m, 2H), 0.81 (q, J = 7.23 Hz, 2H).</td>
<td>355</td>
<td>98%</td>
</tr>
<tr>
<td>2-9</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, MeOD) δ 8.06 (t, J = 38.62 Hz, 2H), 7.68 (dd, J = 8.35, 33.76 Hz, 2H), 7.47 (d, J = 8.87 Hz, 1H), 7.13 – 6.77 (m, 2H), 4.33 (s, 1H), 3.97 (d, J = 7.85 Hz, 3H), 2.20 – 1.90 (m, 2H), 1.35 – 1.22 (m, 1H), 1.05 (s, 1H).</td>
<td>369</td>
<td>98%</td>
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<tr>
<td>2-10</td>
<td><img src="image4.png" alt="Structure" /></td>
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<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, MeOD) δ 9.06 (s, 1H), 8.33 (s, 1H), 8.01 (d, J = 9.18 Hz, 1H), 7.67 (t, J = 24.14 Hz, 2H), 7.17 (s, 1H), 4.37 (s, 1H), 3.94 (s, 3H), 2.66 (s, 3H), 1.32 (d, J = 6.60 Hz, 2H), 1.07 (s, 2H).</td>
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<td>98%</td>
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<tr>
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<td><img src="image5.png" alt="Structure" /></td>
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<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, MeOD) δ 9.05 (s, 1H), 8.29 (s, 2H), 8.09 (d, J = 7.83 Hz, 1H), 7.94 (d, J = 23.80 Hz, 2H), 7.39 – 7.20 (m, 2H), 7.09 (s, 1H), 4.36 (s, 1H), 2.77 (s, 3H), 1.30 (s, 2H), 1.09 (s, 2H).</td>
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<td>Cyclopropyl</td>
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<tr>
<td>2-13</td>
<td><img src="image7.png" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
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<tr>
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<td>Cyclopropyl</td>
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<td>Spectral Data</td>
<td>Retention Time (min)</td>
<td>Purity (%)</td>
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<td>Cyclopropyl</td>
<td>(^{1}H) NMR (400 MHz, DMSO) (\delta) 8.91 (s, 1H), 8.74 (s, 1H), 8.54 (t, (J = 24.30) Hz, 2H), 7.99 (d, (J = 8.68) Hz, 1H), 4.41 (s, 1H), 3.10 (d, (J = 17.91) Hz, 3H), 2.70 (s, 3H), 1.25 (d, (J = 5.66) Hz, 2H), 1.07 (s, 2H).</td>
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<td>99%</td>
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<td>Cyclopropyl</td>
<td>(^{1}H) NMR (400 MHz, DMSO) (\delta) 14.63 (s, 1H), 9.79 (s, 2H), 8.92 (s, 1H), 8.61 (s, 1H), 8.01 (d, (J = 13.11) Hz, 2H), 4.67 (d, (J = 32.94) Hz, 4H), 4.40 (s, 1H), 2.62 (s, 3H), 1.23 (s, 3H), 1.07 (s, 2H).</td>
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<td>97%</td>
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<td>Me</td>
<td>Cyclopropyl</td>
<td>(^{1}H) NMR (400 MHz, DMSO) (\delta) 14.65 (s, 1H), 8.89 (s, 1H), 8.27 (s, 1H), 8.07 (t, (J = 6.62) Hz, 1H), 7.94 (d, (J = 8.87) Hz, 1H), 7.28 (s, 2H), 4.40 (tt, (J = 3.75, 7.16) Hz, 1H), 3.31 (s, 1H), 2.67 (s, 3H), 1.31 - 1.19 (m, 2H), 1.10 - 1.00 (m, 2H).</td>
<td>379</td>
<td>99%</td>
</tr>
<tr>
<td>2-19</td>
<td><img src="image" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>(^{1}H) NMR (400 MHz, DMSO) (\delta) 9.28 (s, 1H), 8.93 (s, 1H), 8.70 (s, 1H), 8.36 (s, 1H), 8.03 (d, (J = 8.65) Hz, 1H), 4.41 (s, 2H), 2.65 (s, 3H), 2.44 (s, 3H), 1.25 (d, (J = 6.79) Hz, 2H), 1.10 (s, 2H).</td>
<td>420</td>
<td>97%</td>
</tr>
<tr>
<td>2-20</td>
<td><img src="image" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>(^{1}H) NMR (400 MHz, DMSO) (\delta) 8.91 (s, 1H), 8.19 (d, (J = 11.25) Hz, 3H), 7.99 (d, (J = 8.83) Hz, 1H), 7.62 (s, 1H), 4.41 (s, 2H), 2.69 (s, 3H), 1.25 (d, (J = 5.80) Hz, 2H), 1.05 (s, 2H).</td>
<td>397</td>
<td>99%</td>
</tr>
<tr>
<td>2-21</td>
<td><img src="image" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>(^{1}H) NMR (400 MHz, DMSO) (\delta) 14.72 (s, 1H), 8.89 (s, 1H), 8.11 - 7.87 (m, 2H), 7.74 (s, 1H), 6.71 (s, 2H), 4.39 (s, 1H), 2.63 (d, (J = 29.40) Hz, 3H), 1.20 (t, (J = 25.86) Hz, 2H), 0.99 (d, (J = 41.43) Hz, 2H).</td>
<td>388</td>
<td>98%</td>
</tr>
<tr>
<td>2-22</td>
<td><img src="image" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>(^{1}H) NMR (400 MHz, DMSO) (\delta) 14.71 (s, 1H), 8.90 (s, 1H), 8.26 (s, 1H), 7.95 (d, (J = 8.81) Hz, 1H), 7.86 (s, 1H), 6.89 (s, 2H), 4.39 (s, 1H), 2.66 (s, 3H), 1.24 (d, (J = 5.61) Hz, 2H), 1.06 (s, 2H).</td>
<td>422</td>
<td>98%</td>
</tr>
<tr>
<td>2-23</td>
<td><img src="image" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>(^{1}H) NMR (400 MHz, DMSO) (\delta) 14.71 (s, 1H), 8.98 (s, 1H), 8.13 - 8.02 (m, 2H), 7.92 (d, (J = 14.79) Hz, 3H), 4.47 (s, 1H), 2.71 (d, (J = 23.60) Hz, 3H), 2.31 (s, 3H), 1.29 (d, (J = 5.54) Hz, 2H), 1.15 (d, (J = 22.69) Hz, 2H).</td>
<td>368</td>
<td>99%</td>
</tr>
<tr>
<td>2-24</td>
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<td>OMe</td>
<td>Cyclopropyl</td>
<td>(^{1}H) NMR (400 MHz, DMSO) (\delta) 14.67 (s, 1H), 8.79 (s, 1H), 8.11 (s, 1H), 7.90 (s, 1H), 7.82 (s, 1H), 6.73 (s, 2H), 4.22 (s, 1H), 3.46 (s, 3H), 3.31 (s, 2H), 1.16 (s, 4H).</td>
<td>404</td>
<td>98%</td>
</tr>
<tr>
<td>2-25</td>
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<td>OMe</td>
<td>Cyclopropyl</td>
<td>(^{1}H) NMR (400 MHz, DMSO) (\delta) 14.66 (s, 1H), 8.80 (s, 1H), 8.39 (s, 1H), 8.13 - 7.81 (m, 2H), 6.91 (s, 2H), 4.23 (s, 1H), 3.31 (s, 3H), 1.17 (d, (J = 6.99) Hz, 3H).</td>
<td>438</td>
<td>99%</td>
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<tr>
<td>2-26</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.74 (d, $J = 61.68$ Hz, 1H), 8.76 (d, $J = 28.90$ Hz, 1H), 8.39 (s, 1H), 7.97 (s, 1H), 7.92 (d, $J = 9.13$ Hz, 1H), 4.23 (s, 1H), 3.46 (s, 3H), 1.17 (d, $J = 7.13$ Hz, 4H).</td>
<td>395</td>
<td>98%</td>
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<tr>
<td>2-27</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 8.89 (s, 1H), 7.95 - 7.93 (m, 2H), 7.83 (s, 1H), 7.60 - 6.57 (d, 1H), 4.39 (s, 1H), 2.63 (d, $J = 29.40$ Hz, 3H), 1.20 (t, $J = 25.86$ Hz, 2H), 0.99 (d, $J = 41.43$ Hz, 2H).</td>
<td>372</td>
<td>98%</td>
</tr>
<tr>
<td>2-28</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 9.95 (s, 1H), 8.94 - 8.66 (m, 1H), 8.49 - 8.39 (m, 1H), 8.26 (d, $J = 1.30$ Hz, 1H), 7.91 (dd, $J = 19.79$, 31.75 Hz, 2H), 4.27 - 4.17 (m, 1H), 3.50 - 3.42 (m, 3H), 1.17 (dt, $J = 7.59$, 17.65 Hz, 3H).</td>
<td>398</td>
<td>98%</td>
</tr>
<tr>
<td>2-29</td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 9.95 (s, 1H), 8.92 (d, $J = 13.25$ Hz, 1H), 8.32 (d, $J = 1.05$ Hz, 1H), 8.17 (d, $J = 1.69$ Hz, 1H), 8.00 (t, $J = 18.18$ Hz, 1H), 7.83 (d, $J = 33.09$ Hz, 1H), 4.40 (dt, $J = 3.59$, 10.71 Hz, 1H), 2.68 (d, $J = 12.78$ Hz, 3H), 1.25 (q, $J = 6.89$ Hz, 2H), 1.14 - 0.93 (m, 2H).</td>
<td>382</td>
<td>98%</td>
</tr>
<tr>
<td>2-30</td>
<td><img src="image5.png" alt="Chemical Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.64 (s, 2H), 8.90 (s, 1H), 7.97 (d, $J = 8.81$ Hz, 1H), 7.64 (d, $J = 1.21$ Hz, 1H), 7.34 (s, 1H), 4.40 (td, $J = 3.75$, 7.19 Hz, 1H), 3.90 (s, 3H), 2.78 - 2.61 (m, 3H), 1.23 (q, $J = 7.19$ Hz, 2H), 1.16 - 0.97 (m, 2H).</td>
<td>384</td>
<td>95%</td>
</tr>
<tr>
<td>2-31</td>
<td><img src="image6.png" alt="Chemical Structure" /></td>
<td>Me</td>
<td></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.64 (s, 2H), 8.90 (s, 1H), 7.97 (d, $J = 8.81$ Hz, 1H), 7.64 (d, $J = 1.21$ Hz, 1H), 7.34 (s, 1H), 4.40 (td, $J = 3.75$, 7.19 Hz, 1H), 3.90 (s, 3H), 2.78 - 2.61 (m, 3H), 1.23 (q, $J = 7.19$ Hz, 2H), 1.16 - 0.97 (m, 2H).</td>
<td>406</td>
<td>99%</td>
</tr>
<tr>
<td>2-32</td>
<td><img src="image7.png" alt="Chemical Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.62 (s, 1H), 8.90 (s, 1H), 7.99 (d, $J = 1.60$ Hz, 1H), 7.95 (t, $J = 10.20$ Hz, 1H), 7.70 - 7.53 (m, 1H), 4.39 (td, $J = 3.61$, 7.03 Hz, 1H), 2.62 (d, $J = 19.25$ Hz, 3H), 1.84 (dd, $J = 5.42$, 8.33, 13.56 Hz, 1H), 1.21 (t, $J = 6.56$ Hz, 1H), 1.05 (d, $J = 8.64$ Hz, 1H), 1.03 - 0.96 (m, 2H), 0.78 - 0.65 (m, 2H).</td>
<td>394</td>
<td>98%</td>
</tr>
<tr>
<td>2-33</td>
<td><img src="image8.png" alt="Chemical Structure" /></td>
<td>Me</td>
<td></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 8.88 (d, $J = 3.01$ Hz, 1H), 8.18 (s, 1H), 8.13 (s, 1H), 8.09 (s, 1H), 7.99 (d, $J = 8.77$ Hz, 1H), 7.54 (s, 1H), 5.29 - 5.01 (m, 1H), 4.50 - 4.31 (m, 1H), 2.71 - 2.57 (m, 2H), 1.76 (ddd, $J = 9.04$, 15.14, 17.62 Hz, 1H), 1.53 (d, $J = 26.94$ Hz, 1H).</td>
<td>415</td>
<td>98%</td>
</tr>
<tr>
<td>2-34</td>
<td>Cl</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 8.92 (s, 1H), 8.11 (d, $J = 8.56$ Hz, 1H), 8.02 (d, $J = 0.96$ Hz, 1H), 7.81 (d, $J = 1.67$ Hz, 1H), 4.44 - 4.39 (m, 2H), 1.32 - 1.17 (m, 2H), 1.17 - 1.04 (m, 2H).</td>
<td>408</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>2-35</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 8.80 (s, 1H), 7.99 (s, 1H), 7.92 (d, $J = 9.3$ Hz, 1H), 7.69 (d, $J = 12.0$ Hz, 1H), 4.29 - 4.14 (m, 1H), 3.47 (s, 3H), 1.24 - 1.04 (m, 4H).</td>
<td>387</td>
<td>99%</td>
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<tr>
<td>2-36</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.67 (s, 1H), 8.92 (s, 1H), 8.37 (s, 1H), 8.30 (d, $J = 2.3$ Hz, 1H), 8.11 - 7.88 (m, 3H), 7.51 (s, 1H), 4.55 - 4.30 (m, 3H), 3.20 (m, 2H), 2.68 (s, 3H), 1.25 (d, $J = 6.4$ Hz, 2H), 1.08 (d, $J = 7.0$ Hz, 2H).</td>
<td>441</td>
<td>98%</td>
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</tr>
<tr>
<td>2-37</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.52 (s, 1H), 8.82 (d, $J = 1.51$ Hz, 1H), 8.38 (s, 1H), 8.11 (s, 1H), 7.94 (d, $J = 9.20$ Hz, 1H), 7.36 (s, 2H), 5.10 (ddd, $J = 5.42, 8.45, 56.07$ Hz, 1H), 4.24 - 4.12 (m, 1H), 1.86 - 1.55 (m, 2H).</td>
<td>413</td>
<td>98%</td>
<td></td>
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<tr>
<td>2-38</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.55 (s, 1H), 8.82 (d, $J = 1.46$ Hz, 1H), 8.15 (d, $J = 36.97$ Hz, 1H), 7.92 (d, $J = 9.24$ Hz, 1H), 7.80 (s, 1H), 6.75 (s, 2H), 5.10 (ddd, $J = 5.43, 8.45, 64.08$ Hz, 1H), 4.29 - 4.12 (m, 1H), 1.93 - 1.53 (m, 2H).</td>
<td>422</td>
<td>98%</td>
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<td>2-39</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.39 (s, 1H), 8.80 (s, 1H), 8.16 - 8.08 (m, 2H), 7.98 - 7.66 (m, 2H), 7.69 - 7.59 (m, 1H), 7.37 (dd, $J = 5.20, 11.82$ Hz, 1H), 7.26 (s, 2H), 1.67 (s, 3H).</td>
<td>451</td>
<td>99%</td>
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</tr>
<tr>
<td>2-40</td>
<td>Ph</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 14.60 - 14.29 (s, 1H), 8.96 - 8.89 (s, 1H), 8.05 - 7.96 (m, 2H), 7.48 - 7.40 (m, 4H), 7.40 - 7.33 (dt, $J = 8.5, 2.8$ Hz, 1H), 7.33 - 7.29 (s, 1H), 4.88 - 4.75 (s, 2H), 4.17 - 3.98 (s, 1H), 2.73 - 2.62 (s, 3H), 1.28 - 1.20 (m, 2H), 1.02 - 0.93 (s, 2H).</td>
<td>430</td>
<td>99%</td>
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<tr>
<td>2-41</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.83 - 14.68 (s, 1H), 8.99 - 8.81 (s, 1H), 7.96 - 7.89 (d, $J = 8.9$ Hz, 1H), 7.88 - 7.81 (s, 1H), 7.36 - 7.20 (s, 1H), 6.19 - 6.08 (s, 2H), 4.47 - 4.31 (s, 1H), 2.75 - 2.60 (s, 3H), 1.36 - 1.10 (m, 6H), 1.10 - 0.94 (t, $J = 3.1$ Hz, 2H).</td>
<td>382</td>
<td>93%</td>
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<tr>
<td>No.</td>
<td>Structure</td>
<td>Substituent</td>
<td>Compound</td>
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<tr>
<td>2-42</td>
<td><img src="image1" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.83 – 14.67 (s, 3H), 8.97 – 8.85 (s, 3H), 8.00 – 7.85 (m, 6H), 7.72 – 7.60 (t, J = 1.7 Hz, 3H), 6.97 – 6.81 (dd, J = 17.3, 11.0 Hz, 3H), 6.45 – 6.27 (s, 6H), 5.85 – 5.70 (m, 4H), 5.44 – 5.26 (dd, J = 11.0, 1.2 Hz, 3H), 4.47 – 4.33 (s, 1H), 2.76 – 2.60 (s, 9H), 1.30 – 1.18 (m, 6H), 1.12 – 0.98 (m, 5H), 1.32 – 1.20 (m, 7H).</td>
<td>380</td>
<td>99%</td>
</tr>
<tr>
<td>2-50</td>
<td>[\text{H}_2\text{N}]</td>
<td>Cl</td>
<td>Cyclopropyl</td>
<td>[^1\text{H} \text{NMR (400 MHz, DMSO) } \delta 8.92 (s, 1H), 8.35 (s, 2H), 8.13 (d, J = 8.6 Hz, 1H), 7.15 (s, 2H), 4.41 (m, 3.8 Hz, 1H), 1.37 - 1.17 (m, 2H), 1.18 - 1.02 (m, 2H).]</td>
<td>375</td>
<td>99%</td>
</tr>
<tr>
<td>2-51</td>
<td>[\text{H}_2\text{N}]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>[^1\text{H} \text{NMR (400 MHz, DMSO) } \delta 8.87 (d, J = 3.2 Hz, 1H), 8.35 (d, J = 1.0 Hz, 2H), 7.97 (d, J = 8.9 Hz, 1H), 7.05 (s, 2H), 5.33 - 4.97 (m, 2H), 4.37 (m, 1H), 2.65 (s, 3H), 1.89 - 1.41 (m, 2H).]</td>
<td>373</td>
<td>99%</td>
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<tr>
<td>2-52</td>
<td>[\text{H}_2\text{N}]</td>
<td>MeO</td>
<td>Cyclopropyl</td>
<td>[^1\text{H} \text{NMR (400 MHz, DMSO) } \delta 14.54 (s, 1H), 8.82 (d, J = 1.2 Hz, 1H), 8.44 (s, 2H), 7.93 (d, J = 9.2 Hz, 1H), 7.10 (s, 2H), 5.09 (m, 1H), 4.37 - 3.96 (m, 1H), 3.50 (s, 3H), 1.98 - 1.52 (m, 2H).]</td>
<td>389</td>
<td>98%</td>
</tr>
<tr>
<td>2-53</td>
<td>[\text{HO}_{2}\text{C}]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>[^1\text{H} \text{NMR (400 MHz, DMSO) } \delta 14.65 (s, 1H), 8.91 (d, J = 4.9 Hz, 1H), 8.76 (s, 2H), 8.15 - 7.85 (m, 1H), 4.63 - 4.29 (m, 1H), 2.50 (s, 3H), 1.29 - 1.15 (m, 2H), 1.06 (d, J = 7.0 Hz, 2H).]</td>
<td>384</td>
<td>99%</td>
</tr>
<tr>
<td>2-54</td>
<td>[\text{H}_2\text{N}]</td>
<td>MeO</td>
<td>Cyclopropyl</td>
<td>[^1\text{H} \text{NMR (400 MHz, DMSO) } \delta 8.86 (s, 1H), 8.52 (s, 2H), 8.00 (d, J = 9.2 Hz, 1H), 7.18 (s, 2H), 4.29 (m, 1H), 3.55 (s, 3H), 1.27 - 1.11 (m, 4H).]</td>
<td>371</td>
<td>99%</td>
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<tr>
<td>2-55</td>
<td>[\text{Cl}]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>[^1\text{H} \text{NMR (400 MHz, DMSO) } \delta 14.67 (s, 1H), 8.79 (s, 1H), 8.19 (s, 1H), 7.90 (d, J = 9.3 Hz, 1H), 7.81 (s, 1H), 6.91 (t, J = 5.6 Hz, 1H), 4.29 - 4.11 (m, 1H), 3.53 - 3.41 (m, 5H), 1.26 - 1.06 (m, 7H).]</td>
<td>432</td>
<td>98%</td>
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<tr>
<td>2-56</td>
<td>[\text{H}_2\text{N}]</td>
<td>Cyclopropyl</td>
<td>[^1\text{H} \text{NMR (400 MHz, DMSO) } \delta 9.06 (s, 1H), 8.38 (s, 1H), 8.13 (d, J = 1.75 Hz, 1H), 7.72 (d, J = 9.80 Hz, 1H), 7.29 (s, 2H), 5.06 - 4.90 (m, 1H), 4.58 (d, J = 10.62 Hz, 1H), 4.44 (d, J = 9.71 Hz, 1H), 1.48 (d, J = 6.75 Hz, 3H).]</td>
<td>381</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>2-57</td>
<td>[\text{H}_2\text{N}]</td>
<td>Cyclopropyl</td>
<td>[^1\text{H} \text{NMR (400 MHz, DMSO) } \delta 14.95 (s, 1H), 8.91 (s, 1H), 8.37 - 8.33 (d, J = 2.5 Hz, 1H), 8.24 - 8.19 (d, J = 8.3 Hz, 1H), 8.14 - 8.10 (d, J = 2.5 Hz, 1H), 7.58 - 7.51 (d, J = 8.3 Hz, 1H), 7.22 (s, 2H), 4.42 - 4.36 (tt, J = 7.1, 3.7 Hz, 1H), 2.71 (s, 3H), 1.30 - 1.25 (m, 2H), 1.05 - 0.94 (m, 2H).]</td>
<td>361</td>
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<td></td>
</tr>
<tr>
<td>2-58</td>
<td>![Chemical Structure 1]</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.95 (s, 1H), 8.89 (s, 1H), 8.32 (d, $J = 3.5$ Hz, 1H), 8.21 (d, $J = 8.2$ Hz, 1H), 8.06 (s, 1H), 7.79 (s, 1H), 7.53 (d, $J = 8.2$ Hz, 1H), 6.61 (s, 2H), 4.39 (s, 1H), 2.72 (s, 3H), 1.27 (d, $J = 6.1$ Hz, 2H), 1.03 (s, 2H)</td>
<td>370</td>
<td>99%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-59</td>
<td>![Chemical Structure 2]</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 15.00 (s, 1H), 9.06 (s, 1H), 8.17 (s, 1H), 7.80 (s, 1H), 7.72 (d, $J = 9.8$ Hz, 1H), 6.86 (t, $J = 5.7$ Hz, 1H), 4.98 (d, $J = 6.7$ Hz, 1H), 4.57 (d, $J = 10.2$ Hz, 1H), 4.48 - 4.32 (m, 1H), 3.55 - 3.37 (m, 2H), 1.48 (d, $J = 6.8$ Hz, 2H), 1.17 (t, $J = 7.1$ Hz, 2H)</td>
<td>418</td>
<td>98%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-60</td>
<td>![Chemical Structure 3]</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.55 (s, 1H), 8.82 (d, $J = 1.6$ Hz, 1H), 8.18 (s, 1H), 7.92 (d, $J = 9.3$ Hz, 1H), 7.80 (s, 1H), 6.92 (t, $J = 5.7$ Hz, 1H), 6.10 (ddd, $J = 64.1, 8.4, 5.4$ Hz, 1H), 4.32 - 4.06 (m, 1H), 3.58 - 3.37 (m, 5H), 1.93 - 1.51 (m, 2H), 1.19 (t, $J = 7.1$ Hz, 3H)</td>
<td>450</td>
<td>98%</td>
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</table>
Table 3

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<th>Compound No.</th>
<th>( R^3 = )</th>
<th>( R^2 = )</th>
<th>( R^1 = )</th>
<th>NMR</th>
<th>MS (MH(^+))</th>
<th>HPLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-1</td>
<td>[\text{Structure}1]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>(^1^H) NMR (400 MHz, DMSO) ( \delta ) 14.59 (s, 1H), 9.08 (s, 1H), 8.94 (s, 1H), 8.33 (d, ( J = 1.3 \text{ Hz} ), 1H), 8.16 (d, ( J = 1.7 \text{ Hz} ), 1H), 8.06 (t, ( J = 8.5 \text{ Hz} ), 2H), 7.85 (d, ( J = 9.4 \text{ Hz} ), 1H), 4.49 – 4.38 (m, 1H), 2.70 (s, 3H), 1.25 (d, ( J = 6.6 \text{ Hz} ), 2H), 1.09 (s, 2H).</td>
<td>378 98%</td>
<td></td>
</tr>
<tr>
<td>3-2</td>
<td>[\text{Structure}2]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>(^1^H) NMR (400 MHz, DMSO) ( \delta ) 14.63 (s, 1H), 9.38 (s, 1H), 8.91 (d, ( J = 25.3 \text{ Hz} ), 1H), 8.79 (s, 1H), 8.13 (s, 1H), 8.06 (d, ( J = 8.8 \text{ Hz} ), 1H), 8.01 (s, 1H), 4.44 (s, 1H), 2.75 (s, 3H), 1.25 (s, 2H), 1.09 (s, 2H).</td>
<td>379 95%</td>
<td></td>
</tr>
<tr>
<td>3-3</td>
<td>[\text{Structure}3]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>(^1^H) NMR (400 MHz, DMSO) ( \delta ) 14.70 (s, 1H), 9.41 (s, 1H), 9.00 (s, 1H), 8.80 (s, 1H), 8.36 (s, 1H), 8.17 (s, 1H), 8.07 (s, 2H), 7.86 (s, 1H), 7.61 (s, 1H), 4.49 (s, 1H), 2.79 (s, 3H), 1.31 (s, 3H), 1.17 (s, 2H).</td>
<td>456 98%</td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td>[\text{Structure}4]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>(^1^H) NMR (400 MHz, DMSO) ( \delta ) 14.57 (d, ( J = 5.1 \text{ Hz} ), 1H), 9.05 (d, ( J = 6.5 \text{ Hz} ), 1H), 8.94 (s, 1H), 8.44 (s, 1H), 8.23 (s, 1H), 8.11 (s, 1H), 8.05 (d, ( J = 8.8 \text{ Hz} ), 1H), 7.54 (d, ( J = 6.4 \text{ Hz} ), 1H), 4.43 (s, 1H), 2.68 (s, 3H), 1.24 (d, ( J = 5.0 \text{ Hz} ), 2H), 1.11 (s, 2H).</td>
<td>378 97%</td>
<td></td>
</tr>
<tr>
<td>3-5</td>
<td>[\text{Structure}5]</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>(^1^H) NMR (400 MHz, DMSO) ( \delta ) 14.64 (s, 1H), 9.13 (d, ( J = 6.3 \text{ Hz} ), 1H), 8.90 (s, 1H), 8.53 (s, 1H), 8.31 (d, ( J = 11.7 \text{ Hz} ), 2H), 8.09 (d, ( J = 9.1 \text{ Hz} ), 1H), 7.72 (d, ( J = 5.8 \text{ Hz} ), 1H), 4.30 (s, 1H), 3.57 (s, 3H), 1.25 (s, 4H).</td>
<td>394 95%</td>
<td></td>
</tr>
<tr>
<td>3-6</td>
<td>[\text{Structure}6]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>(^1^H) NMR (400 MHz, DMSO) ( \delta ) 8.30 (s, 1H), 8.93 (s, 1H), 8.64 (s, 1H), 8.04 (t, ( J = 9.2 \text{ Hz} ), 2H), 7.75 (d, ( J = 9.2 \text{ Hz} ), 1H), 4.42 (s, 1H), 2.69 (s, 3H), 1.24 (s, 2H), 1.09 (s, 2H).</td>
<td>379 97%</td>
<td></td>
</tr>
<tr>
<td>3-7</td>
<td>![Chemical Structure]</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.61 (s, 1H), 9.33 (s, 1H), 8.83 (s, 1H), 8.64 (s, 1H), 8.06 (d, J = 9.2 Hz, 1H), 8.01 (d, J = 9.1 Hz, 1H), 7.86 (d, J = 9.3 Hz, 1H), 4.24 (s, 1H), 3.48 (s, 3H), 1.76 (d, J = 5.2 Hz, 4H).</td>
<td>395</td>
<td>98%</td>
</tr>
<tr>
<td>3-8</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.60 (s, 1H), 9.11 (s, 1H), 8.93 (s, 1H), 8.22 (d, J = 1.2 Hz, 1H), 8.17 (s, 1H), 8.03 (d, J = 8.9 Hz, 1H), 7.84 (d, J = 1.1 Hz, 1H), 4.43 (tt, J = 7.1, 3.7 Hz, 1H), 2.70 (s, 3H), 1.26 (d, J = 6.8 Hz, 2H), 1.09 (s, 2H).</td>
<td>379</td>
<td>98%</td>
</tr>
<tr>
<td>3-9</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.60 (s, 1H), 9.07 (s, 1H), 8.93 (s, 1H), 8.22 (d, J = 8.9 Hz, 1H), 7.81 (s, 1H), 7.80 (s, 1H), 4.49 - 4.37 (m, 1H), 2.70 (d, J = 21.5 Hz, 3H), 1.27 (t, J = 9.8 Hz, 2H), 1.14 - 1.05 (m, 2H).</td>
<td>446</td>
<td>97%</td>
</tr>
<tr>
<td>3-10</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.62 (s, 1H), 8.94 (s, 2H), 8.35 (s, 1H), 8.23 (s, 1H), 8.05 (d, J = 8.7 Hz, 1H), 7.75 (s, 1H), 4.43 (s, 1H), 2.69 (s, 3H), 2.66 (s, 3H), 1.24 (s, 2H), 1.08 (s, 2H).</td>
<td>392</td>
<td>98%</td>
</tr>
<tr>
<td>3-11</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.61 (s, 1H), 8.92 (s, 1H), 8.79 (d, J = 1.2 Hz, 1H), 8.16 (d, J = 1.1 Hz, 1H), 8.01 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 1.1 Hz, 1H), 7.58 (s, 1H), 4.42 (tt, J = 7.2, 3.8 Hz, 1H), 2.70 (d, J = 20.2 Hz, 3H), 1.26 (d, J = 6.9 Hz, 2H), 1.15 - 1.03 (m, 2H).</td>
<td>412</td>
<td>99%</td>
</tr>
<tr>
<td>3-12</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 9.40 (s, 1H), 8.94 (s, 1H), 8.88 (s, 1H), 8.18 (d, J = 9.3 Hz, 1H), 8.05 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 9.3 Hz, 1H), 4.43 (s, 1H), 2.69 (s, 3H), 1.24 (d, J = 6.1 Hz, 2H), 1.12 (s, 2H).</td>
<td>423</td>
<td>96%</td>
</tr>
<tr>
<td>3-13</td>
<td>![Chemical Structure]</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.60 (s, 1H), 8.90 (s, 1H), 8.83 (s, 1H), 8.22 (d, J = 1.0 Hz, 1H), 7.98 (d, J = 9.2 Hz, 1H), 7.75 (d, J = 1.0 Hz, 1H), 7.66 (s, 1H), 4.29 - 4.18 (m, 1H), 3.51 (d, J = 13.2 Hz, 3H), 1.25 - 1.14 (m, 4H).</td>
<td>428</td>
<td>100%</td>
</tr>
<tr>
<td>3-14</td>
<td>![Chemical Structure]</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.59 (s, 1H), 9.19 (s, 1H), 8.83 (s, 1H), 8.28 (s, 1H), 8.01 (d, J = 9.2 Hz, 1H), 7.92 (s, 1H), 7.81 (s, 1H), 4.25 (dt, J = 11.0, 5.7 Hz, 1H), 3.50 (d, J = 12.8 Hz, 3H), 1.19 (m, 4H).</td>
<td>462</td>
<td>98%</td>
</tr>
<tr>
<td>3-15</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 9.61 (s, 1H), 8.93 (s, 1H), 8.51 (s, 1H), 8.13 (s, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.62 (d, J = 9.2 Hz, 1H), 7.55 (s, 1H), 4.42 (s, 1H), 2.69 (s, 3H), 1.24 (s, 2H), 1.10 (s, 2H).</td>
<td>421</td>
<td>98%</td>
</tr>
<tr>
<td>3-16</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.87 – 13.95 (m, 2H), 9.60 (s, 1H), 8.94 (s, 1H), 8.44 (s, 1H), 8.05 (t, $J = 9.5$ Hz, 2H), 7.71 (d, $J = 9.4$ Hz, 1H), 4.46 – 4.39 (m, 1H), 2.71 (m, 3H), 2.46 (s, 3H), 1.25 (d, $J = 6.3$ Hz, 2H), 1.11 (s, 2H).</td>
<td>459</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>3-17</td>
<td>Cl</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.44 – 13.91 (m, 1H), 9.16 (s, 1H), 8.95 (s, 1H), 8.37 (s, 1H), 8.23 (d, $J = 8.6$ Hz, 1H), 8.08 (s, 1H), 7.81 (s, 1H), 4.43 (m, 1H), 1.23 (m, 2H), 1.16 (s, 2H).</td>
<td>398</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>3-18</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.62 (s, 1H), 8.92 (s, 1H), 8.68 (s, 1H), 8.19 (d, $J = 2.9$ Hz, 1H), 8.01 (d, $J = 8.8$ Hz, 1H), 7.73 (d, $J = 1.0$ Hz, 1H), 7.32 (d, $J = 11.7$ Hz, 1H), 4.42 (m, 1H), 2.72 (s, 3H), 1.25 (d, 2H), 1.12 – 1.04 (m, 2H).</td>
<td>396</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>3-19</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 9.29 (s, 1H), 8.94 (s, 1H), 8.54 (s, 1H), 8.36 (s, 1H), 8.05 (d, $J = 8.9$ Hz, 1H), 8.00 (s, 1H), 4.49 – 4.36 (m, 1H), 2.74 (s, 3H), 1.25 (d, $J = 6.9$ Hz, 2H), 1.11 (s, 2H).</td>
<td>423</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>3-20</td>
<td>Cl</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 8.95 (s, 1H), 8.88 (t, $J = 4.2$ Hz, 1H), 8.22 (t, $J = 2.4$ Hz, 1H), 8.20 (d, $J = 8.5$ Hz, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 4.48 – 4.36 (m, 1H), 1.26 – 1.19 (m, 2H), 1.14 (m, 2H).</td>
<td>432</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>3-21</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.60 (s, 1H), 9.32 (d, $J = 1.2$ Hz, 1H), 8.93 (s, 1H), 8.71 (s, 1H), 8.06 (s, 1H), 8.02 (d, $J = 8.8$ Hz, 1H), 4.43 (t, $J = 7.0$, 3.6 Hz, 1H), 2.70 (d, $J = 17.8$ Hz, 3H), 1.30 – 1.20 (m, 2H), 1.15 – 1.05 (m, 2H).</td>
<td>413</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>3-22</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.57 (s, 1H), 9.22 (s, 1H), 8.93 (s, 1H), 8.71 (s, 1H), 8.02 (d, $J = 8.8$ Hz, 1H), 7.85 (d, $J = 10.8$ Hz, 1H), 4.47 – 4.37 (m, 1H), 2.72 (s, 3H), 1.29 – 1.22 (m, 2H), 1.10 (s, 2H).</td>
<td>397</td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td>3-23</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.57 (s, 1H), 9.26 (s, 1H), 8.84 (s, 1H), 8.72 (s, 1H), 8.01 (d, $J = 9.1$ Hz, 1H), 7.92 (d, $J = 10.9$ Hz, 1H), 4.28 – 4.18 (m, 1H), 3.51 (s, 3H), 1.20 (d, $J = 5.5$ Hz, 4H).</td>
<td>413</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>3-24</td>
<td>OMe</td>
<td>H NMR (400 MHz, DMSO) δ 14.47 (s, 1H), 8.89 (t, J = 1.3 Hz, 1H), 8.86 (d, J = 1.8 Hz, 1H), 8.23 (d, J = 1.3 Hz, 1H), 8.00 (d, J = 9.1 Hz, 1H), 7.75 (d, J = 1.2 Hz, 1H), 7.63 (t, J = 1.3 Hz, 1H), 5.31 – 4.93 (dd, J = 64.0, 5.5, 3.3 Hz, 1H), 4.26 – 4.12 (dt, J = 8.9, 5.4 Hz, 1H), 3.54 (s, 3H), 1.93 – 1.49 (m, 2H).</td>
<td>446</td>
<td>98%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-25</td>
<td>Me</td>
<td>H NMR (400 MHz, CDCl3) δ 14.07 (s, 1H), 8.55 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 17.0 Hz, 1H), 7.66 (dd, J = 11.6, 4.8 Hz, 2H), 7.49 (d, J = 4.4 Hz, 1H), 7.13 – 7.03 (m, 2H), 7.01 (d, J = 0.8 Hz, 1H), 5.22 (s, 1H), 1.72 (s, 3H).</td>
<td>484</td>
<td>98%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-26</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>H NMR (400 MHz, DMSO) δ 14.64 (s, 1H), 9.09 (s, 1H), 8.93 (s, 1H), 8.58 (s, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.54 (s, 1H), 4.46 – 4.36 (m, 1H), 2.70 (s, 3H), 2.64 (s, 3H), 1.25 (d, J = 6.2 Hz, 2H), 1.09 (s, 2H).</td>
<td>393</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>3-27</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>H NMR (400 MHz, DMSO) δ 14.48 (s, 1H), 8.90 (d, J = 3.0 Hz, 1H), 8.78 (s, 1H), 8.16 (s, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.75 (s, 1H), 7.57 (s, 1H), 5.16 (d, J = 64.5 Hz, 1H), 4.44 – 4.33 (m, 1H), 2.65 (s, 3H), 1.83 – 1.68 (m, 1H), 1.62 (m, 1H).</td>
<td>430</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>3-28</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>H NMR (400 MHz, DMSO) δ 14.59 (s, 1H), 9.63 (s, 1H), 8.94 (s, 1H), 8.81 (s, 1H), 8.30 (s, 1H), 8.04 (d, J = 8.9 Hz, 1H), 4.50 – 4.37 (m, 1H), 2.73 (s, 3H), 1.24 (d, J = 9.6 Hz, 2H), 1.12 (s, 2H).</td>
<td>447</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>3-29</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>H NMR (400 MHz, DMSO) δ 9.33 (s, 1H), 8.94 (s, 1H), 8.74 (s, 1H), 8.63 (s, 2H), 8.05 (d, J = 8.8 Hz, 1H), 7.84 (s, 1H), 4.51 (s, 2H), 4.46 – 4.36 (m, 1H), 2.71 (s, 3H), 1.26 (d, J = 6.8 Hz, 2H), 1.09 (s, 2H).</td>
<td>408</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>3-30</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>H NMR (400 MHz, DMSO) δ 14.58 (s, 1H), 9.37 (s, 1H), 8.84 (s, 1H), 8.72 (s, 1H), 8.13 (s, 1H), 8.00 (d, J = 9.0 Hz, 1H), 4.29 – 4.18 (m, 1H), 3.51 (s, 3H), 1.20 (d, J = 5.4 Hz, 4H).</td>
<td>429</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>3-31</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>H NMR (400 MHz, DMSO) δ 9.43 (s, 1H), 8.99 (s, 1H), 8.89 (s, 1H), 8.14 – 8.01 (m, 2H), 7.54 (d, J = 9.8 Hz, 1H), 4.49 (s, 2H), 2.77 (s, 3H), 1.30 (s, 2H), 1.14 (s, 2H).</td>
<td>379</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>3-32</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>H NMR (400 MHz, DMSO) δ 9.42 (s, 1H), 8.92 (s, 1H), 8.83 (s, 1H), 8.00 (s, 2H), 7.57 (d, J = 9.3 Hz, 1H), 4.23 (s, 1H), 3.51 (s, 3H), 1.18 (s, 4H).</td>
<td>395</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>3-33</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>H NMR (400 MHz, DMSO) δ 8.98 (s, 1H), 8.74 (s, 1H), 8.48 (s, 1H), 8.23 (s, 1H), 8.04 (d, J = 8.9 Hz, 1H), 4.39 (s, 2H), 2.64 (s, 3H), 1.29 (s, 2H), 1.07 (s, 2H).</td>
<td>379</td>
<td>99%</td>
</tr>
<tr>
<td>3-34</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>H NMR (400 MHz, DMSO) δ 15.02 – 14.73 (m, 1H), 9.01 (s, 1H), 8.10 (s, 3H), 7.54 (s, 1H), 4.51 (s, 1H), 1.33 (s, 2H), 1.18 (s, 2H).</td>
<td>379</td>
<td>95%</td>
</tr>
<tr>
<td>3-35</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>H NMR (400 MHz, DMSO) δ 14.68 (s, 1H), 14.19 (s, 1H), 8.93 (s, 1H), 8.53 (s, 1H), 8.44 (s, 1H), 8.40 (s, 1H), 8.01 (d, J = 8.5 Hz, 1H), 4.42 (s, 1H), 2.64 (s, 3H), 1.22 (m, 2H), 1.12 (m, 2H).</td>
<td>423</td>
<td>98%</td>
</tr>
<tr>
<td>3-36</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>H NMR (400 MHz, DMSO) δ 12.87 (s, 1H), 8.97 (s, 1H), 8.10 (s, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.02 (s, 1H), 6.48 (s, 1H), 4.46 (s, 1H), 2.70 (s, 2H), 1.30 (s, 2H), 1.12 (s, 2H).</td>
<td>393</td>
<td>98%</td>
</tr>
<tr>
<td>3-37</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>H NMR (400 MHz, DMSO) δ 14.83 (s, 1H), 13.45 (b, 1H), 8.98 (s, 1H), 8.26 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.90 (s, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 4.46 (s, 1H), 2.68 (s, 3H), 1.31 (d, J = 5.7 Hz, 2H), 1.14 (s, 2H).</td>
<td>378</td>
<td>92%</td>
</tr>
<tr>
<td>3-38</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>H NMR (400 MHz, DMSO) δ 14.69 (s, 1H), 13.83 (s, 1H), 8.91 (s, 1H), 8.31 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.83 (s, 1H), 7.53 (s, 1H), 4.46 – 4.34 (m, 1H), 2.63 (s, 3H), 1.25 (d, J = 6.9 Hz, 2H), 1.06 (s, 2H).</td>
<td>412</td>
<td>98%</td>
</tr>
<tr>
<td>3-39</td>
<td>![Chemical Structure]</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>H NMR (400 MHz, DMSO) δ 14.74 (s, 1H), 14.27 (s, 1H), 8.90 (s, 1H), 8.62 (d, J = 10.6 Hz, 3H), 8.07 (d, J = 9.1 Hz, 1H), 4.31 (s, 1H), 3.44 (s, 3H), 1.26 (s, 4H).</td>
<td>439</td>
<td>95%</td>
</tr>
<tr>
<td>3-40</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>H NMR (400 MHz, DMSO) δ 14.77 (s, 1H), 13.23 (s, 1H), 8.91 (s, 1H), 8.49 (s, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.67 (s, 1H), 7.25 (d, J = 7.9 Hz, 1H), 4.40 (s, 1H), 2.61 (s, 2H), 1.25 (s, 2H), 1.09 (s, 2H).</td>
<td>378</td>
<td>98%</td>
</tr>
<tr>
<td>3-41</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>H NMR (400 MHz, DMSO) δ 14.72 (s, 1H), 9.52 (s, 1H), 8.92 (s, 1H), 8.30 (s, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 8.8 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 4.40 (s, 1H), 2.62 (s, 3H), 1.25 (d, J = 5.9 Hz, 2H), 1.08 (s, 2H).</td>
<td>395</td>
<td>95%</td>
</tr>
<tr>
<td>3-42</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^{1}H$ NMR (400 MHz, DMSO) δ 14.77 (s, 1H), 11.96 (s, 1H), 8.92 (s, 1H), 8.24 (s, 1H), 8.06 (s, 1H), 7.99 (d, $J = 8.7$ Hz, 1H), 7.61 (s, 1H), 6.57 (s, 1H), 4.41 (s, 1H), 2.64 (s, 3H), 1.26 (d, $J = 6.1$ Hz, 2H), 1.09 (s, 2H).</td>
<td>378</td>
<td>98%</td>
</tr>
<tr>
<td>3-43</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^{1}H$ NMR (400 MHz, DMSO) δ 14.76 – 14.48 (s, 1H), 8.97 – 8.90 (d, $J = 2.7$ Hz, 2H), 8.63 – 8.55 (s, 1H), 8.07 – 7.97 (t, $J = 9.2$ Hz, 2H), 7.69 – 7.58 (m, 1H), 4.48 – 4.39 (s, 2H), 2.73 – 2.65 (s, 3H), 1.27 – 1.20 (m, 2H), 1.14 – 1.06 (s, 2H).</td>
<td>403</td>
<td>95%</td>
</tr>
<tr>
<td>3-44</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^{1}H$ NMR (400 MHz, DMSO) δ 10.02 – 9.98 (s, 1H), 9.48 – 9.43 (s, 1H), 8.95 – 8.90 (s, 1H), 8.67 – 8.62 (s, 1H), 8.12 – 8.07 (d, $J = 9.2$ Hz, 1H), 8.07 – 8.01 (d, $J = 8.9$ Hz, 1H), 7.82 – 7.75 (dd, $J = 9.4$, 1.7 Hz, 1H), 4.48 – 4.36 (s, 1H), 2.72 – 2.67 (s, 3H), 1.25 – 1.21 (t, $J = 3.8$ Hz, 2H), 1.14 – 1.06 (m, 2H).</td>
<td>406</td>
<td>90%</td>
</tr>
<tr>
<td>3-45</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^{1}H$ NMR (400 MHz, DMSO) δ 9.93 (s, 1H), 8.83 (s, 1H), 8.40 (s, 1H), 8.09 – 8.05 (dd, $J = 9.2$, 1.0 Hz, 1H), 8.05 – 8.00 (d, $J = 8.7$ Hz, 1H), 7.81 – 7.72 (dd, $J = 9.3$, 1.7 Hz, 1H), 5.35 – 5.16 (s, 1H), 4.53 – 4.33 (m, 1H), 2.75 – 2.64 (s, 3H), 1.28 – 1.20 (d, $J = 6.2$ Hz, 2H), 1.15 – 1.03 (d, $J = 3.8$ Hz, 2H).</td>
<td>402</td>
<td>98%</td>
</tr>
<tr>
<td>3-46</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^{1}H$ NMR (400 MHz, DMSO) δ 14.70 – 14.56 (s, 1H), 9.23 – 9.15 (m, 1H), 8.99 – 8.89 (s, 1H), 8.72 – 8.65 (s, 1H), 8.08 – 7.99 (d, $J = 8.8$ Hz, 1H), 7.84 – 7.77 (s, 1H), 7.16 – 7.04 (m, 1H), 6.93 – 6.82 (m, 1H), 5.82 – 5.69 (dd, $J = 11.2$, 1.6 Hz, 1H), 4.49 – 4.36 (t, $J = 3.5$ Hz, 1H), 2.75 – 2.68 (s, 3H), 1.33 – 1.19 (t, $J = 6.5$ Hz, 2H), 1.16 – 1.03 (s, 2H).</td>
<td>405</td>
<td>97%</td>
</tr>
<tr>
<td>3-47</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^{1}H$ NMR (400 MHz, DMSO) δ 14.76 – 14.48 (s, 1H), 8.96 – 8.91 (s, 4H), 8.86 – 8.79 (s, 4H), 8.64 – 8.56 (d, $J = 2.3$ Hz, 4H), 8.05 – 7.99 (d, $J = 8.8$ Hz, 4H), 7.86 – 7.79 (d, $J = 9.4$ Hz, 4H), 7.52 – 7.43 (s, 3H), 4.48 – 4.37 (s, 1H), 2.74 – 2.57 (s, 12H), 1.29 – 1.20 (d, $J = 6.8$ Hz, 9H), 1.11 – 1.01 (t, $J = 3.0$ Hz, 6H).</td>
<td>422</td>
<td>96%</td>
</tr>
<tr>
<td>3-48</td>
<td>![Chemical Structure]</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^{1}H$ NMR (400 MHz, DMSO) δ 14.76 – 14.48 (s, 1H), 8.95 – 8.89 (s, 1H), 8.84 – 8.78 (s, 1H), 8.63 – 8.58 (s, 1H), 8.05 – 8.00 (d, $J = 8.8$ Hz, 1H), 7.90 – 7.84 (d, $J = 9.4$ Hz, 1H), 7.53 – 7.45 (d, $J = 9.3$ Hz, 1H), 4.47 – 4.40 (s, 1H), 2.73 – 2.66 (s, 3H), 1.27 – 1.21 (d, $J = 6.6$ Hz, 2H), 1.12 – 1.02 (s, 2H).</td>
<td>446</td>
<td>90%</td>
</tr>
<tr>
<td>3-49</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 8.93 (s, 1H), 8.66 (s, 1H), 8.06 – 7.99 (d, $J = 8.7$ Hz, 1H), 7.99 – 7.95 (s, 1H), 7.94 – 7.88 (d, $J = 9.3$ Hz, 1H), 7.55 – 7.47 (dd, $J = 9.3$, 1.6 Hz, 1H), 4.52 – 4.32 (m, 1H), 2.77 – 2.61 (s, 3H), 1.33 – 1.17 (d, $J = 6.6$ Hz, 2H), 1.19 – 1.05 (t, $J = 3.3$ Hz, 2H).</td>
<td>412</td>
<td>98%</td>
</tr>
<tr>
<td>3-50</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 8.93 (s, 1H), 8.60 (s, 1H), 8.06 – 8.00 (d, $J = 8.7$ Hz, 1H), 8.00 – 7.96 (s, 1H), 7.92 – 7.86 (d, $J = 9.3$ Hz, 1H), 7.55 – 7.48 (d, $J = 9.4$ Hz, 1H), 4.55 – 4.26 (m, 1H), 2.81 – 2.60 (s, 3H), 1.37 – 1.21 (d, $J = 6.5$ Hz, 2H), 1.15 – 1.05 (m, 2H).</td>
<td>456, 458</td>
<td>97%</td>
</tr>
<tr>
<td>3-51</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.71 – 14.62 (s, 1H), 8.96 – 8.88 (s, 1H), 8.83 – 8.75 (s, 1H), 8.25 – 8.16 (d, $J = 7.5$ Hz, 2H), 8.15 – 8.07 (s, 1H), 8.07 – 7.97 (d, $J = 8.8$ Hz, 1H), 7.77 – 7.71 (s, 1H), 7.57 – 7.42 (m, 4H), 4.50 – 4.33 (s, 1H), 2.82 – 2.71 (s, 3H), 1.31 – 1.22 (d, $J = 6.7$ Hz, 2H), 1.15 – 1.04 (s, 2H).</td>
<td>454</td>
<td>99%</td>
</tr>
<tr>
<td>3-52</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.71 – 14.60 (s, 1H), 8.95 – 8.88 (s, 1H), 8.73 – 8.65 (s, 1H), 8.10 – 7.96 (m, 2H), 7.74 – 7.68 (s, 1H), 7.40 – 7.32 (s, 1H), 7.11 – 7.02 (m, 1H), 6.96 – 6.83 (m, 1H), 5.70 – 5.60 (dd, $J = 11.2$, 2.0 Hz, 1H), 4.47 – 4.38 (t, $J = 3.5$ Hz, 1H), 2.78 – 2.69 (s, 3H), 1.31 – 1.20 (d, $J = 6.9$ Hz, 2H), 1.14 – 1.01 (s, 2H).</td>
<td>405</td>
<td>93%</td>
</tr>
<tr>
<td>3-53</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.71 – 14.60 (s, 1H), 8.95 – 8.88 (s, 1H), 8.73 – 8.65 (s, 1H), 8.10 – 7.96 (m, 2H), 7.74 – 7.68 (s, 1H), 7.40 – 7.32 (s, 1H), 7.11 – 7.02 (m, 1H), 6.96 – 6.83 (m, 1H), 5.70 – 5.60 (dd, $J = 11.2$, 2.0 Hz, 1H), 4.47 – 4.38 (t, $J = 3.5$ Hz, 1H), 2.78 – 2.69 (s, 3H), 1.31 – 1.20 (d, $J = 6.9$ Hz, 2H), 1.14 – 1.01 (s, 2H).</td>
<td>403</td>
<td>95%</td>
</tr>
<tr>
<td>3-54</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.76 – 14.39 (s, 1H), 9.20 – 9.07 (d, $J = 7.0$ Hz, 1H), 8.95 – 8.90 (s, 1H), 8.67 – 8.60 (s, 1H), 8.08 – 8.00 (m, 2H), 7.32 – 7.24 (m, 1H), 4.47 – 4.36 (s, 1H), 2.75 – 2.61 (s, 3H), 1.30 – 1.19 (m, 2H), 1.15 – 1.03 (q, $J = 3.8$, 3.1 Hz, 2H).</td>
<td>379</td>
<td>98%</td>
</tr>
<tr>
<td>3-55</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.76 – 14.36 (s, 1H), 9.68 – 9.65 (d, $J = 1.5$ Hz, 1H), 8.95 – 8.92 (s, 1H), 8.84 – 8.81 (s, 1H), 8.63 – 8.59 (d, $J = 1.5$ Hz, 1H), 8.06 – 8.01 (d, $J = 8.8$ Hz, 1H), 4.46 – 4.39 (s, 1H), 2.76 – 2.69 (s, 3H), 1.30 – 1.20 (m, 2H), 1.14 – 1.05 (s, 2H).</td>
<td>404</td>
<td>98%</td>
</tr>
<tr>
<td>Compound</td>
<td>Structure</td>
<td>Functional Group</td>
<td>NMR Details</td>
<td>1H NMR (400 MHz, DMSO) δ 14.73 - 14.06 (s, 1H), 9.21 - 9.18 (m, 1H), 8.87 - 8.83 (d, J = 1.86 Hz, 1H), 8.32 - 8.27 (d, J = 1.33 Hz, 1H), 8.20 - 8.16 (s, 1H), 8.04 - 7.97 (d, J = 9.6 Hz, 1H), 7.87 - 7.80 (d, J = 1.20 Hz, 1H), 5.31 - 4.87 (m, 1H), 4.32 - 4.12 (m, 1H), 3.67 - 3.47 (s, 3H), 1.95 - 1.56 (m, 2H).</td>
<td>437</td>
<td>98%</td>
</tr>
<tr>
<td>---</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3-57</td>
<td><img src="image" alt="Structure" /></td>
<td>OMe Cyclopropyl</td>
<td>1H NMR (400 MHz, DMSO) δ 14.61 (s, 1H), 8.83 (s, 1H), 8.77 (s, 1H), 8.23 (d, J = 2.1 Hz, 1H), 7.99 (d, J = 9.2 Hz, 1H), 7.73 (d, J = 1.0 Hz, 1H), 7.40 (d, J = 11.8 Hz, 1H), 4.46 - 4.08 (m, 1H), 3.51 (d, J = 10.5 Hz, 3H), 1.19 (d, J = 6.9 Hz, 4H).</td>
<td>412</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>3-58</td>
<td><img src="image" alt="Structure" /></td>
<td>Me Cyclopropyl</td>
<td>1H NMR (400 MHz, DMSO) δ 14.83 - 14.57 (s, 1H), 9.82 - 9.48 (s, 2H), 9.01 - 8.84 (d, J = 2.6 Hz, 1H), 8.05 - 7.90 (dd, J = 8.5, 2.7 Hz, 1H), 7.65 - 7.57 (d, J = 7.5 Hz, 1H), 7.51 - 7.46 (s, 1H), 7.45 - 7.36 (d, J = 7.7 Hz, 1H), 4.72 - 4.50 (s, 4H), 4.47 - 4.28 (d, J = 6.8 Hz, 1H), 2.64 - 2.53 (d, J = 2.7 Hz, 3H), 1.31 - 1.14 (d, J = 6.1 Hz, 2H), 1.14 - 0.96 (s, 2H).</td>
<td>379</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>3-59</td>
<td><img src="image" alt="Structure" /></td>
<td>Me Cyclopropyl</td>
<td>1H NMR (400 MHz, DMSO) δ 8.95 - 8.83 (d, J = 2.4 Hz, 1H), 7.98 - 7.86 (d, J = 8.8 Hz, 1H), 7.25 - 7.15 (s, 1H), 7.14 - 7.01 (d, J = 7.9 Hz, 1H), 6.97 - 6.81 (d, J = 7.9 Hz, 1H), 3.65 - 3.50 (m, 2H), 4.45 - 4.29 (dp, J = 9.2, 4.7, 3.9 Hz, 1H), 3.16 - 2.99 (t, J = 8.4 Hz, 2H), 2.65 - 2.56 (s, 3H), 1.28 - 1.16 (d, J = 6.6 Hz, 3H), 1.12 - 0.97 (m, 2H).</td>
<td>379</td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td>3-60</td>
<td><img src="image" alt="Structure" /></td>
<td>Me Cyclopropyl</td>
<td>1H NMR (400 MHz, DMSO) δ 15.01 - 14.39 (m, 1H), 12.95 - 12.53 (s, 2H), 9.03 - 8.82 (t, J = 1.9 Hz, 1H), 8.73 - 8.47 (s, 2H), 8.10 - 7.90 (d, J = 8.4 Hz, 1H), 7.62 - 7.44 (m, 1H), 4.51 - 4.23 (m, 1H), 7.44 - 7.31 (s, 1H), 7.31 - 7.11 (d, J = 8.6 Hz, 1H), 2.65 - 2.55 (s, 3H), 1.30 - 1.16 (m, 2H), 1.16 - 0.96 (s, 2H).</td>
<td>393</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>3-61</td>
<td><img src="image" alt="Structure" /></td>
<td>Me Cyclopropyl</td>
<td>1H NMR (400 MHz, MeOD) δ 9.17 - 9.06 (d, J = 2.8 Hz, 1H), 8.30 - 8.15 (m, 1H), 7.94 - 7.80 (m, 2H), 7.65 - 7.49 (dt, J = 7.5, 3.3 Hz, 2H), 4.47 - 4.32 (d, J = 6.9 Hz, 1H), 2.96 - 2.81 (d, J = 2.8 Hz, 3H), 1.43 - 1.27 (dd, J = 10.8, 4.5 Hz, 2H), 1.21 - 1.05 (s, 2H).</td>
<td>378</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Substitution</td>
<td>Functional Group</td>
<td>NMR Data (400 MHz, DMSO)</td>
<td>Components</td>
<td>Percentage</td>
</tr>
<tr>
<td>-----</td>
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</tr>
<tr>
<td>3-62</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.63 – 14.42 (s, 1H), 8.99 – 8.89 (s, 1H), 8.33 – 8.25 (d, $J = 7.8$ Hz, 1H), 8.25 – 8.18 (d, $J = 8.0$ Hz, 1H), 8.14 – 8.05 (d, $J = 8.7$ Hz, 1H), 7.71 – 7.56 (dt, $J = 22.8, 7.4$ Hz, 2H), 4.51 – 4.31 (s, 1H), 2.85 – 2.70 (s, 3H), 1.30 – 1.20 (d, $J = 7.0$ Hz, 2H), 1.13 – 0.97 (s, 2H).</td>
<td>395</td>
<td>100%</td>
</tr>
<tr>
<td>3-63</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 15.01 – 14.28 (s, 2H), 9.04 – 8.82 (t, $J = 2.3$ Hz, 1H), 8.05 – 7.98 (d, $J = 8.3$ Hz, 1H), 7.98 – 7.92 (dd, $J = 10.5, 2.5$ Hz, 1H), 7.90 – 7.83 (s, 1H), 7.56 – 7.47 (d, $J = 8.2$ Hz, 1H), 4.46 – 4.34 (t, $J = 6.3$ Hz, 1H), 2.87 – 2.78 (t, $J = 2.1$ Hz, 3H), 2.64 – 2.55 (s, 3H), 1.29 – 1.16 (m, 2H), 1.16 – 1.03 (s, 2H).</td>
<td>392</td>
<td>100%</td>
</tr>
<tr>
<td>3-64</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 15.01 – 14.28 (s, 2H), 9.04 – 8.82 (t, $J = 2.3$ Hz, 1H), 8.05 – 7.98 (d, $J = 8.3$ Hz, 1H), 7.98 – 7.92 (dd, $J = 10.5, 2.5$ Hz, 1H), 7.90 – 7.83 (s, 1H), 7.56 – 7.47 (d, $J = 8.2$ Hz, 1H), 4.46 – 4.34 (t, $J = 6.3$ Hz, 1H), 2.87 – 2.78 (t, $J = 2.1$ Hz, 3H), 2.64 – 2.55 (m, 6H), 1.29 – 1.16 (m, 2H), 1.16 – 1.03 (s, 2H).</td>
<td>421</td>
<td>100%</td>
</tr>
<tr>
<td>3-65</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 15.01 – 14.35 (m, 1H), 10.46 – 9.91 (m, 1H), 9.02 – 8.80 (s, 1H), 8.80 – 8.47 (d, $J = 15.2$ Hz, 1H), 8.12 – 7.64 (m, 3H), 7.44 – 7.25 (dd, $J = 23.7, 8.0$ Hz, 1H), 4.84 – 4.63 (d, $J = 8.8$ Hz, 2H), 4.49 – 4.32 (s, 1H), 3.01 – 2.77 (d, $J = 17.9$ Hz, 6H), 1.37 – 1.13 (d, $J = 6.9$ Hz, 2H), 1.01 – 0.56 (s, 2H).</td>
<td>449</td>
<td>96%</td>
</tr>
<tr>
<td>3-66</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.97 – 14.24 (s, 2H), 9.14 – 8.97 (m, 2H), 8.98 – 8.88 (s, 2H), 8.07 – 7.89 (dd, $J = 24.1, 8.9$ Hz, 6H), 7.86 – 7.79 (s, 1H), 7.52 – 7.37 (t, $J = 9.6$ Hz, 3H), 4.57 – 4.31 (t, $J = 6.8$ Hz, 5H), 2.66 – 2.55 (s, 7H), 1.60 – 1.40 (m, 7H), 1.30 – 1.16 (m, 2H), 1.16 – 0.98 (s, 2H).</td>
<td>406</td>
<td>97%</td>
</tr>
<tr>
<td>3-67</td>
<td><img src="image6.png" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.97 – 14.24 (s, 2H), 9.14 – 8.97 (m, 2H), 8.98 – 8.88 (s, 2H), 8.07 – 7.86 (dd, $J = 24.1, 8.9$ Hz, 6H), 7.86 – 7.79 (s, 1H), 7.52 – 7.37 (t, $J = 9.6$ Hz, 3H), 4.57 – 4.31 (t, $J = 6.8$ Hz, 5H), 2.66 – 2.55 (s, 3H), 1.60 – 1.40 (m, 7H), 1.30 – 1.16 (m, 2H), 1.16 – 0.98 (s, 2H).</td>
<td>392</td>
<td>100%</td>
</tr>
<tr>
<td>3-68</td>
<td><img src="image7.png" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 8.95 – 8.91 (s, 1H), 8.65 – 8.59 (s, 1H), 8.31 – 8.25 (s, 1H), 8.23 – 8.17 (s, 1H), 8.05 – 7.98 (m, 1H), 4.48 – 4.35 (s, 1H), 2.68 – 2.61 (s, 3H), 1.30 – 1.22 (s, 2H), 1.16 – 1.06 (s, 2H).</td>
<td>423</td>
<td>97%</td>
</tr>
<tr>
<td>3-69</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.96 - 14.48 (m, 1H), 10.94 - 10.65 (d, J = 25.6 Hz, 2H), 9.01 - 8.77 (m, 1H), 8.05 - 7.81 (d, J = 8.6 Hz, 1H), 7.18 - 7.00 (d, J = 7.8 Hz, 1H), 7.00 - 6.78 (m, 2H), 4.47 - 4.25 (td, J = 6.9, 3.8 Hz, 1H), 2.67 - 2.54 (s, 3H), 1.27 - 1.10 (d, J = 6.3 Hz, 2H), 1.14 - 0.88 (s, 2H).</td>
<td>394</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>3-70</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 15.02 - 14.18 (s, 1H), 9.00 - 8.67 (m, 2H), 8.12 - 7.68 (m, 3H), 7.49 - 7.25 (dd, J = 16.6, 8.2 Hz, 1H), 5.04 - 4.75 (m, 1H), 4.62 - 4.23 (m, 9H), 3.77 - 3.55 (m, 2H), 3.57 - 3.23 (d, J = 7.0 Hz, 1H), 2.70 - 2.53 (s, 3H), 1.37 - 1.15 (t, J = 8.0 Hz, 2H), 1.15 - 0.84 (td, J = 16.0, 7.8 Hz, 2H).</td>
<td>494</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>3-71</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.45 - 14.13 (s, 1H), 11.09 - 10.85 (s, 1H), 8.73 - 8.58 (d, J = 2.7 Hz, 1H), 7.85 - 7.61 (m, 2H), 7.31 - 7.15 (m, 1H), 7.07 - 6.83 (m, 2H), 4.27 - 4.07 (s, 1H), 3.82 - 3.71 (d, J = 2.5 Hz, 3H), 1.27 - 1.08 (m, 2H), 1.08 - 0.86 (s, 2H).</td>
<td>408</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>3-72</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 15.07 - 14.72 (s, 1H), 9.21 - 8.97 (s, 1H), 8.95 - 8.73 (m, 1H), 8.41 - 8.14 (m, 1H), 8.12 - 7.95 (s, 1H), 3.40 - 3.18 (m, 4H), 7.95 - 7.79 (d, J = 8.6 Hz, 1H), 7.79 - 7.60 (dd, J = 8.5, 3.9 Hz, 2H), 4.34 - 4.10 (d, J = 6.3 Hz, 1H), 1.30 - 1.02 (s, 4H).</td>
<td>376</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>3-73</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.85 - 14.61 (s, 1H), 10.68 - 10.51 (s, 1H), 9.04 - 8.78 (m, 1H), 8.01 - 7.81 (m, 1H), 7.36 - 7.11 (m, 2H), 7.11 - 6.87 (dd, J = 7.8, 2.7 Hz, 1H), 4.47 - 4.29 (s, 1H), 3.72 - 3.47 (s, 2H), 1.27 - 1.08 (m, 2H), 1.08 - 0.86 (s, 2H).</td>
<td>393</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>3-74</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.85 - 14.61 (s, 1H), 10.68 - 10.51 (s, 1H), 9.04 - 8.78 (m, 1H), 8.01 - 7.81 (m, 1H), 7.36 - 7.11 (m, 2H), 7.11 - 6.87 (dd, J = 7.8, 2.7 Hz, 1H), 4.47 - 4.29 (s, 1H), 3.72 - 3.47 (s, 2H), 2.66 - 2.57 (d, J = 2.7 Hz, 3H), 2.55 - 2.45 (d, J = 3.4 Hz, 4H).</td>
<td>424</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>3-75</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.80 - 14.62 (m, 1H), 8.38 - 8.18 (m, 1H), 8.03 - 7.83 (m, 1H), 8.96 - 8.82 (m, 1H), 7.77 - 7.69 (m, 1H), 7.37 - 7.22 (m, 1H), 4.48 - 4.29 (m, 1H), 3.24 - 3.08 (m, 2H), 3.94 - 3.70 (m, 2H), 1.32 - 1.12 (m, 2H), 1.12 - 0.86 (m, 2H).</td>
<td>394</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Formula</td>
<td>Spectral Data</td>
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<tr>
<td>3-76</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 15.11 – 14.26 (d, $J = 53.0$ Hz, 1H), 10.22 – 9.45 (m, 1H), 9.01 – 8.84 (m, 1H), 8.77 – 8.58 (s, 1H), 8.09 – 7.92 (d, $J = 8.5$ Hz, 1H), 7.88 – 7.68 (s, 1H), 7.51 – 7.33 (s, 1H), 4.84 – 4.58 (s, 2H), 4.53 – 4.25 (s, 1H), 2.96 – 2.72 (s, 6H), 2.72 – 2.56 (s, 3H), 1.34 – 1.17 (d, $J = 6.5$ Hz, 2H), 1.17 – 0.93 (d, $J = 10.1$ Hz, 2H).</td>
<td></td>
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</tr>
<tr>
<td>3-77</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.87 – 14.59 (s, 1H), 12.20 – 12.00 (s, 1H), 9.01 – 8.79 (s, 1H), 8.09 – 7.83 (d, $J = 8.6$ Hz, 1H), 7.74 – 7.59 (s, 1H), 7.39 – 7.20 (m, 2H), 4.48 – 4.31 (s, 1H), 2.72 – 2.56 (s, 3H), 1.36 – 1.12 (d, $J = 6.9$ Hz, 2H), 1.12 – 0.79 (s, 2H).</td>
<td></td>
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</tr>
<tr>
<td>3-78</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.85 – 14.61 (s, 1H), 10.58 – 10.51 (s, 1H), 9.04 – 8.78 (m, 1H), 8.01 – 7.81 (m, 1H), 7.36 – 7.11 (m, 2H), 7.11 – 6.87 (dd, $J = 7.8$, 2.7 Hz, 1H), 4.47 – 4.29 (s, 1H), 3.72 – 3.47 (s, 2H), 1.27 – 1.08 (m, 2H), 1.08 – 0.86 (s, 2H).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-79</td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.82 – 14.60 (s, 1H), 11.50 – 11.28 (s, 1H), 8.99 – 8.81 (s, 1H), 8.09 – 7.90 (m, 2H), 7.66 – 7.53 (d, $J = 1.1$ Hz, 1H), 6.91 – 6.78 (s, 1H), 6.17 – 5.99 (d, $J = 15.7$ Hz, 1H), 5.38 – 5.23 (d, $J = 9.0$ Hz, 1H), 4.48 – 4.31 (dd, $J = 8.4$, 4.4 Hz, 1H), 3.61 – 3.41 (s, 1H), 2.71 – 2.56 (s, 3H), 1.32 – 1.16 (s, 2H), 1.14 – 0.97 (s, 2H).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-80</td>
<td><img src="image5.png" alt="Chemical Structure" /></td>
<td>MeO</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.82 – 14.60 (s, 1H), 11.50 – 11.28 (s, 1H), 8.99 – 8.81 (s, 1H), 8.09 – 7.90 (m, 2H), 7.66 – 7.53 (d, $J = 1.1$ Hz, 1H), 6.91 – 6.78 (s, 1H), 6.17 – 5.99 (d, $J = 15.7$ Hz, 1H), 5.38 – 5.23 (d, $J = 9.0$ Hz, 1H), 4.48 – 4.31 (dd, $J = 8.4$, 4.4 Hz, 1H), 3.61 – 3.41 (s, 1H), 2.71 – 2.56 (s, 3H), 1.14 – 0.97 (s, 4H).</td>
<td></td>
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<tr>
<td>3-81</td>
<td><img src="image6.png" alt="Chemical Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.85 – 14.61 (s, 1H), 10.95 – 10.69 (s, 1H), 9.06 – 8.79 (s, 2H), 8.05 – 7.90 (d, $J = 8.7$ Hz, 1H), 7.28 – 7.09 (s, 1H), 6.85 – 6.63 (s, 1H), 4.46 – 4.29 (tt, $J = 7.4$, 4.0 Hz, 1H), 2.72 – 2.54 (s, 3H), 1.32 – 1.14 (d, $J = 5.8$ Hz, 2H), 1.14 – 0.97 (d, $J = 3.8$ Hz, 2H).</td>
<td></td>
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</tr>
<tr>
<td>3,62</td>
<td>Cyclopropyl</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>NH₂</td>
<td></td>
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<tr>
<td>3,63</td>
<td>Cyclopropyl</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>Cl</td>
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</tr>
<tr>
<td>3,64</td>
<td>Cyclopropyl</td>
<td>Me</td>
<td>Cyclopropyl</td>
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</tr>
<tr>
<td>3,65</td>
<td>Cyclopropyl</td>
<td>Me</td>
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</tr>
<tr>
<td>3,66</td>
<td>Cyclopropyl</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3,67</td>
<td>Cyclopropyl</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td></td>
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<tr>
<td>Compound No.</td>
<td>R^3</td>
<td>NMR</td>
<td>MS (MH^+)</td>
<td>HPLC</td>
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<tr>
<td>4-1</td>
<td><img src="image" alt="Structure" /></td>
<td>^1^H NMR (400 MHz, DMSO) δ 14.49 (s, 1H), 11.38 (s, 1H), 8.70 (s, 1H), 7.78 (d, J = 9.1 Hz, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.26 (d, J = 8.1 Hz, 1H), 7.00 – 6.92 (m, 1H), 6.86 (t, J = 7.5 Hz, 1H), 6.51 (s, 1H), 4.24 – 4.16 (m, 1H), 2.56 (s, 3H), 1.03 (dd, J = 12.0, 4.5 Hz, 2H), 0.86 (d, J = 7.4 Hz, 2H).</td>
<td>377</td>
<td>95%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-2</td>
<td><img src="image" alt="Structure" /></td>
<td>^1^H NMR (400 MHz, DMSO) δ 14.70 (s, 1H), 11.59 (s, 1H), 8.92 (s, 1H), 8.00 (d, J = 9.1 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 7.3 Hz, 1H), 6.73 (s, 1H), 4.42 (s, 1H), 2.78 (s, 3H), 1.27 (d, J = 6.1 Hz, 2H), 1.07 (s, 2H).</td>
<td>377</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-3</td>
<td><img src="image" alt="Structure" /></td>
<td>^1^H NMR (400 MHz, DMSO) δ 14.66 (s, 1H), 8.93 (s, 1H), 8.05 (d, J = 8.6 Hz, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.30 – 7.24 (m, 1H), 7.14 (t, J = 7.3 Hz, 1H), 6.68 (s, 1H), 4.41 (s, 1H), 3.58 (s, 3H), 2.65 (s, 3H), 1.24 (s, 4H).</td>
<td>391</td>
<td>98%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-4</td>
<td><img src="image" alt="Structure" /></td>
<td>^1^H NMR (400 MHz, DMSO) δ 14.62 (s, 1H), 11.36 (s, 1H), 8.90 (s, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.57 (s, 3H), 7.46 (s, 1H), 7.07 (d, J = 8.5 Hz, 1H), 6.53 (s, 1H), 4.39 (s, 1H), 2.62 (s, 3H), 1.24 (s, 2H), 1.09 (d, J = 18.8 Hz, 2H).</td>
<td>377</td>
<td>87%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-5</td>
<td><img src="image" alt="Structure" /></td>
<td>^1^H NMR (400 MHz, DMSO) δ 14.71 (s, 1H), 11.55 (s, 1H), 8.92 (s, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 6.9 Hz, 1H), 6.57 (s, 1H), 4.42 (s, 1H), 2.79 (s, 3H), 2.09 (s, 3H), 1.28 (d, J = 6.0 Hz, 2H), 1.07 (s, 2H).</td>
<td>391</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td><img src="image" alt="Structure" /></td>
<td>^1^H NMR (400 MHz, DMSO) δ 14.71 (s, 1H), 11.43 (s, 1H), 8.91 (s, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 6.84 (d, J = 8.7 Hz, 1H), 6.63 (s, 1H), 4.41 (s, 1H), 3.78 (s, 4H), 2.77 (s, 3H), 1.26 (d, J = 5.7 Hz, 2H), 1.07 (s, 2H).</td>
<td>407</td>
<td>92.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 4-9 | \[
\text{\textsuperscript{1}H NMR (400 MHz, DMSO)} \delta 14.65 (s, 1H), 12.23 (d, \text{ J = 30.1 Hz, 1H}), 8.93 (s, 1H), 8.20 (d, \text{ J = 11.8 Hz, 1H}), 7.65 (s, 1H), 7.53 (s, 2H), 6.87 (d, \text{ J = 26.1 Hz, 1H}), 4.38 (d, \text{ J = 31.7 Hz, 1H}), 2.74 (d, \text{ J = 19.6 Hz, 3H}), 1.24 (d, \text{ J = 8.9 Hz, 2H}), 1.07 (s, 2H).
\] |
|---|---|
| 4-10 | \[
\text{\textsuperscript{1}H NMR (400 MHz, DMSO)} \delta 14.67 (s, 1H), 11.70 (s, 1H), 8.92 (s, 1H), 8.00 (d, \text{ J = 8.9 Hz, 1H}), 7.52 - 7.44 (m, 1H), 7.41 (d, \text{ J = 9.8 Hz, 1H}), 7.04 (t, \text{ J = 9.3 Hz, 1H}), 6.72 (s, 1H), 4.42 (s, 1H), 2.77 (s, 3H), 1.26 (d, \text{ J = 6.4 Hz, 2H}), 1.07 (s, 2H).
\] |
| 4-11 | \[
\text{\textsuperscript{1}H NMR (400 MHz, DMSO)} \delta 14.68 (s, 1H), 11.98 (s, 1H), 8.93 (s, 1H), 8.02 (d, \text{ J = 9.1 Hz, 1H}), 7.47 (d, \text{ J = 7.3 Hz, 1H}), 7.19 (q, \text{ J = 7.8 Hz, 2H}), 6.76 (s, 1H), 4.42 (s, 1H), 2.78 (s, 3H), 1.27 (d, \text{ J = 6.2 Hz, 2H}), 1.08 (s, 2H).
\] |
| 4-12 | \[
\text{\textsuperscript{1}H NMR (400 MHz, DMSO)} \delta 14.64 (s, 1H), 12.30 (s, 1H), 8.93 (s, 1H), 8.04 (d, \text{ J = 8.3 Hz, 1H}), 7.66 (d, \text{ J = 6.8 Hz, 1H}), 7.64 (s, 1H), 7.36 (s, 1H), 6.91 (s, 1H), 4.43 (s, 1H), 2.78 (s, 3H), 1.28 (s, 2H), 1.09 (s, 2H).
\] |
| 4-13 | \[
\text{\textsuperscript{1}H NMR (400 MHz, DMSO)} \delta 14.66 (s, 1H), 11.93 (s, 1H), 8.92 (s, 1H), 8.01 (d, \text{ J = 9.1 Hz, 1H}), 7.33 (d, \text{ J = 8.3 Hz, 1H}), 7.17 (d, \text{ J = 6.5 Hz, 1H}), 6.87 (t, \text{ J = 8.9 Hz, 1H}), 6.80 (s, 1H), 4.42 (s, 1H), 2.78 (s, 3H), 1.27 (d, \text{ J = 6.4 Hz, 2H}), 1.07 (s, 2H).
\] |
| 4-14 | \[
\text{\textsuperscript{1}H NMR (400 MHz, DMSO)} \delta 14.70 (s, 1H), 11.43 (s, 1H), 8.92 (s, 1H), 8.00 (d, \text{ J = 8.8 Hz, 1H}), 7.46 (s, 1H), 6.98 (s, 2H), 6.67 (s, 1H), 4.42 (s, 1H), 2.77 (s, 3H), 1.26 (d, \text{ J = 6.3 Hz, 2H}), 1.09 (s, 2H).
\] |
| 4-15 | \[
\text{\textsuperscript{1}H NMR (400 MHz, DMSO)} \delta 11.07 (s, 1H), 9.02 (s, 1H), 8.04 (s, 1H), 7.55 (s, 2H), 7.29 (s, 1H), 6.96 (s, 1H), 6.67 (s, 1H), 2.85 (s, 3H), 2.47 (s, 3H), 1.34 (s, 2H), 1.09 (s, 2H).
\] |
| 4-16 | \[
\text{\textsuperscript{1}H NMR (400 MHz, DMSO)} \delta 14.64 (s, 1H), 12.41 (s, 1H), 8.93 (s, 1H), 8.69 (s, 1H), 8.07 (d, \text{ J = 13.8 Hz, 2H}), 7.67 (s, 1H), 7.05 (s, 1H), 4.42 (s, 1H), 2.78 (s, 3H), 1.26 (s, 2H), 1.08 (s, 2H).
\] |
| 4-17 | \[
\text{\textsuperscript{1}H NMR (400 MHz, DMSO)} \delta 14.70 (s, 1H), 11.70 (s, 1H), 8.92 (s, 1H), 8.00 (d, \text{ J = 9.0 Hz, 1H}), 7.65 (s, 1H), 7.24 (d, \text{ J = 10.1 Hz, 1H}), 6.96 (t, \text{ J = 9.1 Hz, 1H}), 6.76 (s, 1H), 4.42 (s, 1H), 2.77 (s, 3H), 1.26 (d, \text{ J = 5.7 Hz, 2H}), 1.07 (s, 2H).
\] |
<p>| 4-18 | ![Chemical Structure] | $^1$H NMR (400 MHz, DMSO) δ 14.68 (s, 1H), 12.08 (s, 1H), 8.92 (s, 1H), 8.01 (d, J = 8.9 Hz, 1H), 7.47 (d, J = 6.4 Hz, 1H), 7.04 (d, J = 9.3 Hz, 2H), 6.79 (s, 1H), 4.42 (s, 1H), 2.76 (s, 3H), 1.26 (d, J = 6.2 Hz, 2H), 1.08 (s, 2H). | 395 | 89.1% |
| 4-19 | ![Chemical Structure] | $^1$H NMR (400 MHz, DMSO) δ 14.65 (s, 1H), 12.66 (s, 1H), 11.98 (s, 1H), 8.93 (s, 1H), 8.12 (s, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.70 (q, J = 8.2 Hz, 2H), 6.83 (s, 1H), 4.43 (s, 1H), 2.78 (s, 3H), 1.27 (d, J = 6.2 Hz, 2H), 1.08 (s, 2H). | 421 | 100% |
| 4-20 | ![Chemical Structure] | $^1$H NMR (400 MHz, DMSO) δ 14.68 (s, 1H), 11.78 (s, 1H), 8.92 (s, 1H), 8.01 (d, J = 9.0 Hz, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.51 (s, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.77 (s, 1H), 4.42 (s, 1H), 2.77 (s, 3H), 1.26 (d, J = 6.1 Hz, 2H), 1.07 (s, 2H). | 411 | 90% |
| 4-21 | ![Chemical Structure] | $^1$H NMR (400 MHz, DMSO) δ 14.49 (s, 1H), 12.71 (s, 1H), 8.92 (s, 1H), 8.15 (s, 1H), 8.04 (d, J = 9.4 Hz, 2H), 7.43 (s, 1H), 7.29 (s, 1H), 4.42 (s, 1H), 2.79 (s, 3H), 1.27 (s, 2H), 1.08 (s, 2H). | 422 | 97% |
| 4-22 | ![Chemical Structure] | $^1$H NMR (400 MHz, MeOD) δ 8.96 (s, 1H), 7.93 (d, J = 9.1 Hz, 1H), 7.55 (d, J = 12.6 Hz, 2H), 7.47 (s, 1H), 7.34 (d, J = 8.1 Hz, 1H), 6.77 (s, 1H), 6.57 (d, J = 7.9 Hz, 1H), 6.51 (s, 1H), 4.29 (s, 1H), 2.78 (s, 3H), 1.36 – 1.24 (m, 2H), 1.20 (s, 2H). | 393 | 90% |
| 4-23 | ![Chemical Structure] | $^1$H NMR (400 MHz, DMSO) δ 14.68 (s, 1H), 11.82 (s, 1H), 8.92 (s, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.70 (s, 1H), 7.50 (d, J = 8.3 Hz, 1H), 7.19 (d, J = 9.4 Hz, 1H), 6.73 (s, 1H), 4.42 (s, 1H), 2.76 (s, 3H), 1.26 (d, J = 6.1 Hz, 2H), 1.07 (s, 2H). | 411 | 90% |
| 4-24 | ![Chemical Structure] | $^1$H NMR (400 MHz, DMSO) δ 14.63 (s, 1H), 11.61 (s, 1H), 8.95 (d, J = 9.5 Hz, 1H), 8.41 (s, 1H), 7.99 (s, 1H), 7.67 (d, J = 9.1 Hz, 1H), 6.52 (s, 1H), 4.43 (s, 1H), 2.78 (s, 3H), 1.25 (s, 2H), 1.08 (s, 2H). | 422 | 90% |
| 4-25 | ![Chemical Structure] | $^1$H NMR (400 MHz, DMSO) δ 14.82 (s, 1H), 11.31 (s, 1H), 8.91 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.45 (s, 1H), 7.41 (s, 1H), 6.99 (d, J = 7.9 Hz, 1H), 6.53 (s, 1H), 4.40 (s, 1H), 2.63 (s, 3H), 1.24 (s, 2H), 1.08 (s, 2H). | 377 | 100% |
| 4-26 | ![Chemical Structure] | $^1$H NMR (400 MHz, DMSO) δ 14.70 (s, 1H), 12.37 (s, 1H), 8.93 (s, 1H), 8.19 (t, J = 9.0 Hz, 2H), 8.01 (d, J = 8.0 Hz, 1H), 7.34 (s, 1H), 7.90 (s, 1H), 4.43 (s, 1H), 2.75 (s, 3H), 1.24 (s, 2H), 1.11 (s, 2H). | 422 | 99% |</p>
<table>
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<tr>
<td>4-27</td>
<td>1H NMR (400 MHz, DMSO) δ 14.73 (s, 1H), 11.45 (s, 1H), 9.17 (s, 1H), 8.92 (s, 1H), 7.99 (d, J = 8.6 Hz, 1H), 7.77 (s, 1H), 7.35 (d, J = 8.5 Hz, 1H), 7.24 (s, 1H), 6.64 (s, 1H), 4.42 (s, 1H), 2.77 (s, 2H), 1.46 (d, J = 29.9 Hz, 9H), 1.25 (s, 2H), 1.05 (s, 2H).</td>
<td>492</td>
</tr>
<tr>
<td>4-28</td>
<td>1H NMR (400 MHz, DMSO) δ 14.67 (s, 1H), 11.94 (s, 1H), 9.97 (s, 2H), 9.83 (s, 1H), 8.02 (d, J = 8.7 Hz, 1H), 7.65 (s, 1H), 7.60 (d, J = 8.6 Hz, 1H), 7.19 – 7.13 (m, 1H), 6.84 (s, 1H), 4.42 (s, 2H), 2.76 (s, 3H), 1.14 – 1.00 (m, 4H).</td>
<td>392</td>
</tr>
<tr>
<td>4-29</td>
<td>1H NMR (400 MHz, DMSO) δ 14.67 (s, 1H), 11.94 (s, 1H), 9.97 (s, 2H), 8.93 (s, 1H), 8.02 (d, J = 8.7 Hz, 1H), 7.65 (s, 1H), 7.60 (d, J = 8.6 Hz, 1H), 7.19 – 7.13 (m, 1H), 6.84 (s, 1H), 4.42 (s, 2H), 2.76 (s, 3H), 1.14 – 1.00 (m, 4H).</td>
<td>391</td>
</tr>
<tr>
<td>4-30</td>
<td>1H NMR (400 MHz, DMSO) δ 14.73 (s, 1H), 11.38 (s, 1H), 9.33 (s, 1H), 8.91 (s, 1H), 7.98 (d, J = 9.1 Hz, 1H), 7.81 (s, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.09 (d, J = 8.7 Hz, 1H), 6.64 (s, 1H), 4.42 (s, 1H), 2.78 (s, 3H), 1.51 (s, 10H), 1.25 (d, J = 8.9 Hz, 2H), 1.08 (dd, J = 14.0, 6.3 Hz, 2H).</td>
<td>492</td>
</tr>
<tr>
<td>4-31</td>
<td>1H NMR (400 MHz, DMSO) δ 14.31 (s, 1H), 11.68 (s, 1H), 8.94 (s, 1H), 8.17 (d, J = 8.7 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 6.80 (s, 1H), 4.44 (s, 1H), 1.25 (d, J = 6.4 Hz, 2H), 1.12 (s, 2H).</td>
<td>397</td>
</tr>
<tr>
<td>4-32</td>
<td>1H NMR (400 MHz, DMSO) δ 14.72 (s, 1H), 11.74 (s, 1H), 9.35 (s, 2H), 8.92 (s, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.34 (s, 1H), 6.94 (d, J = 8.3 Hz, 1H), 6.76 (s, 1H), 4.42 (s, 1H), 2.78 (s, 3H), 1.27 (d, J = 5.6 Hz, 3H), 1.06 (s, 2H).</td>
<td>392</td>
</tr>
<tr>
<td>4-33</td>
<td>1H NMR (400 MHz, DMSO) δ 14.73 (s, 1H), 11.56 (s, 1H), 9.17 (s, 1H), 8.93 (s, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.46 (s, 2H), 7.12 (d, J = 20.9 Hz, 2H), 5.18 – 4.56 (m, 1H), 4.44 (s, 1H), 2.80 (s, 3H), 1.24 (s, 2H), 1.07 (s, 2H).</td>
<td>492</td>
</tr>
<tr>
<td>4-34</td>
<td>1H NMR (400 MHz, DMSO) δ 14.70 (s, 1H), 11.77 (s, 1H), 8.93 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.23 – 7.03 (m, 2H), 6.88 (s, 1H), 6.76 (d, J = 6.4 Hz, 1H), 4.43 (m, 1H), 2.77 (s, 3H), 1.24 (d, J = 6.6 Hz, 2H), 1.12 (s, 2H).</td>
<td>392</td>
</tr>
<tr>
<td>4-35</td>
<td>1H NMR (400 MHz, DMSO) δ 14.28 (s, 1H), 11.79 (s, 1H), 8.94 (s, 1H), 8.17 (d, J = 8.8 Hz, 1H), 7.56 – 7.38 (m, 2H), 7.06 (t, J = 8.8 Hz, 1H), 6.79 (s, 1H), 4.44 (s, 1H), 1.24 (d, J = 6.6 Hz, 2H), 1.12 (s, 2H).</td>
<td>415</td>
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<td>ID</td>
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<td>NMR Data</td>
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<tr>
<td>4-36</td>
<td><img src="image1" alt="Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.28 (s, 1H), 12.16 (s, 1H), 8.95 (s, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 4.2 Hz, 1H), 7.05 (d, J = 8.5 Hz, 2H), 6.85 (s, 1H), 4.43 (s, 1H), 1.24 (s, 2H), 1.13 (s, 2H).</td>
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<tr>
<td>4-37</td>
<td><img src="image2" alt="Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.26 (s, 1H), 12.07 (s, 1H), 8.95 (s, 1H), 8.19 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.29 – 7.07 (m, 2H), 6.81 (s, 1H), 4.44 (s, 1H), 1.25 (s, 2H), 1.13 (s, 2H).</td>
</tr>
<tr>
<td>4-38</td>
<td><img src="image3" alt="Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.28 (s, 1H), 12.04 (s, 1H), 8.95 (s, 1H), 8.19 (d, J = 8.7 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.20 (s, 1H), 6.93 – 6.81 (m, 2H), 4.44 (s, 1H), 1.24 (s, 2H), 1.13 (s, 2H).</td>
</tr>
<tr>
<td>4-39</td>
<td><img src="image4" alt="Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.71 (s, 1H), 11.66 (s, 1H), 10.06 (s, 1H), 8.92 (s, 1H), 8.02 (s, 3H), 7.46 (s, 1H), 7.31 (s, 1H), 7.19 (s, 1H), 7.06 (s, 1H), 6.90 (s, 1H), 4.42 (s, 1H), 3.85 (s, 3H), 2.79 (s, 3H), 1.26 (s, 2H), 1.07 (s, 2H).</td>
</tr>
<tr>
<td>4-40</td>
<td><img src="image5" alt="Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.71 (s, 1H), 11.62 (s, 1H), 10.05 (s, 1H), 8.93 (s, 1H), 7.99 (d, J = 9.2 Hz, 1H), 7.70 (d, J = 7.5 Hz, 2H), 7.28 – 6.87 (m, 6H), 4.42 (s, 1H), 3.75 (s, 3H), 2.68 (s, 3H), 1.25 (d, J = 9.3 Hz, 2H), 1.05 (d, J = 18.8 Hz, 2H).</td>
</tr>
<tr>
<td>4-41</td>
<td><img src="image6" alt="Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.73 (s, 1H), 11.66 (s, 1H), 9.62 (s, 1H), 8.93 (s, 1H), 8.02 (d, J = 8.7 Hz, 1H), 7.72 (s, 1H), 7.21 (s, 1H), 7.12 (s, 1H), 7.04 (s, 1H), 4.44 (s, 1H), 3.05 (s, 1H), 2.82 (d, J = 25.3 Hz, 3H), 1.12 (d, J = 24.4 Hz, 10H).</td>
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<tr>
<td>4-42</td>
<td><img src="image7" alt="Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 11.87 (s, 1H), 9.18 (s, 1H), 8.08 – 7.63 (m, 2H), 7.48 (s, 2H), 7.20 (s, 2H), 6.95 (s, 2H), 4.54 (s, 1H), 4.24 (s, 2H), 2.81 (s, 3H), 1.26 (s, 2H), 1.06 (s, 2H).</td>
</tr>
<tr>
<td>4-43</td>
<td><img src="image8" alt="Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.78 (s, 1H), 11.70 (s, 1H), 8.98 (s, 1H), 8.06 (d, J = 9.0 Hz, 1H), 7.49 (s, 1H), 7.43 (d, J = 7.4 Hz, 1H), 7.20 (s, 1H), 7.00 (d, J = 6.8 Hz, 1H), 6.91 (s, 1H), 4.49 (s, 3H), 2.84 (s, 3H), 1.46 (s, 9H), 1.30 (s, 2H), 1.13 (s, 2H).</td>
</tr>
<tr>
<td>4-44</td>
<td><img src="image9" alt="Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.76 (s, 1H), 12.92 (s, 1H), 8.92 (s, 1H), 8.79 (s, 1H), 8.07 (s, 1H), 7.99 (d, J = 8.6 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 4.40 (s, 1H), 2.62 (s, 3H), 1.25 (d, J = 5.7 Hz, 2H), 1.10 (s, 2H).</td>
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<td>Structure</td>
<td>NMR Data (400 MHz, DMSO) δ</td>
<td>Other Data</td>
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<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>1H NMR (400 MHz, DMSO) δ 11.65 (s, 1H), 9.57 (s, 1H), 8.82 (s, 1H), 7.93 (d, J = 8.3 Hz, 1H), 7.71 (d, J = 5.5 Hz, 1H), 7.19 (s, 1H), 7.09 (s, 1H), 7.00 (s, 1H), 4.32 (s, 1H), 2.72 (d, J = 18.9 Hz, 3H), 1.89 - 1.77 (m, 5H), 1.65 (s, 1H), 1.45 (d, J = 10.5 Hz, 2H), 1.35 - 1.16 (m, 6H), 0.97 (s, 2H).</td>
<td></td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>1H NMR (400 MHz, DMSO) δ 14.69 (s, 1H), 11.94 (s, 1H), 9.39 (s, 1H), 8.92 (s, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.72 (s, 1H), 7.28 (s, 1H), 7.15 (s, 1H), 6.81 (s, 1H), 4.43 (s, 1H), 4.27 - 4.13 (m, 2H), 2.79 (s, 3H), 2.33 (s, 1H), 2.17 (s, 1H), 1.59 (d, J = 14.2 Hz, 2H), 1.26 (s, 5H), 1.07 (s, 2H), 0.85 (dd, J = 54.3, 14.6 Hz, 1H).</td>
<td></td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>1H NMR (400 MHz, DMSO) δ 14.73 (s, 1H), 11.74 (s, 1H), 10.60 (s, 1H), 9.30 (s, 1H), 8.92 (s, 1H), 8.61 (d, J = 7.6 Hz, 1H), 8.11 (d, J = 7.9 Hz, 1H), 8.01 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 6.7 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 6.97 (s, 1H), 4.43 (s, 1H), 2.79 (s, 3H), 1.25 (s, 2H), 1.07 (s, 2H).</td>
<td></td>
</tr>
<tr>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>1H NMR (400 MHz, DMSO) δ 14.70 (s, 1H), 11.74 (s, 1H), 9.76 (s, 1H), 9.83 (s, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.93 (d, J = 6.6 Hz, 1H), 7.32 (d, J = 7.2 Hz, 2H), 3.49 (d, J = 14.6 Hz, 1H), 0.06 (d, J = 14.8 Hz, 1H), 2.37 (dd, J = 27.4, 15.5 Hz, 2H), 2.04 (s, 1H), 1.91 (d, J = 17.7 Hz, 2H), 1.51 (d, J = 11.3 Hz, 1H), 1.41 (d, J = 10.3 Hz, 1H), 1.25 (s, 2H), 1.09 (d, J = 11.8 Hz, 3H), 0.98 (s, 2H), 0.77 (d, J = 22.2 Hz, 3H).</td>
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</tr>
<tr>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>1H NMR (400 MHz, DMSO) δ 14.69 (s, 1H), 11.58 (s, 1H), 10.29 (s, 1H), 8.91 (s, 1H), 8.40 (s, 1H), 8.05 (d, J = 15.6, 8.6 Hz, 2H), 7.93 (s, 2H), 7.83 (d, J = 8.2 Hz, 1H), 7.72 - 7.56 (m, 2H), 7.18 (d, J = 8.0 Hz, 1H), 7.04 (t, J = 8.0 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 6.81 (s, 1H), 4.35 (s, 1H), 2.54 (s, 3H), 1.23 (2H), 1.04 (s, 2H).</td>
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</tr>
<tr>
<td><img src="image6.png" alt="Structure 6" /></td>
<td>1H NMR (400 MHz, DMSO) δ 14.72 (s, 1H), 11.68 (s, 1H), 10.26 (s, 1H), 8.92 (s, 1H), 8.00 (s, 1H), 7.74 (s, 1H), 7.29 (s, 1H), 7.19 (s, 1H), 7.03 (s, 1H), 6.93 (s, 2H), 4.43 (s, 1H), 2.79 (s, 3H), 2.31 (s, 6H), 2.10 (s, 3H), 1.24 (s, 2H), 1.07 (s, 2H).</td>
<td></td>
</tr>
<tr>
<td><img src="image7.png" alt="Structure 7" /></td>
<td>1H NMR (400 MHz, DMSO) δ 14.73 (s, 1H), 11.62 (s, 1H), 10.08 (s, 1H), 8.93 (s, 1H), 8.00 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 8.6 Hz, 2H), 7.18 (d, J = 7.7 Hz, 2H), 7.02 (d, J = 18.7 Hz, 2H), 4.44 (s, 1H), 3.63 (s, 3H), 2.76 (s, 3H), 1.24 (s, 2H), 1.06 (s, 2H).</td>
<td></td>
</tr>
<tr>
<td><img src="image8.png" alt="Structure 8" /></td>
<td>1H NMR (400 MHz, DMSO) δ 14.72 (s, 1H), 11.68 (s, 1H), 9.29 (s, 1H), 8.93 (s, 1H), 8.81 (s, 1H), 8.31 (s, 1H), 8.03 (d, J = 8.9 Hz, 1H), 7.15 (s, 2H), 7.02 (dd, J = 24.0, 8.3 Hz, 2H), 6.94 (s, 1H), 4.44 (s, 1H), 3.91 (s, 3H), 2.80 (s, 3H), 1.25 (d, J = 15.5 Hz, 2H), 1.08 (s, 2H).</td>
<td></td>
</tr>
<tr>
<td>4-53</td>
<td>( ^1H \text{NMR (400 MHz, DMSO)} \delta 14.71 (s, 1H), 11.72 (s, 1H), 10.04 (s, 1H), 8.94 (s, 1H), 8.02 (d, J = 10.3 Hz, 1H), 7.71 (d, J = 7.0 Hz, 1H), 7.24 (s, 1H), 7.15 (d, J = 7.3 Hz, 1H), 7.04 (s, 1H), 4.44 (s, 1H), 3.98 (s, 2H), 3.76 (s, 2H), 3.43 (s, 2H), 3.07 (d, J = 24.3 Hz, 4H), 2.78 (s, 3H), 2.69 (d, J = 10.9 Hz, 1H), 1.26 (s, 2H), 1.08 (s, 2H). )</td>
<td>533</td>
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<tr>
<td>4-54</td>
<td>( ^1H \text{NMR (400 MHz, DMSO)} \delta 14.71 (s, 1H), 11.72 (s, 1H), 10.03 (s, 1H), 8.94 (s, 1H), 8.02 (d, J = 8.9 Hz, 1H), 7.70 (s, 1H), 7.24 (s, 1H), 7.14 (s, 1H), 7.03 (s, 1H), 5.33 (s, 1H), 4.43 (s, 1H), 4.03 (s, 2H), 3.03 (s, 4H), 2.78 (s, 3H), 2.00 (d, J = 7.6 Hz, 2H), 1.24 (s, 9H), 1.08 (s, 2H), 0.85 (s, 2H). )</td>
<td>632</td>
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<tr>
<td>4-55</td>
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<td>491</td>
</tr>
<tr>
<td>4-56</td>
<td>( ^1H \text{NMR (400 MHz, DMSO)} \delta 14.71 (s, 1H), 11.87 (s, 1H), 10.45 (s, 1H), 8.93 (s, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.23 (s, 1H), 7.07 (d, J = 7.9 Hz, 1H), 6.68 (s, 1H), 4.42 (s, 1H), 2.78 (s, 3H), 2.68 (s, 3H), 1.26 (s, 2H), 1.08 (s, 2H). )</td>
<td>490</td>
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<tr>
<td>4-57</td>
<td>( ^1H \text{NMR (400 MHz, DMSO)} \delta 14.78 (s, 1H), 11.75 (s, 1H), 9.64 (s, 1H), 8.92 (s, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.83 (s, 1H), 7.70 (s, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 8.6 Hz, 1H), 4.48 (s, 2H), 4.40 (s, 1H), 2.72 (d, J = 27.2 Hz, 7H), 2.62 (s, 3H), 1.25 (s, 2H), 1.08 (s, 2H). )</td>
<td>M-(Me)(_2)N</td>
</tr>
<tr>
<td>4-58</td>
<td>( ^1H \text{NMR (400 MHz, DMSO)} \delta 14.79 (s, 1H), 9.84 (s, 1H), 8.92 (s, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.7 Hz, 1H), 7.62 (s, 1H), 7.56 (s, 1H), 7.20 (d, J = 8.0 Hz, 1H), 6.63 (s, 1H), 4.64 (s, 2H), 4.39 (s, 1H), 3.57 (s, 2H), 2.88 (s, 6H), 2.65 (d, J = 22.8 Hz, 3H), 1.24 (s, 2H), 1.08 (s, 2H). )</td>
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<tr>
<td>4-59</td>
<td>( ^1H \text{NMR (400 MHz, DMSO)} \delta 14.76 (s, 1H), 11.62 (s, 1H), 9.68 (s, 1H), 8.92 (s, 1H), 7.99 (s, 1H), 6.95 (s, 2H), 6.77 (s, 1H), 6.46 (s, 1H), 4.43 (s, 1H), 2.80 (s, 3H), 1.27 (s, 2H), 1.07 (s, 4H). )</td>
<td>393</td>
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<tr>
<td>4-60</td>
<td>( ^1H \text{NMR (400 MHz, DMSO)} \delta 14.77 (s, 1H), 11.29 (s, 1H), 8.91 (s, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.13 (s, 1H), 6.97 (s, 1H), 6.61 (s, 1H), 4.42 (s, 1H), 3.80 (d, J = 13.7 Hz, 7H), 2.78 (s, 3H), 1.26 (s, 2H), 1.06 (s, 2H). )</td>
<td>437</td>
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<tr>
<td>4-61</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.74 (s, 1H), 11.29 (s, 1H), 8.91 (s, 1H), 8.81 (s, 1H), 7.98 (d, $J = 9.1$ Hz, 1H), 7.27 (d, $J = 8.8$ Hz, 1H), 6.93 (s, 1H), 6.71 (d, $J = 8.4$ Hz, 1H), 6.53 (s, 1H), 4.41 (s, 2H), 2.77 (s, 3H), 1.25 (s, 2H), 1.06 (s, 2H).</td>
</tr>
<tr>
<td>4-62</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.75 (s, 1H), 11.50 (s, 1H), 9.79 (s, 1H), 8.91 (s, 1H), 7.97 (d, $J = 8.7$ Hz, 1H), 7.07 (d, $J = 6.7$ Hz, 1H), 6.86 (s, 1H), 6.60 (s, 2H), 4.41 (s, 1H), 2.76 (s, 3H), 1.23 (s, 2H), 1.08 (s, 2H).</td>
</tr>
<tr>
<td>4-63</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 12.18 (s, 1H), 10.24 (s, 1H), 8.93 (s, 1H), 8.04 (d, $J = 8.8$ Hz, 1H), 7.87 (d, $J = 8.8$ Hz, 2H), 7.78 (d, $J = 7.0$ Hz, 1H), 7.46 (d, $J = 7.3$ Hz, 2H), 7.35 (s, 1H), 4.43 (s, 1H), 2.77 (s, 3H), 1.27 (s, 2H), 1.09 (s, 2H).</td>
</tr>
<tr>
<td>4-64</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.55 (s, 1H), 13.88 (s, 1H), 8.94 (s, 1H), 8.10 (d, $J = 8.4$ Hz, 1H), 8.01 (dd, $J = 14.5, 7.6$ Hz, 2H), 7.62 (s, 1H), 4.44 (s, 1H), 2.71 (s, 3H), 1.24 (s, 2H), 1.08 (s, 2H).</td>
</tr>
<tr>
<td>4-65</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.44 (s, 1H), 11.53 (s, 1H), 8.84 (s, 1H), 8.16 (d, $J = 9.1$ Hz, 1H), 7.95 (d, $J = 7.2$ Hz, 1H), 7.69 (d, $J = 9.7$ Hz, 1H), 7.58 (t, $J = 10.6$ Hz, 1H), 7.42 (d, $J = 7.4$ Hz, 2H), 7.16 (t, $J = 7.5$ Hz, 1H), 7.04 (t, $J = 7.4$ Hz, 1H), 6.62 (s, 1H), 5.77 (s, 1H), 1.77 (d, $J = 17.9$ Hz, 3H).</td>
</tr>
<tr>
<td>4-66</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.79 (s, 1H), 11.42 (s, 1H), 8.70 (s, 1H), 8.04 (d, $J = 8.2$ Hz, 1H), 7.57 (d, $J = 8.2$ Hz, 1H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.25 (s, 1H), 6.96 (d, $J = 8.1$ Hz, 1H), 6.86 (d, $J = 7.7$ Hz, 1H), 6.61 (s, 1H), 4.23 (s, 1H), 2.70 (s, 3H), 1.06 (s, 2H), 0.81 (s, 2H).</td>
</tr>
<tr>
<td>4-67</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 11.76 (s, 1H), 8.71 (s, 1H), 8.16 (d, $J = 4.8$ Hz, 1H), 7.81 (d, $J = 8.8$ Hz, 1H), 7.36 (s, 1H), 5.94 (dd, $J = 3.4, 1.8$ Hz, 1H), 5.10 (s, 1H), 4.22 - 4.08 (m, 1H), 2.33 (s, 3H), 1.09 - 0.88 (m, 4H).</td>
</tr>
<tr>
<td>4-68</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 12.33 (s, 1H), 8.92 (s, 1H), 8.35 (d, $J = 4.4$ Hz, 1H), 7.99 (d, $J = 8.8$ Hz, 1H), 7.87 (s, 1H), 7.77 (d, $J = 7.8$ Hz, 1H), 7.21 (dd, $J = 7.7, 4.0$ Hz, 1H), 4.47 - 4.34 (m, 2H), 2.69 (s, 3H), 1.28 (d, $J = 6.6$ Hz, 2H), 1.10 (s, 2H).</td>
</tr>
<tr>
<td>4-69</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 8.94 (s, 1H), 8.39 (t, $J = 3.1$ Hz, 1H), 8.08 (t, $J = 9.0$ Hz, 2H), 7.22 (dd, $J = 8.1, 4.1$ Hz, 1H), 6.74 (d, $J = 2.9$ Hz, 1H), 4.48 - 4.36 (m, 1H), 2.67 (s, 3H), 1.26 (d, $J = 7.0$ Hz, 4H), 1.09 (s, 4H).</td>
</tr>
<tr>
<td>4-70</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 8.94 (s, 1H), 8.39 (t, J = 3.1 Hz, 1H), 8.07 (t, J = 9.0 Hz, 1H), 7.21 (dt, J = 7.7, 3.7 Hz, 1H), 6.74 (d, J = 2.9 Hz, 1H), 4.50 – 4.32 (m, 1H), 2.67 (s, 3H), 1.33 – 1.19 (d, J = 7.0 Hz, 2H), 1.09 (s, 2H).</td>
</tr>
<tr>
<td>4-71</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.73 (s, 1H), 11.96 (s, 1H), 8.92 (s, 1H), 8.24 (s, 1H), 8.06 (s, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.61 (t, J = 2.8 Hz, 1H), 6.57 (s, 1H), 4.59 – 4.15 (d, 1H), 2.64 (s, 3H), 1.26 (d, J = 6.8 Hz, 2H), 1.09 (s, 2H).</td>
</tr>
<tr>
<td>4-72</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.67 (s, 1H), 13.15 (s, 1H), 8.93 (s, 1H), 8.27 (d, J = 6.1 Hz, 1H), 8.01 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.19 (t, J = 7.1 Hz, 1H), 6.88 (s, 1H), 4.49 – 4.33 (m, 1H), 2.77 (s, 3H), 1.39 – 1.21 (d, J = 7.0 Hz, 2H), 1.15 – 1.01 (m, 2H).</td>
</tr>
<tr>
<td>4-73</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.63 (s, 1H), 12.94 (s, 1H), 8.93 (s, 1H), 8.72 (s, 1H), 8.65 (s, 1H), 8.04 (d, J = 8.7 Hz, 1H), 6.93 (s, 1H), 4.53 – 4.29 (m, 1H), 2.77 (s, 3H), 1.32 – 1.19 (m, 3H), 1.17 – 0.95 (m, 2H).</td>
</tr>
<tr>
<td>4-74</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.65 (s, 1H), 13.00 (s, 1H), 8.94 (s, 1H), 8.53 (s, 1H), 8.04 (d, J = 8 HZ, 1H), 7.69 (dd, J = 4.4, 2.4 Hz, 1H), 7.01 (s, 6H), 4.58 – 4.31 (m, 1H), 2.78 (s, 3H), 1.27 (d, J = 6.9 Hz, 15H), 1.18 – 1.01 (m, 16H).</td>
</tr>
<tr>
<td>4-75</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.57 (s, 1H), 13.95 (s, 1H), 8.94 (s, 1H), 8.58 (s, 2H), 8.09 (d, J = 8.7 Hz, 1H), 7.60 – 7.51 (m, 1H), 4.53 – 4.33 (m, 1H), 2.73 (s, 3H), 1.35 – 1.17 (m, 2H), 1.15 – 1.01 (m, 2H).</td>
</tr>
<tr>
<td>4-76</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 13.25 (s, 1H), 8.99 (s, 1H), 8.36 (d, J = 5.9 Hz, 1H), 8.07 (d, J = 8.7 Hz, 1H), 7.95 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 6.8 Hz, 1H), 4.54 – 4.44 (m, 1H), 2.76 (s, 3H), 1.34 (d, J = 6.8 Hz, 2H), 1.26 – 1.06 (m, 2H).</td>
</tr>
<tr>
<td>4-77</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 12.56 (s, 1H), 8.93 (s, 1H), 8.38 (t, J = 3.6 Hz, 1H), 8.20 (d, J = 7.4 Hz, 1H), 8.02 (d, J = 9.1 Hz, 1H), 7.26 (dd, J = 8.0, 4.1 Hz, 1H), 6.83 (s, 1H), 4.57 – 4.33 (m, 1H), 2.78 (s, 3H), 1.35 – 1.19 (d, J = 6.9 Hz, 2H), 1.15 – 1.01 (s, 2H).</td>
</tr>
<tr>
<td>4-78</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.65 (s, 1H), 12.47 (s, 1H), 11.98 (s, 1H), 8.91 (s, 1H), 7.95 (m, 2H), 6.76 (s, 1H), 4.51 – 4.36 (m, 1H), 2.78 (s, 3H), 1.26 (d, J = 6.9 Hz, 2H), 1.17 – 1.01 (m, 2H).</td>
</tr>
<tr>
<td>4-79</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>(^1)H NMR (400 MHz, DMSO) δ 14.57 (s, 1H), 13.19 (d, (J = 8.5) Hz, 1H), 9.29 (d, (J = 2.9) Hz, 1H), 9.02 (d, (J = 2.4) Hz, 1H), 8.94 (s, 1H), 8.05 (d, (J = 8.8) Hz, 1H), 7.06 (s, 1H), 4.49 - 4.35 (m, 1H), 2.77 (s, 3H), 1.26 (d, (J = 7.2) Hz, 2H), 1.13 - 0.99 (s, 2H).</td>
</tr>
<tr>
<td>4-80</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>(^1)H NMR (400 MHz, DMSO) δ 15.167 (s, 1H), 14.59 (s, 1H), 13.80 (s, 1H), 9.32 (s, 1H), 8.96 (d, (J = 2.3) Hz, 1H), 8.40 (d, (J = 6.1) Hz, 1H), 8.25 (d, (J = 6.0) Hz, 1H), 8.10 (d, (J = 8.4) Hz, 1H), 7.27 (s, 1H), 4.51 - 4.39 (m, 1H), 2.76 (m, 3H), 1.29 - 1.17 (d, (J = 7.0) Hz, 2H), 1.17 - 0.97 (m, 2H).</td>
</tr>
<tr>
<td>4-81</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>(^1)H NMR (400 MHz, DMSO) δ 14.56 (s, 1H), 13.05 (s, 1H), 8.95 (s, 1H), 8.69 (s, 1H), 8.08 (d, (J = 9.1) Hz, 1H), 7.62 (s, 1H), 7.12 (s, 1H), 4.51 - 4.36 (m, 1H), 2.76 (s, 3H), 1.33 - 1.19 (d, (J = 7.1) Hz, 2H), 1.13 - 1.05 (s, 2H).</td>
</tr>
<tr>
<td>4-82</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>(^1)H NMR (400 MHz, DMSO) δ 14.88 (s, 1H), 14.57 (s, 1H), 13.46 (s, 1H), 9.41 (s, 1H), 8.96 (s, 1H), 8.52 (d, (J = 6.5) Hz, 1H), 8.21 - 7.93 (m, 2H), 7.38 (s, 1H), 4.53 - 4.29 (m, 1H), 2.77 (s, 3H), 1.35 - 1.17 (d, (J = 6.7) Hz, 2H), 1.19 - 1.03 (s, 2H).</td>
</tr>
<tr>
<td>4-83</td>
<td><img src="image5" alt="Chemical Structure" /></td>
<td></td>
</tr>
<tr>
<td>4-84</td>
<td><img src="image6" alt="Chemical Structure" /></td>
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</tr>
<tr>
<td>4-85</td>
<td><img src="image7" alt="Chemical Structure" /></td>
<td></td>
</tr>
<tr>
<td>4-86</td>
<td><img src="image8" alt="Chemical Structure" /></td>
<td>(^1)H NMR (400 MHz, DMSO) δ 14.60 (s, 1H), 10.06 (s, 1H), 8.81 (s, 1H), 7.88 (d, (J = 8.5) Hz, 1H), 7.21 (s, 1H), 7.05 (d, (J = 8.1) Hz, 1H), 6.80 (d, (J = 8.1) Hz, 1H), 4.36 (m, 1H), 3.08 (s, 2H), 1.06 (m, 4H).</td>
</tr>
<tr>
<td>4-87</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.57 (s, 1H), 8.91 (s, 1H), 8.03 (d, J = 9.3 Hz, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.56 – 7.22 (m, 3H), 4.57 – 4.32 (m, 3H), 2.84 (s, 3H), 1.27 (m, 2H).</td>
</tr>
<tr>
<td>4-88</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.50 (s, 1H), 13.22 (s, 1H), 8.84 (s, 1H), 8.10 – 7.80 (m, 2H), 7.74 – 7.58 (s, 1H), 7.49 (s, 1H), 4.38 (m, 1H), 2.78 (s, 3H), 1.30 – 1.12 (m, 2H), 1.00 (m, 2H).</td>
</tr>
<tr>
<td>4-89</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.56 (s, 1H), 8.93 (s, 1H), 8.02 (d, J = 9.2 Hz, 1H), 7.76 (dd, J = 8.8, 3.5 Hz, 1H), 7.61 (d, J = 8.6 Hz, 1H), 7.41 (s, 1H), 7.28 (t, J = 9.3 Hz, 1H), 4.43 (m, 1H), 2.82 (s, 3H), 1.26 (d, J = 6.4 Hz, 3H), 1.05 (s, 2H).</td>
</tr>
<tr>
<td>4-90</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 8.88 (s, 1H), 7.95 (d, J = 8.9 Hz, 1H), 7.76 (s, 1H), 7.61 (d, J = 8.9 Hz, 1H), 7.36 (s, 1H), 7.20 (t, J = 9.0 Hz, 1H), 4.35 (m, 1H), 2.76 (s, 3H), 1.30 – 1.09 (m, 3H), 0.96 (s, 2H).</td>
</tr>
<tr>
<td>4-91</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.57 (s, 1H), 8.86 (s, 1H), 7.96 (m, 3H), 7.59 (s, 1H), 7.41 (d, J = 5.1 Hz, 2H), 4.35 (m, 1H), 2.72 (s, 3H), 1.17 (m, 2H), 1.00 (m, 2H).</td>
</tr>
<tr>
<td>4-92</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.65 (s, 1H), 8.86 (s, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.97 (m, 2H), 7.36 (m, 3H), 4.32 (m, 1H), 2.57 (s, 3H), 1.03 (m, 4H).</td>
</tr>
<tr>
<td>4-93</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.51 (s, 1H), 8.92 (s, 1H), 8.32 (d, J = 8.1 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H), 8.05 (t, J = 13.1 Hz, 1H), 7.90 (s, 1H), 7.70 (t, J = 8.2 Hz, 1H), 4.45 (m, 1H), 2.86 (s, 3H), 1.26 (t, J = 11.6 Hz, 2H), 1.10 (d, J = 21.6 Hz, 2H).</td>
</tr>
<tr>
<td>4-94</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.46 (s, 1H), 8.69 (s, 1H), 8.14 (s, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.52 (dd, J = 8.8, 3.5 Hz, 1H), 7.20-7.11 (m, 3H), 4.43 (s, 1H), 2.64 (s, 3H), 1.26 (d, J = 6.4 Hz, 3H), 1.05 (s, 2H).</td>
</tr>
<tr>
<td>4-95</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.55 (s, 1H), 8.94 (s, 1H), 8.05 (d, J = 9.3 Hz, 1H), 7.64 (d, J = 2.9 Hz, 1H), 7.54 (s, 1H), 7.36 (d, J = 6.6 Hz, 2H), 4.44 (m, 1H), 2.85 (s, 3H), 1.34 – 1.19 (m, 2H), 1.06 (s, 2H).</td>
</tr>
<tr>
<td>4-96</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>$^1$H NMR (400 MHz, DMSO) δ 8.91 (s, 1H), 8.38 (s, 1H), 8.04 (d, J = 9.2 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.55 (s, 1H), 4.44 (m, 1H), 2.83 (s, 3H), 1.35 – 1.18 (m, 2H), 1.06 (m, 2H).</td>
</tr>
</tbody>
</table>
$^1$H NMR (400 MHz, DMSO) δ 14.56 (s, 1H), 8.84 (s, 1H), 8.64 (d, $J = 9.1$ Hz, 1H), 7.95 - 7.77 (m, 4H).

2H) 7.53 - 7.33 (m, 2H), 4.45 (m, 1H), 2.83 (s, 3H), 1.27 (d, $J = 6.3$ Hz, 2H), 1.05 (s, 2H).

$^1$H NMR (400 MHz, DMSO) δ 14.51 (s, 1H), 8.86 (s, 1H), 7.55 (d, $J = 9.0$ Hz, 1H), 7.43 (s, 1H), 7.03 (m, 2H).

$^1$H NMR (400 MHz, DMSO) δ 6.14 (m, 2H), 6.77 (d, $J = 7.4$ Hz, 1H), 6.39 (d, $J = 7.4$ Hz, 1H), 4.38 (m, 1H), 2.77 (s, 3H), 1.19 (m, 1H), 0.88 (m, 1H).

$^1$H NMR (400 MHz, DMSO) δ 7.83 (s, 1H), 7.43 (s, 1H), 7.32 (m, 2H), 6.26 (d, $J = 7.4$ Hz, 1H), 4.38 (m, 1H), 2.77 (s, 3H), 1.19 (m, 1H), 0.88 (m, 1H).
Table 5

<table>
<thead>
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<th>Compound No.</th>
<th>R³</th>
<th>R²</th>
<th>R¹</th>
<th>NMR</th>
<th>MS (MH⁺)</th>
<th>HPLC</th>
</tr>
</thead>
<tbody>
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<td>5-1</td>
<td></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>¹H NMR (400 MHz, DMSO) δ 14.72 (s, 1H), 10.91 (s, 1H), 8.89 (s, 1H), 7.94 (d, J = 8.60 Hz, 1H), 7.13 - 6.90 (m, 3H), 4.67 (s, 2H), 4.38 (s, 1H), 2.62 (s, 3H), 1.23 (d, J = 5.80 Hz, 2H), 1.04 (s, 2H).</td>
<td>409</td>
<td>97%</td>
</tr>
<tr>
<td>5-2</td>
<td></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>¹H NMR (400 MHz, DMSO) δ 14.71 (s, 1H), 10.78 (s, 1H), 8.90 (s, 1H), 7.95 (d, J = 8.72 Hz, 1H), 7.41 (s, 1H), 7.22 (d, J = 8.03 Hz, 1H), 7.13 (d, J = 8.17 Hz, 1H), 4.38 (s, 1H), 3.57 (s, 2H), 2.62 (s, 3H), 1.24 (d, J = 6.14 Hz, 2H), 1.05 (s, 2H).</td>
<td>425</td>
<td>98%</td>
</tr>
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<td>5-3</td>
<td></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>¹H NMR (400 MHz, DMSO) δ 14.70 (s, 1H), 10.64 (s, 1H), 8.98 (s, 1H), 8.05 (d, J = 8.72 Hz, 1H), 7.90 (s, 1H), 7.62 (s, 1H), 4.92 (s, 2H), 4.46 (s, 1H), 2.71 (s, 3H), 1.30 (s, 3H), 1.15 (s, 2H).</td>
<td>454</td>
<td>97%</td>
</tr>
<tr>
<td>5-4</td>
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<td>Me</td>
<td>Cyclopropyl</td>
<td>¹H NMR (400 MHz, DMSO) δ 14.66 (s, 1H), 11.39 (s, 1H), 8.90 (s, 1H), 7.96 (d, J = 8.72 Hz, 1H), 7.57 (s, 1H), 7.43 (s, 1H), 4.75 (s, 2H), 4.39 (s, 1H), 2.62 (s, 3H), 1.23 (d, J = 5.26 Hz, 2H), 1.06 (s, 2H).</td>
<td>434</td>
<td>98%</td>
</tr>
<tr>
<td>5-5</td>
<td>OMe</td>
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<td>Cyclopropyl</td>
<td>¹H NMR (400 MHz, DMSO) δ 14.72 (s, 1H), 10.94 (s, 1H), 8.80 (s, 1H), 7.90 (s, 1H), 7.11 (d, J = 26.18 Hz, 2H), 4.87 (s, 2H), 1.15 (s, 4H).</td>
<td>425</td>
<td>98%</td>
</tr>
<tr>
<td>5-6</td>
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<td>Me</td>
<td>Cyclopropyl</td>
<td>¹H NMR (400 MHz, DMSO) δ 14.75 (s, 1H), 10.87 (s, 1H), 8.90 (s, 1H), 7.96 (d, J = 8.58 Hz, 1H), 7.14 (d, J = 8.35 Hz, 1H), 6.97 (d, J = 8.15 Hz, 1H), 6.89 (s, 1H), 4.69 (s, 2H), 4.39 (s, 1H), 2.62 (s, 3H), 1.23 (s, 2H), 1.04 (s, 2H).</td>
<td>409</td>
<td>98%</td>
</tr>
<tr>
<td>5-9</td>
<td></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>¹H NMR (400 MHz, DMSO) δ 14.74 (s, 1H), 10.28 (s, 1H), 8.90 (s, 1H), 7.94 (d, J = 8.20 Hz, 1H), 7.23 (s, 1H), 7.17 (s, 1H), 7.03 (s, 1H), 4.38 (s, 2H), 2.97 (s, 2H), 2.63 (s, 2H), 1.23 (s, 2H), 1.04 (s, 2H).</td>
<td>407</td>
<td>85%</td>
</tr>
<tr>
<td>5-10</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.71 (s, 1H), 11.47 (s, 1H), 11.39 (s, 1H), 8.91 (s, 1H), 7.98 (d, J = 8.50 Hz, 1H), 7.89 (s, 1H), 7.70 (d, J = 8.10 Hz, 1H), 7.35 (d, J = 8.11 Hz, 1H), 4.40 (s, 1H), 3.49 (d, J = 8.70 Hz, 2H), 2.62 (s, 3H), 1.23 (s, 2H), 1.08 (s, 3H).</td>
<td>422</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>5-11</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.67 (s, 1H), 11.96 (s, 1H), 11.63 (s, 1H), 8.92 (s, 1H), 8.69 (s, 1H), 8.34 (s, 1H), 8.00 (d, J = 8.65 Hz, 1H), 4.41 (s, 1H), 2.61 (d, J = 29.62 Hz, 3H), 1.24 (d, J = 5.11 Hz, 2H), 1.09 (s, 2H).</td>
<td>423</td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td>5-12</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.73 (s, 1H), 12.44 – 11.74 (m, 2H), 8.91 (s, 1H), 7.98 (d, J = 8.01 Hz, 1H), 7.53 – 7.03 (m, 3H), 4.39 (s, 1H), 2.61 (s, 3H), 1.20 (s, J = 26.27 Hz, 3H), 1.05 (s, 2H).</td>
<td>422</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>5-13</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.83 (s, 1H), 8.88 (s, 1H), 7.90 (s, 2H), 6.70 (s, 3H), 4.27 (d, J = 77.51 Hz, 4H), 2.60 (d, J = 25.07 Hz, 3H), 1.23 (s, 2H), 1.02 (s, 2H).</td>
<td>395</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>5-14</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.78 (s, 1H), 8.76 (s, 1H), 7.83 (d, J = 9.18 Hz, 1H), 6.92 – 6.81 (m, 2H), 6.70 (d, J = 7.26 Hz, 1H), 6.19 (d, J = 22.26 Hz, 1H), 4.16 (s, 4H), 3.39 (s, 3H), 2.50 (s, 7H).</td>
<td>411</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>5-15</td>
<td>8-N</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.55 (s, 1H), 8.61 (s, 1H), 8.19 (d, J = 11.38 Hz, 1H), 7.55 (d, J = 8.31 Hz, 1H), 7.47 (s, 1H), 6.68 (s, 1H), 6.54 (d, J = 8.26 Hz, 1H), 4.00 (s, 2H), 3.73 (s, 1H), 1.15 – 0.91 (m, 5H).</td>
<td>382</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>5-16</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.90 (s, 1H), 8.94 (s, 1H), 7.94 (d, J = 9.06 Hz, 1H), 6.95 (d, J = 8.81 Hz, 2H), 6.63 (d, J = 7.73 Hz, 1H), 6.14 (s, 1H), 4.43 (s, 1H), 3.31 (s, 2H), 2.79 (s, 2H), 2.70 (s, 3H), 1.90 (s, 2H), 1.30 (s, 2H), 1.08 (s, 2H).</td>
<td>393</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>5-17</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 14.71 (s, 1H), 8.89 (s, 1H), 8.60 (s, 1H), 7.94 (d, J = 8.81 Hz, 1H), 7.67 (s, 1H), 7.10 (s, 1H), 4.38 (s, 1H), 4.27 (s, 2H), 3.63 (s, 2H), 2.66 (s, 3H), 1.24 (d, J = 5.67 Hz, 2H), 1.07 (s, 2H).</td>
<td>440</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>5-18</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 10.19 (s, 1H), 8.89 (s, 1H), 7.91 (d, J = 8.74 Hz, 1H), 6.33 (s, 1H), 6.24 (s, 1H), 4.57 (s, 2H), 4.38 (s, 2H), 2.64 (s, 3H), 1.23 (d, J = 5.42 Hz, 3H), 1.03 (s, 2H).</td>
<td>424</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>5-19</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) δ 8.88 (s, 1H), 7.91 (s, 1H), 6.29 (s, 1H), 6.18 (s, 1H), 4.37 (s, 2H), 4.18 (s, 3H), 3.10 (s, 2H), 2.65 (d, J = 16.81 Hz, 6H), 1.23 (s, 3H), 1.03 (s, 2H).</td>
<td>424</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>5-20</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>1H NMR (400 MHz, DMSO) δ 8.97 (s, 1H), 8.01 (d, J = 9.26 Hz, 1H), 7.85 - 7.65 (m, 2H), 7.64 - 7.40 (m, 1H), 7.36 (s, 1H), 4.46 (s, 1H), 4.32 (s, 3H), 3.63 (s, 3H), 2.74 (s, 3H), 1.30 (d, J = 5.75 Hz, 2H), 1.11 (s, 2H).</td>
<td>396</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>5-21</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>1H NMR (400 MHz, DMSO) δ 14.72 (s, 1H), 8.85 (d, J = 23.76 Hz, 1H), 7.87 (t, J = 19.93 Hz, 1H), 7.17 (s, 1H), 6.99 (d, J = 9.29 Hz, 2H), 4.37 (s, 1H), 4.20 (s, 2H), 3.59 (s, 1H), 3.44 (s, 2H), 2.63 (s, 3H), 1.24 (s, 2H), 1.07 (d, J = 23.80 Hz, 2H).</td>
<td>420</td>
<td>95%</td>
<td></td>
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<tr>
<td>5-22</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>1H NMR (400 MHz, DMSO) δ 8.77 (s, 1H), 7.87 (d, J = 9.24 Hz, 1H), 7.26 (d, J = 10.63 Hz, 1H), 7.17 (s, 1H), 7.04 (s, 1H), 4.20 (s, 3H), 2.00 (dd, J = 7.56, 15.22 Hz, 1H), 1.21 (d, J = 14.05 Hz, 4H).</td>
<td>436</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>5-24</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>1H NMR (400 MHz, DMSO) δ 8.77 (s, 1H), 7.87 (d, J = 9.25 Hz, 1H), 7.75 (s, 1H), 7.20 (s, 1H), 7.14 (s, 1H), 4.17 (s, 3H), 3.47 (s, 3H), 1.32 - 1.05 (m, 8H).</td>
<td>412</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>5-25</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>1H NMR (400 MHz, DMSO) δ 14.82 (s, 1H), 10.92 (s, 1H), 10.86 (s, 1H), 8.96 (s, 1H), 7.98 (t, J = 12.31 Hz, 1H), 7.15 (d, J = 7.60 Hz, 1H), 7.00 (d, J = 8.89 Hz, 2H), 4.44 (s, 1H), 2.67 (s, 3H), 1.28 (s, 2H), 1.12 (s, 2H).</td>
<td>394</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>5-26</td>
<td>OMe</td>
<td>Cyclopropyl</td>
<td>1H NMR (400 MHz, DMSO) δ 14.63 (s, 1H), 10.94 (s, 1H), 10.87 (s, 1H), 8.86 (s, 1H), 7.97 (d, J = 8.82 Hz, 1H), 7.17 (d, J = 7.41 Hz, 3H), 4.29 (s, 1H), 1.23 (s, 4H).</td>
<td>410</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>5-27</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>1H NMR (400 MHz, DMSO) δ 8.95 (s, 1H), 7.96 (d, J = 8.75 Hz, 1H), 6.96 (d, J = 10.17 Hz, 1H), 6.92 (d, J = 8.04 Hz, 1H), 6.72 (d, J = 7.83 Hz, 1H), 4.44 (s, 1H), 3.63 (s, 2H), 3.09 (s, 2H), 2.70 (s, 3H), 1.30 (d, J = 5.29 Hz, 2H), 1.10 (s, 2H).</td>
<td>411</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>5-28</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>1H NMR (400 MHz, DMSO) δ 14.74 (s, 1H), 8.89 (s, 1H), 7.94 (d, J = 8.48 Hz, 1H), 7.53 (s, 1H), 7.44 (s, 1H), 7.33 (d, J = 8.57 Hz, 1H), 6.94 (d, J = 8.45 Hz, 1H), 4.39 (s, 1H), 3.80 (s, 2H), 3.48 (s, 2H), 2.64 (s, 3H), 1.23 (s, 2H), 1.06 (s, 2H).</td>
<td>443</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>5-29</td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>1H NMR (400 MHz, DMSO) δ 14.67 (s, 1H), 10.84 (s, 1H), 8.83 (s, 1H), 7.86 (d, J = 8.65 Hz, 1H), 6.52 (s, 2H), 4.38 (s, 2H), 4.31 (s, 1H), 3.89 (s, 2H), 2.54 (s, 3H), 1.16 (s, 2H), 1.00 (s, 2H).</td>
<td>436</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Functional Group</td>
<td>NMR Data</td>
<td>Percentage</td>
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<tr>
<td>5-30</td>
<td><img src="image" alt="Structure Image" /></td>
<td>OMe, Cyclopropyl</td>
<td>4H NMR (400 MHz, DMSO) δ 14.71 (s, 1H), 10.91 (s, 1H), 8.79 (s, 1H), 7.88 (d, J = 9.15 Hz, 1H), 6.75 (d, J = 14.51 Hz, 2H), 4.45 (t, J = 4.51 Hz, 2H), 4.27 - 4.16 (m, 1H), 3.96 (t, J = 4.53 Hz, 2H), 1.17 (d, J = 7.20 Hz, 4H).</td>
<td>99%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-31</td>
<td><img src="image" alt="Structure Image" /></td>
<td>Me, Cyclopropyl</td>
<td>4H NMR (400 MHz, DMSO) δ 8.94 (s, 1H), 7.95 (d, J = 8.62 Hz, 1H), 6.79 (dd, J = 7.23, 14.68 Hz, 3H), 4.43 (s, 1H), 4.23 (d, J = 10.57 Hz, 1H), 4.06 (d, J = 10.42 Hz, 1H), 3.60 - 3.41 (m, 3H), 2.70 (s, 3H), 1.30 (d, J = 5.98 Hz, 2H), 1.09 (s, 2H).</td>
<td>99%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-32</td>
<td><img src="image" alt="Structure Image" /></td>
<td>Me, Cyclopropyl</td>
<td>4H NMR (400 MHz, DMSO) δ 8.95 (s, 1H), 7.98 (d, J = 8.04 Hz, 1H), 7.09 (s, 1H), 6.96 (s, 2H), 4.44 (s, 1H), 4.15 (s, 2H), 3.29 (s, 3H), 2.69 (s, 3H), 2.02 (s, 2H), 1.30 (s, 2H), 1.10 (s, 2H).</td>
<td>99%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-33</td>
<td><img src="image" alt="Structure Image" /></td>
<td>Me, Cyclopropyl</td>
<td>4H NMR (400 MHz, DMSO) δ 8.76 (s, 1H), 7.77 (d, J = 8.81 Hz, 1H), 6.59 (s, 3H), 4.25 (s, 1H), 4.04 (s, 2H), 3.27 (d, J = 11.94 Hz, 1H), 2.96 - 2.79 (m, 1H), 2.52 (s, 3H), 1.18 (t, J = 8.54 Hz, 3H), 1.12 (d, J = 5.48 Hz, 2H), 0.91 (s, 2H).</td>
<td>98%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-34</td>
<td><img src="image" alt="Structure Image" /></td>
<td>Me, Cyclopropyl</td>
<td>4H NMR (400 MHz, DMSO) δ 8.71 (s, 1H), 7.72 (d, J = 8.62 Hz, 1H), 6.54 (s, 3H), 4.20 (s, 2H), 4.03 (d, J = 10.38 Hz, 2H), 3.52 (t, J = 8.97 Hz, 1H), 3.31 (s, 1H), 2.46 (s, 3H), 1.07 (d, J = 5.70 Hz, 2H), 0.96 (d, J = 4.88 Hz, 3H), 0.86 (s, 2H).</td>
<td>98%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-35</td>
<td><img src="image" alt="Structure Image" /></td>
<td>Me, Cyclopropyl</td>
<td>4H NMR (400 MHz, DMSO) δ 10.57 (s, 1H), 8.89 (s, 1H), 7.93 (d, J = 8.73 Hz, 1H), 7.48 (d, J = 52.24 Hz, 1H), 6.96 (d, J = 7.83 Hz, 1H), 6.80 (s, 1H), 6.74 (d, J = 7.83 Hz, 1H), 4.38 (s, 1H), 3.76 (d, J = 12.76 Hz, 1H), 2.63 (s, 3H), 2.07 (s, 1H), 1.85 (s, 1H), 1.66 (s, 1H), 1.58 - 1.37 (m, 3H), 1.23 (d, J = 6.52 Hz, 2H), 1.06 (s, 2H).</td>
<td>98%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-36</td>
<td><img src="image" alt="Structure Image" /></td>
<td>Cl, Cyclopropyl</td>
<td>4H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 10.70 (s, 1H), 8.92 (s, 1H), 8.09 (d, J = 8.43 Hz, 1H), 7.82 (s, 1H), 7.04 (d, J = 22.18 Hz, 1H), 6.64 (d, J = 10.90 Hz, 2H), 4.52 - 4.28 (m, 3H), 4.01 - 3.82 (m, 2H), 1.20 (t, J = 10.03 Hz, 2H), 1.12 (d, J = 3.28 Hz, 2H).</td>
<td>97%</td>
<td></td>
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</tr>
<tr>
<td>5-37</td>
<td><img src="image" alt="Structure Image" /></td>
<td>8-Me</td>
<td>4H NMR (400 MHz, DMSO) δ 8.85 (d, J = 3.12 Hz, 1H), 7.90 (d, J = 8.88 Hz, 1H), 6.71 (d, J = 5.48 Hz, 3H), 5.23 (d, J = 3.10 Hz, 1H), 5.07 (d, J = 2.78 Hz, 1H), 4.42 - 4.27 (m, 1H), 4.22 - 4.12 (m, 2H), 2.55 (s, 3H), 1.74 (dd, J = 8.97, 14.93, 17.91 Hz, 1H), 1.62 - 1.45 (m, 1H).</td>
<td>98%</td>
<td></td>
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</tr>
<tr>
<td>5-38</td>
<td><img src="image" alt="Structure Image" /></td>
<td>8-Me</td>
<td>4H NMR (400 MHz, DMSO) δ 14.44 (d, J = 137.56 Hz, 2H), 10.82 (d, J = 68.59 Hz, 1H), 8.85 (t, J = 9.38 Hz, 1H), 7.93 (t, J = 10.51 Hz, 1H), 6.56 (t, J = 40.40 Hz, 2H), 4.44 (d, J = 5.45 Hz, 3H), 4.39 - 4.29 (m, 1H), 4.04 - 3.90 (m, 3H), 2.54 (s, 3H), 1.64 (m, 2H).</td>
<td>98%</td>
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</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Ligand</td>
<td>NMR Data</td>
<td>Percentage</td>
<td>Notes</td>
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<tr>
<td>5-39</td>
<td><img src="image1" alt="Structure" /></td>
<td>Cl</td>
<td>Cyclopropyl</td>
<td>98%</td>
<td></td>
<td></td>
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<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 8.92 (s, 1H), 8.10 (d, $J = 8.56$ Hz, 1H), 7.69 (s, 1H), 7.18 (s, 1H), 4.41 (s, 2H), 4.23 - 4.19 (m, 3H), 3.51 (s, 2H), 1.22 (d, $J = 6.34$ Hz, 2H), 1.11 (s, 2H).</td>
<td>416</td>
<td></td>
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<tr>
<td>5-40</td>
<td><img src="image2" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>98%</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.67 (s, 1H), 8.91 (s, 1H), 7.97 (d, $J = 8.68$ Hz, 1H), 7.35 (s, 1H), 6.99 (s, 1H), 4.68 (d, $J = 4.53$ Hz, 2H), 4.58 (d, $J = 4.64$ Hz, 2H), 4.40 (dd, $J = 3.32, 6.77$ Hz, 1H), 2.61 (s, 3H), 1.24 (d, $J = 6.14$ Hz, 2H), 1.10 (s, 2H).</td>
<td>434</td>
<td></td>
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<tr>
<td>5-41</td>
<td><img src="image3" alt="Structure" /></td>
<td>8-OMe</td>
<td>Cyclopropyl</td>
<td>98%</td>
<td></td>
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<tr>
<td></td>
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<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.59 (s, 1H), 10.91 (s, 1H), 8.82 (s, 1H), 7.89 (d, $J = 9.04$ Hz, 1H), 6.74 (d, $J = 14.28$ Hz, 2H), 5.08 (d, $J = 64.31$ Hz, 1H), 4.45 (s, 2H), 4.19 (s, 1H), 3.96 (s, 2H), 1.80 (d, $J = 26.47$ Hz, 1H), 1.65 (dd, $J = 7.14, 16.55$ Hz, 1H).</td>
<td>470</td>
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<tr>
<td>5-42</td>
<td><img src="image4" alt="Structure" /></td>
<td>8-OMe</td>
<td>Cyclopropyl</td>
<td>98%</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 8.80 (s, 1H), 7.86 (d, $J = 9.34$ Hz, 1H), 6.87 (d, $J = 8.16$ Hz, 1H), 6.84 (s, 1H), 6.70 (d, $J = 8.14$ Hz, 1H), 5.18 - 4.96 (m, 1H), 4.17 (s, 3H), 3.36 (s, 2H), 1.84 - 1.58 (m, 2H).</td>
<td>429</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-43</td>
<td><img src="image5" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>90%</td>
<td></td>
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<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.75 - 14.70 (s, 1H), 8.80 - 8.76 (s, 1H), 7.89 - 7.83 (d, $J = 9.4$ Hz, 1H), 6.92 - 6.86 (d, $J = 11.4$ Hz, 1H), 6.77 - 6.73 (s, 1H), 6.16 - 6.10 (s, 1H), 4.27 - 4.15 (s, 3H), 3.47 - 3.41 (s, 3H), 3.40 - 3.34 (q, $J = 3.6$ Hz, 2H), 1.20 - 1.09 (dd, $J = 14.4, 5.5$ Hz, 4H).</td>
<td>429</td>
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<tr>
<td>5-44</td>
<td><img src="image6" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>100%</td>
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<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.77 - 14.65 (s, 1H), 8.80 - 8.76 (s, 1H), 7.89 - 7.83 (d, $J = 9.3$ Hz, 1H), 7.09 - 7.03 (t, $J = 1.6$ Hz, 1H), 6.90 - 6.84 (t, $J = 1.6$ Hz, 1H), 6.19 - 6.10 (s, 1H), 4.26 - 4.15 (m, 3H), 3.48 - 3.39 (s, 5H), 1.20 - 1.09 (ddd, $J = 10.6, 5.5, 3.0$ Hz, 4H).</td>
<td>445</td>
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<tr>
<td>5-45</td>
<td><img src="image7" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>100%</td>
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<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 8.80 - 8.74 (s, 1H), 7.88 - 7.80 (d, $J = 9.3$ Hz, 1H), 6.81 - 6.71 (dd, $J = 17.1, 2.1$ Hz, 2H), 4.28 - 4.18 (tt, $J = 7.2, 4.3$ Hz, 1H), 4.18 - 4.12 (t, $J = 4.2$ Hz, 2H), 3.44 - 3.35 (m, 5H), 2.16 - 2.10 (s, 3H), 1.20 - 1.08 (m, 4H).</td>
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<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 8.79 - 8.76 (s, 1H), 7.87 - 7.81 (d, $J = 9.3$ Hz, 1H), 6.55 - 6.49 (s, 1H), 6.43 - 6.39 (s, 1H), 4.27 - 4.18 (s, 1H), 4.16 - 4.10 (t, $J = 4.3$ Hz, 2H), 3.33 - 3.5 (s, 2H), 2.57 - 2.52 (s, 3H), 1.20 - 1.09 (m, 4H).</td>
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<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.83 - 14.56 (s, 1H), 8.81 - 8.77 (s, 1H), 8.66 - 8.59 (m, 1H), 7.95 - 7.89 (d, $J = 9.3$ Hz, 1H), 7.89 - 7.84 (t, $J = 1.7$ Hz, 1H), 7.24 - 7.19 (s, 1H), 4.30 - 4.18 (m, 3H), 3.67 - 3.60 (q, $J = 3.8$ Hz, 2H), 3.52 - 3.44 (s, 3H), 1.20 - 1.12 (td, $J = 6.5, 5.8, 2.7$ Hz, 4H).</td>
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<td><img src="image2.png" alt="Structure" /></td>
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<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 15.52 - 14.17 (m, 1H), 8.97 - 8.90 (s, 1H), 8.84 - 8.80 (s, 1H), 7.97 - 7.90 (d, $J = 9.0$ Hz, 1H), 7.51 - 7.47 (s, 1H), 7.07 - 7.02 (s, 1H), 4.69 - 4.57 (s, 4H), 4.28 - 4.18 (p, $J = 5.7$ Hz, 1H), 3.42 - 3.35 (s, 3H), 1.21 - 1.12 (d, $J = 5.6$ Hz, 4H).</td>
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<td><img src="image3.png" alt="Structure" /></td>
<td>Me</td>
<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.70 - 14.66 (s, 1H), 8.84 - 8.80 (s, 1H), 7.97 - 7.92 (d, $J = 9.0$ Hz, 1H), 7.75 - 7.74 (s, 1H), 7.08 - 7.04 (s, 1H), 5.00 - 4.94 (t, $J = 4.9$ Hz, 2H), 4.82 - 4.74 (t, $J = 4.8$ Hz, 2H), 4.27 - 4.18 (p, $J = 5.7$ Hz, 1H), 3.43 - 3.38 (s, 3H), 1.21 - 1.13 (d, $J = 5.6$ Hz, 4H).</td>
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<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.72 (s, 1H), 8.94 (s, 1H), 7.87 (d, $J = 9.4$ Hz, 1H), 6.89 (d, $J = 11.4$ Hz, 1H), 6.75 (s, 1H), 6.16 (s, 1H), 4.21 (m, 3H), 3.40 (s, 3H), 1.31 - 0.94 (m, 4H).</td>
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<td>90%</td>
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<tr>
<td>5-51</td>
<td><img src="image5.png" alt="Structure" /></td>
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<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.72 (s, 1H), 8.88 (s, 1H), 7.91 (d, $J = 8.8$ Hz, 1H), 6.91 (s, 1H), 6.67 (s, 1H), 5.67 (s, 1H), 4.48 - 4.30 (m, 1H), 4.20 (m, 2H), 3.43 (m, 2H), 2.70 - 2.56 (m, 3H), 1.24 (d, $J = 4.0$ Hz, 2H), 1.04 (s, 2H).</td>
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<td>Cyclopropyl</td>
<td>$^1$H NMR (400 MHz, DMSO) $\delta$ 14.5 (b, 1H), 8.91 (s, 1H), 8.86 (s, 1H), 7.97 (d, $J = 8.8$ Hz, 1H), 7.34 (s, 1H), 6.90 (s, 1H), 4.63 (s, 4H), 4.39 (mz, 1H), 2.61 (s, 3H), 1.24 (d, $J = 4.6$ Hz, 2H), 1.09 (s, 2H).</td>
<td>420</td>
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<td><img src="image7.png" alt="Structure" /></td>
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<td>521</td>
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<td>$^1$H NMR (400 MHz, DMSO) δ 14.73 (s, 1H), 8.89 (s, 1H), 7.91 (d, $J = 7.8$ Hz, 1H), 6.75 (d, $J = 11.3$ Hz, 1H), 6.59 (s, 1H), 4.37 (m, 1H), 4.22 (s, 2H), 3.39 (s, 2H), 2.65 (s, 3H), 1.22 (m, 2H), 1.00 (m, 2H).</td>
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<td>$^1$H NMR (400 MHz, DMSO) δ 8.90 (s, 1H), 8.05 (d, $J = 8.6$ Hz, 1H), 6.91 – 6.49 (m, 3H), 4.46 – 4.36 (m, 1H), 4.16 (m, 2H), 3.49 (m, 2H), 2.67 (s, 3H), 1.19 (t, $J = 15.1$ Hz, 2H), 1.09 (s, 2H).</td>
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<td>$^1$H NMR (400 MHz, DMSO) δ 8.77 (s, 1H), 8.15 (d, $J = 7.00$ Hz, 1H), 7.24 – 7.02 (m, 2H), 6.78 (d, $J = 8.23$ Hz, 1H), 4.28 – 4.13 (m, 2H), 4.05 – 3.86 (m, 1H), 3.49 – 3.34 (m, 2H), 2.90 (d, $J = 2.66$ Hz, 3H), 1.44 – 1.32 (m, 2H), 1.28 – 1.17 (m, 2H).</td>
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<td>$^1$H NMR (400 MHz, DMSO) δ 15.13 (s, 1H), 8.84 (s, 1H), 8.16 (d, $J = 8.2$ Hz, 1H), 7.71 (s, 1H), 7.20 – 7.06 (m, 2H), 6.73 (t, $J = 16.6$ Hz, 1H), 4.30 (m, 1H), 4.22 – 4.17 (m, 2H), 3.68 (s, 2H), 3.44 (s, 3H), 1.43 – 0.95 (m, 4H).</td>
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<td>$^1$H NMR (400 MHz, DMSO) δ 14.78 (s, 1H), 8.88 (s, 1H), 7.91 (d, J = 8.6 Hz, 1H), 6.95 (d, J = 7.4 Hz, 1H), 6.62 (s, 1H), 6.52 (d, J = 6.8 Hz, 1H), 4.94 (s, 2H), 4.39 (s, 1H), 3.84 (s, 3H), 2.63 (s, 3H), 1.23 (s, 2H), 1.03 (s, 2H).</td>
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<td>$^1$H NMR (400 MHz, DMSO) δ 14.80 (s, 1H), 12.93 (s, 1H), 8.97 (s, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.70 (s, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.38 (d, J = 0.8 Hz, 1H), 4.39 (m, 1H), 3.67 (s, 3H), 2.62 (s, 3H), 1.52 (s, 9H), 1.30 (m, 2H), 1.13 (m, 2H).</td>
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6-54

1H NMR (400 MHz, DMSO) δ 14.58 (s, 1H), 11.65 (s, 1H), 9.83 (s, 1H), 8.16 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.27 (s, 1H), 7.10 (s, 1H), 6.22 (s, 1H), 5.10 (m, 1H), 4.18 (m, 1H), 3.47 (s, 3H), 1.82-1.63 (m, 4H)

6-55

1H NMR (400 MHz, DMSO) δ 14.47 (s, 1H), 8.82 (s, 1H), 8.10 (d, J = 8.7 Hz, 1H), 8.00 - 7.87 (m, 1H), 7.66 (t, J = 9.4 Hz, 1H), 7.37 (t, J = 8.3 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 3.81 (s, 3H).

6-56

1H NMR (400 MHz, DMSO) δ 15.44 - 15.10 (s, 1H), 9.12 - 8.99 (t, J = 1.7 Hz, 1H), 8.03 - 7.92 (dt, J = 3.4, 1.8 Hz, 1H), 7.67 - 7.56 (dd, J = 8.6, 2.5 Hz, 3H), 7.16 - 6.98 (m, 2H), 5.03 - 4.89 (d, J = 7.3 Hz, 1H), 4.60 - 4.47 (d, J = 11.4 Hz, 1H), 4.44 - 4.33 (d, J = 11.5 Hz, 1H), 3.86 - 3.75 (t, J = 1.7 Hz, 3H), 1.53 - 1.42 (d, J = 6.3 Hz, 3H).
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<td>Me</td>
<td>( ^1\text{H NMR (400 MHz, DMSO)} \delta )</td>
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### Table 8-2

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<th>Compound No.</th>
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Table 9

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<th>Compound No.</th>
<th>$R^3$ =</th>
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<td>MW</td>
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<td>327.31</td>
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<td>406.2</td>
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<td>342.36</td>
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</tbody>
</table>
9-24

Me

411.47
Experimental Example 1

**In Vitro Antibacterial Activity**

All compounds were dissolved in dimethyl sulfoxide (DMSO, Merck, purity >99.9%) to achieve final 1 mg/ml desired concentrations.

MICs (minimum inhibitory concentrations) were determined by the broth microdilution technique with 96-well microdilution plates. The antimicrobials were tested using the following MIC ranges: 0.008 to 8 μg/ml. The plates were filled with 100 μl of reinforced clostridial medium (Oxoid; Unipath Ltd., Basingstoke, United Kingdom) per well containing the final antibiotic concentrations. The plates were thawed and preincubated for 3 hours in an anaerobic chamber (Thermal, USA) containing an atmosphere of 80% N₂, 15% CO₂, and 5% H₂. The bacterial inocula were prepared by suspending growth from 48 hours cultures in reinforced clostridial medium. The final inoculum was approximately 1.0 x 10⁵-⁶ CFU/well. The plates were incubated for 48 hours at 37°C in the anaerobic chamber. The MIC was defined as the lowest antibiotic concentration that inhibited visible growth. Ciprofloxacin, vancomycin and metronidazole were used as a positive control. The results are shown in Table 10.
Table 10: MIC of example compounds against *C. difficile* (µg/mL)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>C. difficile ATCC43255</th>
<th>C. difficile ATCC700057</th>
<th>C. difficile ATCC70092</th>
<th>C. difficile IQCC23903</th>
</tr>
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<tbody>
<tr>
<td>2-18</td>
<td>0.016-0.063</td>
<td>0.016-0.063</td>
<td>≤0.008-0.063</td>
<td>0.032-0.063</td>
</tr>
<tr>
<td>2-46</td>
<td>0.032-0.125</td>
<td>0.032-0.25</td>
<td>0.063-0.25</td>
<td>0.125-0.25</td>
</tr>
<tr>
<td>5-14</td>
<td>0.125-0.25</td>
<td>0.125-0.25</td>
<td>0.125-0.25</td>
<td>0.125-0.5</td>
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<td>0.063-0.25</td>
<td>0.063-0.25</td>
<td>0.063-0.25</td>
</tr>
<tr>
<td>3-11</td>
<td>≤0.008-0.032</td>
<td>0.016-0.032</td>
<td>≤0.008-0.032</td>
<td>≤0.008-0.063</td>
</tr>
<tr>
<td>2-31</td>
<td>≤0.008-0.032</td>
<td>0.016-0.032</td>
<td>0.016-0.032</td>
<td>0.016-0.063</td>
</tr>
<tr>
<td>1-2</td>
<td>0.032-0.125</td>
<td>0.032-0.125</td>
<td>0.032-0.125</td>
<td>0.063-0.25</td>
</tr>
<tr>
<td>3-21</td>
<td>0.016-0.032</td>
<td>0.016-0.063</td>
<td>0.016-0.063</td>
<td>0.032-0.063</td>
</tr>
<tr>
<td>2-38</td>
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<td>0.016-0.032</td>
<td>0.032-0.063</td>
<td>0.016-0.032</td>
</tr>
<tr>
<td>3-30</td>
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<td>0.063-0.125</td>
<td>0.063-0.125</td>
<td>0.063-0.25</td>
</tr>
</tbody>
</table>

Experimental Example 2

5 *In Vivo Antibacterial Efficacy*

In *vivo* efficacy was evaluated in a hamster intestinal infection treatment model. Male Golden Syrian hamsters were purchased from Charles River Laboratories (Kingston, NY, USA) and were about 6 weeks of age, with weights ranging from 80 to 100 g at the start of the study. The animals were housed individually in filtered polycarbonate shoe-box style cages equipped with water bottles, and Harlan Teklab Global Diet 2016 was available *ad libitum* via food hoppers. The hamsters were pre-treated with clindamycin (1 mg/kg, p.o.) and vancomycin (50 mg/kg, p.o.), formulated in arabic gum, at Day 0. At Day 7, each hamster was inoculated via oral gavage with 0.5 mL of a suspension of *C. difficile* ATCC 43255 (10⁵ CFU/body, p.o.). To prepare this inoculum, *C. difficile* was grown in GAM agar (Japan) for 5 days at 37°C, and the bacteria were harvested by centrifugation, rinsed twice with arabic gum, resuspended in
arabic gum and the exact bacteria density was determined using the dilution plate count method. Oral dosing of compounds, pulverized and formulated in arabic gum was commenced the following day (Day 8). Treatments were administered once a day for 5 consecutive days at specified doses (10, 2, and 0.4 mg/kg), with five hamsters per group. Controls were included an uninfected group and an infected but untreated group, and vancomycin was used as positive control. The hamsters were observed daily to record clinical signs (duration, time of onset, time of recovery or death), and animals in a lethargic, clearly moribund state were euthanized. A necropsy was performed on animals that were either found dead or were euthanized at the end of the study (37 days). The results are shown in Fig. 1 and Fig. 2.

Preparation Example 1

An injection preparation is prepared from the following components.

<table>
<thead>
<tr>
<th>Components</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 1-2</td>
<td>200 mg</td>
</tr>
<tr>
<td>Glucose</td>
<td>250 mg</td>
</tr>
<tr>
<td>Distilled water for injection</td>
<td>q.s.</td>
</tr>
<tr>
<td>Total</td>
<td>5 ml</td>
</tr>
</tbody>
</table>

Compound 1-2 and glucose are dissolved in distilled water for injection, and the solution is added to a 5 ml ampoule, which is purged with nitrogen gas and then subjected to sterilization at 121°C for 15 minutes to give an injection preparation.

Preparation Example 2

Film coated tablets are prepared from the following components.

<table>
<thead>
<tr>
<th>Components</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 2-18</td>
<td>100 g</td>
</tr>
<tr>
<td>Avicel (registered trademark)</td>
<td>40 g</td>
</tr>
<tr>
<td>Corn starch</td>
<td>30 g</td>
</tr>
</tbody>
</table>
Magnesium stearate 2 g
TC-5 (registered trademark) 10 g
Polyethylene glycol 6000 3 g
Castor oil 40 g
Ethanol 40 g

Compound 2-18, Avicel (registered trademark of microcrystalline cellulose, manufactured by Asahi Kasei Corporation, Japan), corn starch and magnesium stearate are mixed and kneaded, and the mixture is tabletted using a conventional pounder (R 10 mm) for sugar coating (manufactured by Kikusui Seisakusho Ltd., Japan). The tablets thus obtained are coated with a film coating agent consisting of TC-5 (registered trademark of hydroxypropyl methylcellulose, manufactured by Shin-Etsu Chemical Co., Ltd., Japan), polyethylene glycol 6000, castor oil and ethanol to give film coated tablets.

Preparation Example 3

An ointment is prepared from the following components.

<table>
<thead>
<tr>
<th>Components</th>
<th>Amount</th>
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</thead>
<tbody>
<tr>
<td>Compound 3-11</td>
<td>2 g</td>
</tr>
<tr>
<td>Purified lanolin</td>
<td>5 g</td>
</tr>
<tr>
<td>Bleached beeswax</td>
<td>5 g</td>
</tr>
<tr>
<td>White petrolatum</td>
<td>88 g</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100 g</strong></td>
</tr>
</tbody>
</table>

Bleached beeswax is made liquid by heating, and thereto are added compound 3-11, purified lanolin and white petrolatum, and the mixture is heated until it becomes liquid. The mixture is stirred until it is solidified to give an ointment.
1. A compound represented by the formula (I)

\[
\begin{array}{c}
\text{X} \\
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{R}^4 \\
\end{array}
\]

(I)

wherein
X is a hydrogen atom or a fluorine atom;
R is a hydrogen atom or alkyl;
R^1 is (1) cyclopropyl optionally substituted by 1 to 3 halogen atoms or (2) phenyl optionally substituted by 1 to 3 halogen atoms;
R^2 is a hydrogen atom; alkyl optionally substituted by 1 or 2 substituents selected from the group consisting of a halogen atom and hydroxyl; alkoxy; haloalkoxy; a halogen atom; cyano; cyclopropyl; nitro; amino; formyl; alkenyl or alkynyl; or
R^1 and R^2 are bonded to form a 5- or 6-membered ring optionally substituted by alkyl;
R^3 is
(1) a fused heterocyclic group of the formula

\[
\begin{array}{c}
\text{N} \\
\text{R}^4 \\
\text{X}^1 \\
\text{R}^5 \\
\end{array}
\]

(A) or

\[
\begin{array}{c}
\text{N} \\
\text{R}^4 \\
\text{R}^5 \\
\end{array}
\]

(B)

wherein
----- represents a single bond or a double bond,
X^1 is C(R^5) or N,
R^4 is a hydrogen atom or alkyl, and
R^5 is (a) a hydrogen atom,
(b) a halogen atom,
(c) cyano,
(d) nitro,
(e) hydroxy,
(f) alkyl optionally substituted by 1 to 3 halogen atoms,
(g) alkenyl or alkynyl,
(h) aryl, or
(i) alkoxy optionally substituted by 1 to 3 halogen atoms,

when \( X^1 \) is \( C(R^5) \), \( R^4 \) and \( R^6 \) are optionally bonded to form a 5- or 6-membered ring optionally substituted by oxo,

said fused heterocyclic group is optionally substituted by 1 or 2 substituents selected from the group consisting of a halogen atom, cyano, nitro, hydroxy and alkyl,

(2) a group of the formula

\[
\begin{array}{c}
\text{R}^7 \\
\text{N} \\
\text{R}^6 \\
\text{X}^2 \\
\text{X}^1 \\
\end{array}
\]

wherein

\( X^2 \) is \( C(R^5) \) or \( N \), and
\( R^6, R^7 \) and \( R^8 \) are each independently,

(a) a hydrogen atom,
(b) a halogen atom,
(c) cyano,
(d) nitro,
(e) amino,
(f) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, alkoxy and amino,
(g) alkenyl,
(h) alkynyl,
(i) aryl,
(j) formyl or \( CH=NH \),
(k) carboxy,
(l) carbamoyl,
(m) a 5- to 13-membered aromatic heterocyclic group optionally substituted by alkyl, or

(n) alkenyloxy.

(3) a group of the formula

\[
\begin{align*}
\text{(D) } & \\
\text{(E) }
\end{align*}
\]

wherein

- \(X^3\) and \(X^4\) are \(N\), or
- \(X^3\) is \(N\) and \(X^4\) is \(CR''\), wherein \(R''\) is hydrogen atom, amino, hydroxy, alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of alkoxy and dimethylamino or mercapto, or
- \(X^3\) is \(CH\) and \(X^4\) is \(N\),
- \(R'\) is a hydrogen atom or alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of substituted hydroxyl and amino, and
- \(R^5\) is as defined above,

(4) a group of the formula
wherein

- represents a single bond or a double bond and $R^6$ is as
defined above,

(5) 3-pyridyl optionally substituted by 1 or 2 substituents selected from the group consisting of

(a) a halogen atom,
(b) cyano,
(c) nitro,
(d) hydroxy,
(e) amino,
(f) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, alkylamino, dialkylamino and hydroxy,
(g) alkenyl, alkynyl
(h) aryl,
(i) cycloalkyl,
(j) alkoxy,
(k) alkylamino,
(l) dialkylamino,
(m) phenylamino optionally substituted by 1 to 3 halogen atoms,
(n) a cyclic amino group optionally substituted by alkoxy carbonyl,
(o) formyl,
(p) carbamoyl optionally substituted by alkyl optionally substituted by hydroxy, and
(q) a 5- to 10-membered aromatic heterocyclic group optionally substituted by alkyl,

(6) 4-pyridyl optionally substituted by a halogen atom,

(7) 5-pyrimidinyl optionally substituted by 1 or 2 substituents selected from the group consisting of amino, alkylamino, dialkylamino and carboxy,

(8) 2-indolyl, 3-indolyl, 5-indolyl, 6-indolyl, benzofuranyl, benzothiophenyl, benzoazolyl or benzothiazolyl, each optionally substituted by 1 or 2 substituents selected from the group consisting of

(a) a halogen atom,
(b) cyano,
(c) nitro,
(d) hydroxy,
(e) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of amino, alkoxy carbonylamino, alkylamino and dialkylamino,
(f) alkoxy,
(g) formyl,
(h) carboxy, and
(j) amino optionally substituted by 1 or 2 substituents selected from the group consisting of
(i) alkoxy carbonyl,
(ii) alkyl carbonyl optionally substituted by a substituent selected from the group consisting of
(A) cycloalkyloxy optionally substituted by 1 to 3 alkyl,
(B) alkylamino,
(C) dialkylamino,
(D) a cyclic amino group optionally substituted by alkoxy carbonyl, and
(E) a halogen atom,
(iii) phenyl carbonyl optionally substituted by 1 to 3 substituents selected from the group consisting of alkyl and alkoxy,
(iv) cycloalkyl carbonyl,
(v) a 5- to 10-membered aromatic heterocyclic carbonyl group optionally substituted by alkyl optionally substituted by 1 to 3 halogen atoms,
(vi) benzyl carbonyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom and alkoxy,
(vii) arylsulfonyl optionally substituted by alkoxy,
(viii) cycloalkylalkyl sulfonyl optionally substituted by 1 to 3 substituents selected from the
group consisting of alkyl and exo,

(9) a 5- to 10-membered aromatic
heterocyclylsulfonyl group optionally substituted by
1 to 3 alkyl, and

(x) \(-\text{C}(-\text{N}-\text{CN})-\text{SR}^1\) wherein \(\text{R}^1\) is alkyl,

(9) a group of the formula

\[
\begin{align*}
\text{Y}^1 \text{Y}^2 \text{Y}^3 \text{Y}^4 \text{W}^{R^{24}} \\
\text{or} \\
\text{Y}^1 \text{Y}^2 \text{Y}^3 \text{Y}^4 \text{W}^{R^{24}} \\
\end{align*}
\]

wherein

one of \(\text{Y}^1, \text{Y}^2, \text{Y}^3\) and \(\text{Y}^4\) is \(\text{N}\) or \(\text{N}(-\text{CN})\), and the remaining three
are each \(\text{C}(\text{R}^{25})\), \(\text{C}(\text{R}^{25})\) and \(\text{C}(\text{R}^{25})\),

\(\text{W}\) is \(\text{O}, \text{S}, \text{NE}\) or \(\text{N}(\text{R}^{25})\)

\(\text{R}^{25}\) is a hydrogen atom or alkyl, and

\(\text{R}^{26}, \text{R}^{27}, \text{R}^{28}\) and \(\text{R}^{29}\) are each independently,

(a) a hydrogen atom,

(b) cyano, or

(c) nitro,

(10) a group of the formula

\[
\begin{align*}
\text{R}^{28} \text{N} \text{N} \text{N} \text{N} \text{H}^{R^{29}} \\
\text{or} \\
\text{R}^{28} \text{N} \text{N} \text{N} \text{N} \text{H}^{R^{29}} \\
\end{align*}
\]

wherein

\(\text{R}^{28}\) is a hydrogen atom or hydroxy, and

\(\text{R}^{29}\) is a hydrogen atom or alkyl,

(11) a group of the formula
wherein

$X^5$ is $C(R^{11})$ or $N$,

$X^6$ is $CH_2$, $C(=O)$, $O$, $S$, $SO_2$ or $N(R^{12})$,

$X^7$ is $CH(R^{13})$, $C(=O)$ or $N(R^{14})$,

$X^8$ is $CH(R^{15})$ or $C(=O)$,

$R^{10}$, $R^{12}$ and $R^{14}$ are each independently,

(a) a hydrogen atom or

(b) alkyl, and

$R^{11}$, $R^{13}$ and $R^{15}$ are each independently,

(a) a hydrogen atom,

(b) a halogen atom,

(c) cyano,

(d) nitro,

(e) amino,

(f) alkylamino,

(g) dialkylamino,

(h) alkyl optionally substituted by hydroxy, or

(i) alkenyl,

when $X^5$ is $C(R^{11})$, $R^{10}$ and $R^{11}$ are optionally bonded to form a 5- or 6-membered ring optionally substituted by alkyl or oxo, and when $X^6$ is $N(R^{12})$ and $X^7$ is $CH(R^{13})$, $R^{12}$ and $R^{15}$ are optionally bonded to form a 5- or 6-membered ring,

(a) a hydrogen atom,
(b) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of cyano, alkylamino and dialkylamino,
(c) alkenyl optionally substituted by carboxy,
(d) formyl,
(e) carboxy,
(f) carbamoyl,
(g) \(-\text{C}(\text{R}^{17})\text{-N-}\text{OH}\) wherein \(\text{R}^{17}\) is a hydrogen atom, cyano or hydroxy,
(h) a 5- to 10-membered aromatic heterocyclic group optionally substituted by alkyl, alkoxy carbonyl, carboxy or phenyl, or
(i) cyano,

(13) a group of the formula

\[
\begin{align*}
\text{(M)}
\end{align*}
\]

wherein
\(\text{R}^{18}\) is a hydrogen atom or alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom and phenyl,
\(\text{n}\) is 0 or 1,
\(\text{R}^{19}, \text{R}^{20}\) and \(\text{R}^{33}\) are each independently,
(a) a hydrogen atom,
(b) a halogen atom,
(c) cyano,
(d) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of
(i) a halogen atom,
(ii) cyano,
(iii) hydroxy,
(iv) amino,
(v) alkylamino,
(vi) dialkylamino, and
(vii) a cyclic amino group optionally substituted by alkyl,
(e) alkoxy,
(f) amino optionally substituted by 1 or 2 substituents selected from the group consisting of
   (i) alkylcarbonyl optionally substituted by a cyclic amino group,
   (ii) alkylsulfonyl,
   (iii) carbamoyl,
   (iv) alkyl, cycloalkyl or cycloalkylalkyl, and
   (v) 5- to 10-membered saturated heterocyclic group,
(g) carboxy,
(h) alkoxy carbonyl,
(i) carbamoyl optionally substituted by alkyl optionally substituted by amino, alkylation, dialkylation or alkoxy carbonylamino,
(j) formyl,
(k) a 5- to 10-membered aromatic heterocyclic group optionally substituted by alkyl,
(l) -CH=N-OR\(^{21}\) wherein R\(^{21}\) is a hydrogen atom or alkyl optionally substituted by alkylation or dialkylation,
(m) nitro,
(n) a 5- to 10-membered saturated heterocyclic group optionally substituted by amino,
(o) phenyl, or
(p) -NHC(SMe)=CHCN,
(14) a group of the formula

\[ \text{(N)} \]

wherein
R" is (a) a hydrogen atom,
(b) a halogen atom,
(c) cyano,
(d) alkyl optionally substituted by 1 to 3 substituents
selected from the group consisting of a halogen atom
and hydroxy,
(e) alkenyl,
(f) alkynyl,
(g) alkoxy,
(h) formyl,
(i) -CHO, or
(j) carbamoyl,
(15) naphthyl or isochorenchenyl,
(16) quinclinyl or isoquinolyl, or their oxide derivatives,
(17) a group of the formula

\[ \text{[Diagram]} \]

(18) a group of the formula

\[ \text{[Diagram]} \]

wherein

20 U is O or S, and
R" is (a) a hydrogen atom,
(b) a halogen atom,
(c) alkyl optionally substituted by 1 to 3 halogen
atoms,
(d) carboxy,
(e) nitro,
(f) cyano, or
(q) amino,

(19) a group of the formula

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{R}^{32}
\end{array}
\]

wherein

> \( R^{32} \) is (a) a halogen atom,

(b) phenyl, or

(c) a group of the formula

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{H}
\end{array}
\]

or

(20) a group of the formula

\[
\begin{array}{c}
\text{R}^{24} \\
\text{N} \\
\text{R}^{34}
\end{array}
\]

wherein

\( R^{24} \) and \( R^{34} \) are each independently,

(a) a hydrogen atom, or

(b) aminoalkyl,

or

\( R^{24} \) and \( R^{34} \) are bonded to form a 6-membered ring optionally substituted by amino or oxo,

(21) a group of the formula

\[
\begin{array}{c}
\text{R}^{26} \\
\text{O} \\
\text{N}
\end{array}
\]

wherein \( R^{26} \) is

(a) a hydrogen atom,
(b) a halogen atom,
(c) nitro, or
(d) thieryl, or

(22) a group of the formula

\[
\begin{align*}
\text{HN} & \quad \text{HN} \\
\text{HN} & \quad \text{HN} \\
\text{F} & \quad \text{C} \\
\text{O} & \quad \text{N}
\end{align*}
\]

or a salt thereof.

2. The compound of claim 1, wherein X is a fluorine atom, or a salt thereof.

3. The compound of claim 1, wherein \( R^1 \) is a fused heterocyclic group of the formula

\[
\begin{align*}
\text{R}^4 & \quad \text{N} & \quad \text{A} \\
\text{X}^1 & \quad \text{X} & \quad \text{N} & \quad \text{B}
\end{align*}
\]

wherein \( X^1 \) and \( R^1 \) are as defined in claim 1, and said fused heterocyclic group is optionally substituted by 1 or 2 substituents selected from the group consisting of a halogen atom, cyano, nitro, hydroxy and alkyl, or a salt thereof.

4. The compound of claim 1, wherein \( R^1 \) is a group of the formula
wherein $X'$, $R'$ and $R''$ are as defined in claim 1, or a salt thereof.

5. The compound of claim 1, wherein $R'$ is a group of the formula

wherein $X'$, $X''$, $R''$ and $R'$ are as defined in claim 1, or a salt thereof.

6. The compound of claim 1, wherein $R'$ is a group of the formula
wherein ______ and R^6 are as defined in claim 1, or a salt thereof.
7. The compound of claim 1, wherein R³ is a group of the formula

\[
\begin{align*}
R^{22} & \quad \text{H}_2\text{N} \\
& \quad \text{N}
\end{align*}
\]

wherein \( R^{22} \) is

(a) a halogen atom,
(b) cyano,
(c) nitro,
(d) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, alkylamino, dialkylamino and hydroxy,
(e) alkenyl, alkynyl,
(f) aryl,
(g) cycloalkyl,
(h) alkoxy,
(i) formyl, or
(j) carbamoyl optionally substituted by alkyl optionally substituted by hydroxy,

or a salt thereof.

8. The compound of claim 1, wherein R³ is 5-pyrimidinyl substituted by 1 or 2 substituents selected from the group consisting of amino, alkylamino, dialkylamino and carboxy, or a salt thereof.

9. The compound of claim 1, wherein R³ is 2-indolyl optionally substituted by 1 or 2 substituents selected from the group consisting of

(a) a halogen atom,
(b) cyano,
(c) nitro,
(d) hydroxy,
(e) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of amino, alkoxy carbonylamino, alkylamino and dialkylamino,

(f) alkoxy,

(g) formyl,

(h) carboxy, or

(i) amino optionally substituted by 1 or 2 substituents selected from the group consisting of

(i) alkoxy carbonyl,

(ii) alkyl carbonyl optionally substituted by a substituent selected from the group consisting of

(A) cycloalkyloxy optionally substituted by 1 to 3 alkyl,

(B) alkylamino,

(C) dialkylamino,

(D) a cyclic amino group optionally substituted by alkoxy carbonyl, and

(E) a halogen atom,

(iii) phenyl carbonyl optionally substituted by 1 to 3 substituents selected from the group consisting of alkyl and alkoxy,

(iv) cycloalkyl carbonyl,

(v) a 5- to 10-membered aromatic heterocyclic carbonyl group optionally substituted by alkyl optionally substituted by 1 to 3 halogen atoms,

(vi) benzyl carbonyl optionally substituted by 1 to 3 substituents selected from the group consisting of a halogen atom and alkoxy,

(vii) arylsulfanyl optionally substituted by alkoxy,

(viii) cycloalkylalkylsulfanyl optionally substituted by 1 to 3 substituents selected from the group consisting of alkyl and oxo,

(ix) a 5- to 10-membered aromatic heterocyclylsulfanyl group optionally substituted by
1 to 3 alkyl, and

(x) \(-\text{C}(=\text{N-CN})-\text{SR}\) wherein R is alkyl,
or a salt thereof.

5 10. The compound of claim 1, wherein R is a group of the formula

\begin{align*}
\text{(F)} & \quad \text{or} \\
\text{(G)}
\end{align*}

wherein Y, Y, Y, Y, W and R are as defined in claim 1, or a salt thereof.

11. The compound of claim 1, wherein R is a group of the formula

\begin{align*}
\text{(H)} & \quad \text{or} \\
\text{(I)}
\end{align*}

wherein R and R are as defined in claim 1, or a salt thereof.

12. The compound of claim 1, wherein R is a group of the formula

\begin{align*}
\text{(J)} & \quad \text{or} \\
\text{(K)}
\end{align*}

wherein X, X, X, X and R are as defined in claim 1, or a
13. The compound of claim 1, wherein \( R^2 \) is a group of the formula

![Chemical Structure](image)

wherein \( R^{16a} \) is

(a) alkyl optionally substituted by 1 to 3 substituents selected from the group consisting of cyano, alkylamino and dialkylamino,

(b) alkenyl optionally substituted by carboxy,

(c) formyl,

(d) carboxy,

(e) carbamoyl,

(f) \(-\text{C}(\text{R}^{17})=\text{N}-\text{OH}\) wherein \( \text{R}^{17} \) is a hydrogen atom, cyano or hydroxy,

(g) a 5- to 10-membered aromatic heterocyclic group optionally substituted by alkyl, alkoxy carbonyl, carboxy or phenyl, or

(h) cyano,

or a salt thereof.

14. The compound of claim 1, wherein \( R^2 \) is a group of the formula

![Chemical Structure](image)

wherein

\( R^{18a} \) is alkyl, and

\( R^{19a} \) is (a) a halogen atom,

(b) cyano,

(c) alkyl optionally substituted by 1 to 3 substituents
selected from the group consisting of
(i) a halogen atom,
(ii) cyano,
(iii) hydroxy,
(iv) amino,
(v) alkylamino,
(vi) dialkylamino, and
(vii) a cyclic amino group optionally substituted by alkyl,
(d) alkoxy,
(e) amino optionally substituted by 1 or 2 substituents
selected from the group consisting of
(i) alkylcarbonyl optionally substituted by a cyclic amino group,
(ii) alkylsulfonyl,
(iii) carbamoyl, and
(iv) alkyl or cycloalkyl,
(f) carboxy,
(g) alkoxycarbonyl,
(h) carbamoyl optionally substituted by alkyl
optionally substituted by amino, alkylamino, dialkylamino or alkoxycarbonylamino,
(i) formyl,
(j) a 5- to 10-membered aromatic heterocyclic group
optionally substituted by alkyl,
(k) -CH=N-OR\(^{21}\) wherein R\(^{21}\) is a hydrogen atom or alkyl
optionally substituted by alkylamino or dialkylamino, or
(l) nitro,
or a salt thereof.

15. The compound of claim 1, wherein R\(^3\) is a group of the formula
wherein $R^{30}$ is as defined in claim 1, or a salt thereof.

16. The compound of claim 1, wherein $R^3$ is naphthyl or isochromenyl, or a salt thereof.

17. The compound of claim 1, wherein $R^3$ is quinolyl or isoquinolyl, or their oxide derivatives, or a salt thereof.

18. The compound of claim 1, wherein $R$ is a hydrogen atom, or a salt thereof.

19. The compound of claim 1, wherein $R^1$ is cyclopropyl, 2-fluorocyclopropyl or 2,4-difluorophenyl, or a salt thereof.

20. The compound of claim 1, wherein $R^2$ is methyl, methoxy or a chlorine atom, or a salt thereof.

21. A pharmaceutical composition comprising a compound of claim 1 or a salt thereof and a pharmaceutically acceptable carrier.

22. An antimicrobial agent comprising a compound of claim 1 or a salt thereof.

23. A compound of claim 1 or a salt thereof for use as a medicament.

24. A compound of claim 1 or a salt thereof for use as an antimicrobial agent.

25. A compound of claim 1 or a salt thereof for use in the
prevention or treatment of a bacterial infection.

26. Use of a compound of claim 1 or a salt thereof for the manufacture of a medicament for preventing or treating a bacterial infection.

27. A method for preventing or treating a bacterial infection which comprises administering an effective amount of a compound of claim 1 or a salt thereof to a human or an animal.
**Fig. 1**

**Fig. 2**
### INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

See extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

- C07D 215/56
- C07D 411/04
- A61K 31/47
- A61K 31/435

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and where practicable, search terms used)

- WPE, EPDOC, CNKI, CNPAT, CASLINK (STN)
- Keywords: pyridyl, pyrimidinyl, quinolone carboxylate, quinolone, antibacterial, antiviral, bacterial, bactericidal

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of Document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>X</td>
<td>WO99076452A1 (TOYAMA CHEMICAL CO., LTD.) 18 February 1999 (18.02.1999) see (A) 21 compound on page 50, claims 1-10</td>
<td>1-2.12.18-27</td>
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<tr>
<td>A</td>
<td>EP0333964A2 (BAYER AG) 20 November 1989 (29.11.1989) see table 1, examples and claims 1-10</td>
<td>3-4.7-8</td>
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<tr>
<td>X</td>
<td>EP0433962A2 (BAYER AG) 20 November 1989 (29.11.1989) see table 1, examples and claims 1-10</td>
<td>1-2.7-8.18-27</td>
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</table>

**Further documents are listed in the continuation of Box C.**

**See patent family annex**

- **A** document defining the general state of the art which is not considered at particular relevance
- **E** earlier application or patent but published on or after the international filing date
- **L** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- **O** document referring to an oral disclosure, photo, exhibition or other means
- **P** document published prior to the international filing date but later than the priority date claimed
- **T** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- **X** document of particular relevance the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- **Y** document of particular relevance the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- **&** document member of the same patent family

**Date of the actual completion of the international search**

12 November 2012 (12.11.2012)

**Date of mailing of the international search report**


**Name and mailing address of the ISA/CA**

The State Intellectual Property Office, the P.R. China, 6 XueYingHui Rd., Jiamen Bridge, Haidian District, Beijing, China 100080

**Form FCT 895 (second sheet) (July 2009)**

**Authorized officer**

SUN, Wenqian

**Telephone No.**: 186-10-82246724
# INTERNATIONAL SEARCH REPORT

**Box No. II**  
Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **Claim No.: 27**  
   - because it relates to the subject-matter not required to be searched by this Authority, namely:
     - Although claim 27 is directed to a method of treatment of the human-animal body, the search has been carried out and based on the alleged effects of the compounds.

2. **Claims Nos.: 1-2, 5-6, 9-11, 13-17, 18-20**  
   - because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
     - see earlier sheet.

3. **Claim Nos.:**  
   - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 64(a).

**Box No. III**  
Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. **Yes**  
   - As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. **No**  
   - As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of additional fee.

3. **Yes**  
   - As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid specifically claims Nos.:

4. **No**  
   - No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.:

**Remark on protest**

- **Yes**  
  - The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

- **No**  
  - The additional search fees were not accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

- **No**  
  - No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (29 July 2009))
<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
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<tr>
<td>A</td>
<td>CN1299356A (TOYAMA CHEMICAL CO. LTD.) 13 June 2001 (13.06.2001) see paragraphs 1-13,15-16,18-25,27-36,37-101,105 compound and claims 1-7</td>
<td>3-4,12</td>
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<td>A</td>
<td>US4797499A (PFIZER INC.) 16 January 1989 (10.01.1989) see examples and from line 50 of column 1 to line 40 of column 2</td>
<td>1-2.7.8.18-27</td>
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

<table>
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<tr>
<th>Patent Documents referred in the Report</th>
<th>Publication Date</th>
<th>Patent Family</th>
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<tr>
<td>CN 1299356 A</td>
<td>15.06.2001</td>
<td>WO 9951888 A1</td>
<td>14.10.1999</td>
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<tr>
<td></td>
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<td>EP 1970015 A1</td>
<td>24.01.2001</td>
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<td>BR 9909156 A</td>
<td>02.10.2001</td>
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<td>KR 20010042463 A</td>
<td>25.05.2001</td>
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<td>US 6334447 B1</td>
<td>01.01.2002</td>
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<td>JP 2000543380 T2</td>
<td>29.11.2002</td>
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<td>JP 22461764 B2</td>
<td>18.11.2002</td>
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<td>IN 2009000087 E</td>
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<td>CN 1152029 C</td>
<td>02.06.2004</td>
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<td>EP 1970012 B1</td>
<td>18.10.2006</td>
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<td>DE 69936860 E</td>
<td>30.11.2006</td>
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<td>KR 100350078 B1</td>
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<td>ES 2273474 T3</td>
<td>01.05.2007</td>
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<td>23.08.2007</td>
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<td>CA 2273428 C</td>
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<td>IN 2211946 B</td>
<td>20.04.2008</td>
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<tr>
<td>US 4799456 A</td>
<td>10.04.1989</td>
<td>NONE</td>
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</table>
The subject-matter of claim 1 is broader than the compounds which have been synthesized and tested in the description. To comply with PCT Article 6, the breadth of the claims should represent a reasonable generalization over the examples provided with test data. The present claims, by contrast, define a vast range of compounds, and in many cases the compounds cannot be regarded as equivalents or obvious modifications of the examples. The exemplary compounds of which the antibacterial activity has been tested all share a common structure: the 1,4-dihydroquinol-4-one-3-carboxylate/carboxylic acid with the substituent R3 of (I), (II), (III), (IV) as the general definition of claim 1. The other subject-matter of claim 1 is not considered to be a reasonable generalization of the examples. In this regard, the description is not enabling for the full scope of claimed subject-matter and thus does not comply with PCT Article 6.

Accordingly, the search was restricted to those claimed compounds which appear to be supported and a generalization of their structure formulae, namely to compounds as defined in part of claims 1-2, 10-16 and claims 3-4, 7-8, 12.

At continuance: CLASSIFICATION OF SUBJECT MATTER
W07D 215-50 (2004.01)
W07D 421-04 (2006.01)
A61K 31-37 (2006.01)
A61K 31-03 (2006.01)
Title: 2-A-(dihydro-4-nitrimidazo[1,2-b]oxazole compounds for the treatment of tuberculosis)

![Chemical Structure](image)

(57) Abstract: The present invention provides a 2,3-dihydro-4-nitrimidazo[1,2-b]oxazole compound represented by the following general formula: 

$$
\text{O}_2 \text{N} \quad (\text{CH}_2\text{R})_2 \quad \{1\}
$$

This general formula (1). R represents a hydrogen atom or C1-C6 alkyl group, n represents an integer of 0 to 6, R1 and 4CH2R may form a spiro ring represented by the formula (30) below; together with the adjacent carbon atom in the formula below, RRR represents a piperidyl group which may have substituents on the piperidine rings. 

(30) and R2 represents a benzothiazolyl group, quinolinyl group, pyridinyl group or the like. The present compound has an excellent bactericidal action against Mycobacterium tuberculosis, multi-drug-resistant Mycobacterium tuberculosis, and atypical acid-fast bacteria.
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For two-letter codes and other abbreviations refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
DESCRIPTION

2,3-DIHYDRO-6-NITROIMIDAZO (2,1-B) OXAZOLE COMPOUNDS FOR THE TREATMENT OF TUBERCULOSIS

TECHNICAL FIELD

The present invention relates to a 2,3-dihydroimidazo[2,1-b]oxazole compound.

BACKGROUND ART

From among acid-fast bacteria, human Mycobacterium tuberculosis has been widely known. It is said that the one-third of the human population is infected with this bacterium. In addition to the human Mycobacterium tuberculosis, Mycobacterium africanum and Mycobacterium bovis have also been known to belong to the Mycobacterium tuberculosi group. These bacteria are known as Mycobacteria having a strong pathogenicity to humans.

Against these tuberculoses, treatment is carried out using three agents, rifampicin, isoniazid, and ethambutol (or streptomycin) that are regarded as first-line agents, or using four agents such as the above three agents and pyrazinamide.

However, since the treatment of tuberculosis requires extremely long-term administration of agents, it might result in poor compliance, and the treatment often ends in failure.

Moreover, in respect of the above agents, it has been reported that rifampicin causes hepatopathy,
flu syndrome, drug allergy, and its concomitant administration with other drugs is contraindicated due to P450-associated enzyme induction; that isoniazid causes peripheral nervous system disorder and induces serious hepatopathy when used in combination with rifampicin; that ethambutol brings on failure of eyesight due to optic nerve disorder; that streptomycin brings on diminution of the hearing faculty due to the 8th cranial nerve disorder; and that pyrazinamide causes adverse reactions such as hepatopathy, gouty attack associated with increase of uric acid level, vomiting (A Clinician’s Guide To Tuberculosis, Michael D. Iseman 2000 by Lippincott Williams & Wilkins, printed in the USA, ISBN 0-7817-1749-3, Tuberculosis, 2nd edition, Fumiyuki Kuze and Takehide Izumi, Igaku-Shoin Ltd., 1992).

Actually, it has been reported that cases where the standard chemotherapy could not be carried out due to the adverse reactions to these agents made up 70% (approximately 23%, 52 cases) of the total cases where administration of the agents was discontinued (the total 228 hospitalized patients who were subject to the research) (Kekkaku, Vol. 74, 77-82, 1999).

In particular, hepatotoxicity, which is induced by rifampicin, isoniazid, and ethambutol out of the 5 agents used in combination for the aforementioned first-line treatment, is known as an adverse reaction that is developed most frequently. At the same time,
Mycobacterium tuberculosis resistant to antitubercular agents, multi-drug-resistant Mycobacterium tuberculosis, and the like have been increasing, and the presence of these types of Mycobacterium tuberculosis makes the treatment more difficult.

According to the investigation made by WHO (1996 to 1999), the proportion of Mycobacterium tuberculosis that is resistant to any of the existing antitubercular agents to the total types of Mycobacterium tuberculosis that have been isolated over the world reaches 19%, and it has been published that the proportion of multi-drug-resistant Mycobacterium tuberculosis is 5.1%. The number of carriers infected with such multi-drug-resistant Mycobacterium tuberculosis is estimated to be 60,000,000, and concerns are still rising that multi-drug-resistant Mycobacterium tuberculosis will increase in the future (April 2001 as a supplement to the journal Tuberculosis, the "Scientific Blueprint for TB Drug Development.")

In addition, the major cause of death of AIDS patients is tuberculosis. It has been reported that the number of humans suffering from both tuberculosis and HIV reaches 10,700,000 at the time of year 1997 (Global Alliance for TB drug development). Moreover, it is considered that the mixed infection of tuberculosis and HIV has an at least 30 times higher risk of developing tuberculosis than the ordinary
circumstances.

Taking into consideration the aforementioned current situation, the profiles of the desired antitubercular agent is as follows: (1) an agent, which is effective even for multi-drug-resistant *Mycobacterium tuberculosis*, (2) an agent enabling a short-term chemotherapy, (3) an agent with fewer adverse reactions, (4) an agent showing an efficacy to latent infecting *Mycobacterium tuberculosis* (i.e., latent *Mycobacterium tuberculosis*), and (5) an orally administrable agent.

Examples of bacteria known to have a pathogenicity to humans include offending bacteria of recently increasing MAC infection (*Mycobacterium avium*-intracellulare complex infection) such as *Mycobacterium avium* and *Mycobacterium intracellulare*, and atypical acid-fast bacteria such as *Mycobacterium kansasii*, *Mycobacterium marinum*, *Mycobacterium simiae*, *Mycobacterium scrofulaceum*, *Mycobacterium szulgai*, *Mycobacterium xenopi*, *Mycobacterium malmöense*, *Mycobacterium haemophilum*, *Mycobacterium ulcerans*, *Mycobacterium shimoidei*, *Mycobacterium fortuitum*, *Mycobacterium chelonae*, *Mycobacterium smegmatis*, and *Mycobacterium aurum*.

Nowadays, there are few therapeutic agents effective for these atypical acid-fast bacterial infections. Under the presence circumstances, antitubercular agents such as rifampicin, isoniazid,
ethambutol, streptomycin and kanamycin, a new quinolone agent that is a therapeutic agent for common bacterial infections, macrolide antibiotics, aminoglycoside antibiotics, and tetracycline antibiotics are used in combination.

However, when compared with the treatment of common bacterial infections, the treatment of atypical acid-fast bacterial infections requires a long-term administration of agents, and there have been reported cases where the infection is changed to an intractable one, finally leading to death. To break the aforementioned current situation, the development of an agent having a stronger efficacy is desired.

For example, National Publication of International Patent Application No. 11-508270 (WO97/01552) discloses that a 6-nitro-1,2,3,4-tetrahydro[2,1-b]-imidazopyran compound has a bactericidal action in vitro to *Mycobacterium tuberculosis* (H37Rv strain) and multi-drug-resistant *Mycobacterium tuberculosis*, and that the above compound has a therapeutic effect to a tuberculosis-infected animal model when it is orally administered and thus useful as antitubercular agent.

However, the compound described in the above publication differs from the compound of the present invention in terms of the basic skeleton, and it is considered to be a compound nonsimilar to the inventive compound.

Kuppsuwamy Nagarajan et al. have reported on
European Journal of Medicinal Chemistry, 1989, Vol. 24, pp. 631-633 that compounds represented by the following general formula (I):

![Chemical Structure](attachment:image)

(II)

wherein R' represents a hydrogen atom or methyl group and -(CH₃)ₙR² represents a chloromethyl group, Cl-C7 alkyl group, isopropoxyethyl group, 3-propenyloxyethyl group, or unsubstituted phenoxyethyl group, and compounds represented by the same above general formula (I), wherein R¹ and -(CH₃)ₙR² bind to each other to form a cyclopentane or cyclohexane ring (16 types of compounds in total) have a bactericidal action to Mycobacterium tuberculosis (H37Rv strain).

However, the above publication describes that only the 4 types of compounds out of the above compounds are effective when they are orally administered. It also describes that the compound having the highest activity, that is, the compound (CGI-17341) represented by the above general formula (II) wherein R² represents a hydrogen atom and -(CH₃)ₙR² represents ethyl, was found to have mutagenicity, and that accordingly, the development of these series of compounds as agents were abandoned.

In addition, Dilip R. Astekar et al. have reported on Antimicrobial Agents and Chemotherapy, Feb. 1993, pp. 183-186 about the antimicrobial profile of
the above compound CGI-17341. According to the report, the compound CGI-17341 has a bactericidal action to 
*Mycobacterium tuberculosis* (H37Rv strain) and multi-

drug-resistant *Mycobacterium tuberculosis*, but it does 
not have the activity to atypical acid-fast bacteria, 
*M. avium, M. intracellulare*, and *M. fortuitum* when it 
is used at 250 μg/ml or less.

Moreover, Journal of Medicinal Chemistry, 
1981, Vol. 24, pp. 601-604 discloses that 6-nitro-2,3-

10 dihydroimidazo[2,1-b]oxazole compounds have a 
radiosensitizing ability for hypoxic mammalian cells.

DISCLOSURE OF THE INVENTION

It is an object of the present invention to 
provide a compound having an excellent bactericidal 
action to *Mycobacterium tuberculosis* and multi-drug-

15 resistant *Mycobacterium tuberculosis*.

It is another object of the present invention 
to provide a compound having an excellent bactericidal 
action to atypical acid-fast bacteria.

As a result of intensive studies, the present 

inventors have succeeded in synthesizing a novel 2,3-
dihydroimidazo[2,1-b]oxazole compound, which has an 

20 excellent bactericidal action to *Mycobacterium 
tuberculosis*, multi-drug-resistant *Mycobacterium 
tuberculosis*, and atypical acid-fast bacteria. The 
present invention have completed based on such 
findings.
The present invention provides a 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound represented by the following general formula (1), optically active form thereof, or pharmaceutically acceptable salt thereof:

![Chemical structure](image)

wherein $R^1$ represents a hydrogen atom or a C1-C6 alkyl group, 

$n$ represents an integer between 0 and 6, 

$R^1$ and $-(CH_2)_nR^2$ may bind to each other together with carbon atoms adjacent thereto, so as to form a spiro ring represented by general formula (30):

![Spiro ring](image)

wherein $RRR$ represents a piperidyl group (wherein, on the piperidine ring, at least one phenoxy group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), and

$R^2$ represents a group described in any one of the following (a) to (y):

(a) a phenyl group (wherein, on the phenyl ring, at least one piperidyl group may be substituted
[wherein, on the piperidine ring, at least one phenoxy group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)];

(b) a benzothiazolylxloxy group (wherein, on the benzothiazole ring, at least one selected from the group consisting of the following (b-1) to (b-5) may be substituted:

(b-1) a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted),

(b-2) a piperazinyl group (wherein, on the piperazine ring, at least one selected from the group consisting of a phenyl C1-C6 alkyl group (wherein, on the phenyl group, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a phenyl C2-C6 alkenyl group (wherein, on the phenyl group, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted).]
10 substituted or unsubstituted C1-C6 alkoxy group, may be substituted), and a phenyl group (wherein, on the phenyl group, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), may be substituted).

(b-3) a piperidyl group (wherein, on the piperidine ring, at least one selected from the group consisting of an amino group (wherein, on the amino group, at least one selected from the group consisting of a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted) and a C1-C6 alkyl group may be substituted), a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), and a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), may be substituted).

(b-4) a pytrolyl group (wherein, on the
pyrrole ring, at least one selected from the group consisting of a C1-C6 alkyl group and a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), and (b-5) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted));

(c) a quinolyloxy group (wherein, on the quinoline ring, at least one selected from the group consisting of the following (c-1) to (c-4) may be substituted:

(c-1) a halogen atom,
(c-2) a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted),
(c-3) a piperazinyl group (wherein, on the piperazine ring, at least one selected from the group consisting of a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted),

(c-4) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-5) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-6) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-7) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-8) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-9) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-10) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-11) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-12) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-13) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-14) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-15) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-16) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-17) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-18) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-19) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-20) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-21) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-22) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-23) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-24) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(c-25) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)
consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted}, a phenyl group (wherein, on the phenyl ring, at least one group selected from the group consisting of a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), and a phenyl C2-C6 alkenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], may be substituted; and

c-4) a piperidyl group (wherein, on the piperidyl ring, at least one selected from the following group may be substituted: an amino group (wherein, on the amino group, at least one selected from the group consisting of a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy
group, may be substituted) and a C1-C6 alkyl group may be substituted); a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a pheny1 C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a C1-C6 alkoxy group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a pheny1 C1-C6 alkoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a naphthyl C1-C6 alkyl group; and a phenyl C1-C6 alkylidene group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted));
(d) a pyridyloxy group [wherein, on the pyridine ring, at least one selected from the group consisting of the following (d-1) and (d-2) may be substituted:

(d-1) a piperidyl group [wherein, on the piperidine ring, at least one selected from the group consisting of a phenoxy group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]; a phenyl C1-C6 alkoxy substituted C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], a phenoxy C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], and a phenyl C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], may be substituted]; and

(d-2) a piperazinyl group [wherein, on the
piperazine ring, at least one selected from the group consisting of a C1-C6 alkoxy carbonyl group, a furyl C1-C6 alkyl group [wherein, on the furan ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)], a pyridyl C1-C6 alkyl group [wherein, on the pyridine ring, at least one selected from the group consisting of a furyl group and a phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)], a benzothienyl C1-C6 alkyl group (wherein, on the benzothiophene ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a benzofuranyl C1-C6 alkyl group [wherein, on the benzofuran ring, at least one selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted], a benzofuryl C2-C6 alkenyl group [wherein, on the
benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted], a thiazoly1 Cl-C6 alkyl group [wherein,
on the thiazole ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]), a phenoxy Cl-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted], an indolyl Cl-C6 alkyl group [wherein, on the indole ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted], and a phenyl Cl-C6 alky1 group [wherein, on the phenyl ring, at least one selected from the group consisting of a benzofuryl group, a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group, may be
substituted; may be substituted});

(e) a 1,2,3,4-tetrahydroquinolyoxy group

[wherein, on the 1,2,3,4-tetrahydroquinoline ring, at
least one selected from the group consisting of an oxo
group, a phenyl group [wherein, on the phenyl ring, at
least one selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted

C1-C6 alkyl group, and a halogen substituted or
unsubstituted C1-C6 alkoxy group, may be substituted],

and a phenyl C1-C6 alkyl group [wherein, on the phenyl
ring, at least one selected from the group consisting
of a halogen atom, a halogen substituted or

unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group, may be
substituted], may be substituted});

(f) a 1,2,3,4-tetrahydronaphthyloxy group

[wherein, on the 1,2,3,4-tetrahydronaphthalene ring, at

least one oxo group may be substituted];

(g) a 2H-chromenyloxyl group [wherein, on the

2H-chromene ring, at least one oxo group may be

substituted];

(h) a naphthyloxy group [wherein, on the

naphthalene ring, at least one piperidyl group may be

substituted [wherein, on the piperidine ring, at least

one phenoxy group may be substituted] [wherein, on the

phenyl ring, at least one selected from the group]
consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted));

(i) a 1,2,3,4-tetrahydroisoquinolyloxy group (wherein, on the 1,2,3,4-tetrahydroisoquinoline ring, at least one selected from the group consisting of a C1-C6 alkoxy carbonyl group, a phenyl C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], and a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]);

(j) a group -NR'R'' (wherein R'' represents a hydrogen atom or C1-C6 alkyl group, and R' represents at least one selected from the following (j-1) to (j-5):

(j-1) a phenyl group [wherein, on the phenyl ring, at least one piperidyl group is substituted

(j-2) a phenyl group [wherein, on the piperidine ring, at least one phenoxy group may be substituted [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted
C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(j-2) a phenyl C1-C6 alkyl group [wherein, on the phenyl ring, at least one group selected from the group consisting of a piperidyl group (wherein, on the piperidine ring, a phenoxy group is substituted [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]) and a group -NR²R⁸ (wherein R² represents a hydrogen atom or C1-C6 alkyl group, and R⁸ represents a phenyl C2-C6 alkenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]), is substituted],

(j-3) a piperidyl C1-C6 alkyl group [wherein, on the piperidine ring, at least one phenyl group is substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]),

(j-4) a thiazolyl group [wherein, on the thiazole ring, at least one group selected from the
group consisting of a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a piperazinyl C1-C6 alkyl group (wherein, on the piperazine ring, at least one phenyl group may be substituted [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]), and a piperidyl C1-C6 alkyl group (wherein, on the piperidine ring, at least one phenoxy group may be substituted [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]); may be substituted], and (j-5) a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]);

(k) a benzoxazolyl group (wherein, on the benzoxazole ring, at least one selected from the group consisting of a piperazinyl group [wherein, on the
piperazine ring, at least one selected from the group consisting of a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), and a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a piperidyl group (wherein, on the piperidine ring, at least one selected from the group consisting of a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted) and an amino group (wherein, on the amino group, at least one selected from the group consisting of a C1-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), may be substituted), or
least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted;,

(1) a benzoimidazolylloxy group (wherein, on the benzimidazole ring, at least one selected from the group consisting of a Cl-C6 alkyl group, a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted], a piperidyl group [wherein, on the piperidine ring, at least one phenoxyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted; may be substituted]), a piperazinyl group [wherein, on the piperazine ring, at least one phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted; may be substituted] and a phenyl Cl-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), may be substituted); 

(m) a 1,2,3,4-tetrahydroisoquinolyl group

(wherein, on the 1,2,3,4-tetrahydroisoquinoline ring, at least one selected from the group consisting of the following (m-1) and (m-2) may be substituted:

(m-1) an amino group (wherein, on the amino group, at least one selected from the group consisting of a C1-C6 alkyl group, a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), and a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), may be substituted) and

(m-2) a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted));

(n) a piperidyl group (wherein, on the piperidine ring, at least one selected from the group
consisting of the following (n-1) to (n-4) may be substituted:

(n-1) a phenyl group [wherein, on the phenyl ring, at least one group -NR²⁶R²⁷ is substituted [wherein R²⁶ represents a hydrogen atom or Cl-C6 alkyl group, and R²⁷ represents a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]],

(n-2) a group -W₁NR²⁸R²⁹ [wherein W₁ represents a Cl-C6 alkyiene group, R²₈ represents a hydrogen atom or Cl-C6 alkyl group, and R²⁹ represents a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted)],

(n-3) a Cl-C6 alkoxy group wherein two phenyl groups are substituted [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted],

and

(n-4) a phenyl Cl-C6 alkyl group [wherein, on the phenyl group ring, at least one phenyl group is
substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted));

(o) a piperazinyl group (wherein, on the piperazine ring, at least one selected from the following group is substituted: a C1-C6 alkyl group wherein two phenyl groups are substituted [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], a phenyl C1-C6 alkyl group [wherein, on the phenyl ring, at least one phenoxy group is substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, is substituted)], a thiazolyl group (wherein, on the thiazole ring, at least one phenyl group may be substituted), a phenoxy C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a phenyl group (wherein, on the phenyl ring, halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, is substituted), and an imidazoyl group (wherein, on the imidazole ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted));

(p) a thiazoyl C1-C6 alkoxy group (wherein, on the thiazole ring, at least one type selected from the group consisting of the following (p-1) to (p-5) may be substituted:

(p-1) a phenoxy C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted),

(p-2) an anilino C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a
halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted],

(p-3) a phenyl C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted],

(p-4) a piperazinyl C1-C6 alkyl group

[wherein, on the piperazine ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)],

and

(p-5) a piperidyl C1-C6 alkyl group [wherein, on the piperidine ring, at least one phenoxy group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)];

(q) an 8-azabicyclo[3.2.1]octyl group

[wherein, on the 8-azabicyclo[3,2,1]octane ring, at least one phenoxy group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group, may be
substituted);}

(i) a group represented by the following
chemical formula (31):

\[
\begin{align*}
&\text{\begin{tikzpicture}
  \node at (0,0) {
    \begin{tikzpicture}
      \draw[thick] (0,0) -- (0.5,0.5) -- (1,0) -- (0.5,-0.5) -- cycle;
      \draw[thick] (0.5,0.5) -- (1,1) -- (1.5,0.5) -- (1,0) -- cycle;
      \node at (0.75,0) \(X\);
      \node at (1.25,0) \(m\);
    \end{tikzpicture}
  \end{tikzpicture}}
  \node at (2,0) \(R^3\);
\end{align*}
\]

(wherein \(X\) represents a halogen atom, or an amino
substituted C1-C6 alkyl group which may have a C1-C6
alkyl group as a substituent, \(m\) represents an integer
between 0 and 3, and \(R^3\) represents a group described in
any one of the following (i) to (xxii):

(i) a group \(-(W)O-NR^2R^3\) (wherein \(W\) represents a group
-CO- or a C1-C6 alkyene group, \(o\) represents 0 or 1, \(R^i\)
represents a hydrogen atom, C1-C6 alkyl group, or
phenylcarbamoyl group (wherein, on the phenyl ring, at
least one selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted
C1-C6 alkyl group, and a halogen substituted or
unsubstituted C1-C6 alkoxy group, may be substituted),
and \(R^3\) represents: a phenyl C1-C6 alkoxy carbonyl group
(wherein, on the phenyl ring, at least one selected
from the group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a
halogen substituted or unsubstituted C1-C6 alkoxy
group, may be substituted); a phenyl C2-C6
alkenylic carbonyl group (wherein, on the phenyl ring, at
least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a piperidyl C1-C6 alkyl group (wherein, on the piperidine ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)); a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one phenyl group is substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)); a benzofuryl C1-C6 alkyl group (wherein, on the benzofuran ring, at least one halogen substituted or unsubstituted C1-C6 alkyl group may be substituted); a piperidinylcarbonyl C1-C6 alkyl group (wherein, on the piperidine ring, at least one phenoxy group may be substituted (wherein, on the phenyl ring,
at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted);

or a group represented by the following chemical formula (32):

\[
\begin{array}{c}
\text{N} \\
\text{R}^8 \\
\end{array}
\]

(32)

wherein \( R^8 \) represents: a Cl-C6 alkyl group; a phenyl group (wherein, on the phenyl ring, at least one selected from the following group may be substituted: a Cl-C4 alkylenedioxy group, a cyano group, a nitro group, an amino group that may have a Cl-C6 alkyl group as a substituent, an amino substituted sulfonymyl group that may have a Cl-C6 alkyl group as a substituent, a Cl-C6 alkoxy carbonyl group, a Cl-C6 alkylthioc group, a phenoxy group, a phenyl Cl-C6 alkoxy group, a pyrrolidinyl group [wherein, on the pyrrolidine ring, at least one oxo group may be substituted], an imidazolyl group, an isoxazolyl group, an oxazolyl group, a phenyl Cl-C6 alkyl group, a phenyl group, an amino Cl-C6 alkyl group that may have a Cl-C6 alkyl group as a substituent, a pyrrolidinyl Cl-C6 alkoxy group, a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group); a phenyl Cl-C6 alkoxy carbonyl group (wherein, on the
phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a benzofuryl C1-C6 alkyl group (wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a benzofuryl C2-C6 alkenyl group (wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a phenoxy C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a thiazolyl C1-C6 alkyl group (wherein, on the thiazole ring, at least one phenyl group may be substituted [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]); a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group
consisting of a phenyl group (wherein, on the phenyl ring, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a pyridyl C1-C6 alkyl group (wherein, on the pyridine ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)); a C1-C6 alkoxy carbonyl group; a benzoyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a phenyl carbamoyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a benzothienyl C1-C6 alkyl group (wherein, on the benzothiophene ring, at least one halogen atom may be substituted); an indolyl C1-C6 alkyl group (wherein, on the indole ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted); a 4H-1,3-benzodioxinyl group (wherein, on the 4H-1,3-benzodioxine ring, at least one halogen atom may be substituted); benzothienyl group; a naphthyl group; a quinolyl group; a benzothiazolyl group (wherein, on the benzothiazole ring, at least one Cl-C6 alkyl group may be substituted); a 2,3-dihydro-1H-indenyl group (wherein, on the 2,3-dihydro-1H-indan ring, at least one oxo group may be substituted); or a 9H-fluorenly group or phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted));

(ii) a group represented by the following chemical formula (33):

\[
\begin{align*}
\text{R}^7 & \text{N}^- \\
\text{R}^8
\end{align*}
\]

(33)

(wherein W and o are the same as above, a dotted line represents that the bond may be a double bond, and when the dotted line represents a double bond, it means that only \( \text{R}^8 \) is substituted; \( \text{R}^7 \) represents a hydrogen atom, hydroxyl group, Cl-C6 alkoxy group, or phenyl group (wherein, on the phenyl ring, halogen may be
substituted); and \( R^8 \) represents a group described in any one of the following (1) to (63):

1. a phenyl C1-C6 alkoxy substituted C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a C1-C4 alkylenedioxy group, a halogen atom, a cyano group, a phenyl group, a phenyl C1-C6 alkoxy group, a phenyl C2-C6 alkenyl group, a phenoxy group, a C1-C6 alkylthio group, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted);

2. a phenyl C1-C6 alkoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a cyano group, a phenyl group, a C1-C6 alkoxy carbonyl group, a phenoxy group, a C1-C6 alkylthio group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted);

3. a phenyl C2-C6 alkenyloxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted);

4. a group \(-(\text{W})o-\text{NR}^8\text{R}^{10}\)

(wherein \( \text{W} \) and \( o \) are the same as above, and \( R^8 \) and \( R^{10} \) each identically or differently represent a.
hydrogen atom; a C1-C6 alkyl group that may have a hydroxyl group as a substituent; a C1-C6 alkanoyl group; a C1-C6 alkoxy carbonyl group; a phenyl C1-C6 alkoxy carbonyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]; a phenyl group [on the phenyl ring, at least one selected from the following group may be substituted as a substituent: a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, a halogen substituted or unsubstituted C1-C6 alkoxy group, an amino group that may have, as a substituent, a group selected from the group consisting of a C1-C6 alkanoyl group and a C1-C6 alkyl group, a C1-C6 alkoxy carbonyl group, a phenyl group, a phenoxy group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], an aminosulfonyl group, a 1,2,3,4-tetrahydroquinolyl group [wherein, on the 1,2,3,4-tetrahydroquinoline ring, at least one oxo group may be substituted as a substituent], a C1-C6 alkyl sulfonyl group, a C3-C6 cycloalkyl group, a nitro group, a cyano group, a C1-C6 alkylithio group, a phenyl sulfonyl group [wherein, on the phenyl ring, at least one selected
from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted, a hydroxy group

substituted Cl-C6 alkyl group, and a group represented by the following chemical formula (34):

\[ \text{O} \quad \text{R}^{11} \]
\[ \text{R}^{12} \]

\[ \text{W}_1 \] \[ \text{P} \]

(wherein \( \text{W}_1 \) represents a Cl-C6 alkylene group, and \( \text{R}^{11} \) and \( \text{R}^{12} \) each identically or differently represent a Cl-C6 alkoxy group); a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a Cl-C4 alkylidenedioxy group, a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted), a group \(-\text{N}(\text{R}^{13A})\text{R}^{12A}\) (wherein \( \text{R}^{13A} \) and \( \text{R}^{12A} \) each identically or differently represent a hydrogen atom, Cl-C6 alkyl group, or phenyl group, and \( \text{R}^{13A} \) and \( \text{R}^{12A} \) may bind to each other together with nitrogen atoms adjacent thereto directly or through nitrogen, oxygen or sulfur atoms, so as to form a 5-7 membered saturated heterocyclic ring), a phenoxy group (wherein, on the phenyl ring, at least one selected...
from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a phenyl C1-C6 alkoxy group, an amino group substituted C1-C6 alkoxy group that may have a C1-C6 alkyl group as a substituent, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C10 alkoxy group, may be substituted as a substituent); a benzofuryl C1-C6 alkyl group [wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]; a phenylsulfonyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, and a C1-C4 alkylenedioxy may be substituted]; a phenoxy carbonyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]; a phenyl C2-C6 alkenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a C1-C6 alkoxy substituted C1-C6 alkyl group; a C2-C6 alkenyl group; a C1-C6 alkoxy substituted C2-C6 alkanoyl group; a C3-C6 cycloalkyl substituted C1-C6 alkyl group; a phenoxy C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a benzoyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a phenylcarbamoyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a pyridyl group; a pyridyl C1-C6 alkyl group; an imidazolyl C1-C6 alkyl group; a 1,2,3,4-tetrahydroquinolyl group (wherein, on the 1,2,3,4-tetrahydroquinoline ring, at least one selected from the group consisting of an oxo group and a C1-C6 alkyl group may be substituted as a substituent); a quinolyl group; an indolyl group; an amino group that may have a C1-C6 alkyl group as a substituent; an
indazolyl group; a naphthyl group; a C3-C8 cycloalkyl group; an amino substituted Cl-C6 alkyl group that may have a Cl-C6 alkyl group as a substituent; a cyano substituted Cl-C6 alkyl group; a furyl substituted Cl-C6 alkyl group; a group of the formula (35)

(35)

(wherein RR represents a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted)); or a piperazinyl substituted Cl-C6 alkyl group (wherein, on the piperazine ring, at least one phenyl group may be substituted as a substituent (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted)), further, R⁹ and R¹₀ may bind to each other together with nitrogen atoms adjacent thereto directly or through nitrogen, oxygen or sulfur atoms, so as to form a 1,2,3,4-tetrahydroisoquinolyl group, isoindolyl group, or 5-7 membered saturated heterocyclic ring, wherein, on the heterocyclic ring, at least one selected from the following group may be substituted; a halogen atom,
a halogen substituted or unsubstituted C1-C6 alkyl group, a halogen substituted or unsubstituted C1-C6 alkoxy group, a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting

of a phenyl group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], a benzoyl group [wherein, on the phenyl ring, at least one selected from the

group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], a pyridyl C1-C6 alkyl group, a C3-C8 cycloalkyl group, a phenyl C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a C1-C4 alkylenedioxy group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], a piperidyl C1-C6 alkyl group, a piperidyl group, a phenyl C1-C6 alkoxy group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], a phenoxy group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), an amino group wherein at least one selected from the group consisting of a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], a C1-C6 alkyl group, and a phenyl C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], may be substituted as a substituent, a benzóxazolyl group, a phenyl C2-C6 alkenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], and a benzoimidazolyl group;

(5) a phenyl C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be
substituted), a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); (6) a carbamoyloxy group (wherein, on the amino group, at least one selected from the group consisting of a C1-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted) may be substituted); (7) a carbamoyloxy substituted C1-C6 alkyl group (wherein, on the amino group, at least one selected from the group consisting of a C1-C6 alkyl group, a phenyl C1-C6 alkyl group, a C3-C8 cycloalkyl group, a naphthyl group, a 2,3-dihydro-1H-indenyl group, a 2,3-dihydrobenzofuryl group, and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a C1-C4 alkylenedioxy group, a cyano group, a phenoxy group, a C1-C6 alkylthio group, a C1-C6 alkanoyl group, a phenyl group, a phenyl C1-C6 alkyl group, a halogen atom, a halogen substituted or unsubstituted C1-C10 alkyl group, and a halogen substituted or unsubstituted C1-C10 alkoxy group, may be substituted), may be substituted); (8) a phenoxy C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the following group may be substituted: a halogen atom; a C1-C4
alkylenedioxy group; a C1-C6 alkoxy carbonyl group; a phenyl group; a phenoxyl group; a pyrrolyl group; a benzothiazolyl group; a 1,2,4-triazolyl group; an imidazolyl group; an isoxazolyl group; a benzoxazolyl group; a benzotriazolyl group; a cyano group; a nitro group; a C2-C6 alkenyl group; a C1-C6 alkanoyl group; a C1-C6 alkoxy carbonyl substituted C1-C6 alkyl group; a C1-C6 alkanoyl substituted C1-C6 alkyl group; a group \(-N(R^{11})R^{12n}\) (wherein \(R^{11}\) and \(R^{12}\) each identically or differently represent a hydrogen atom, C1-C6 alkyl group, C1-C6 alkanoyl group, or phenyl group, and \(R^{11}\) and \(R^{12}\) may bind to each other together with nitrogen atoms adjacent thereto directly or through nitrogen, oxygen or sulfur atoms, so as to form a 5-7 membered saturated heterocyclic ring, wherein, on the heterocyclic ring, at least one selected from the group consisting of a C1-C6 alkoxy carbonyl group and an amino group (wherein, on the amino group, at least one selected from a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted) and a C1-C6 alkyl group may be substituted) may be substituted); a phenyl C1-C6 alkoxy group; a phenyl C1-C6 alkyl group; a C1-C6 alkylthio group; a C3-C8 cycloalkyl group; a halogen substituted or unsubstituted C1-C6 alkyl group; and a halogen
substituted or unsubstituted C1-C10 alkoxy group);
(9) a tetrahydropyranoxy C1-C6 alkyl group;
(10) a hydroxyl substituted C1-C6 alkyl group;
(11) a furyl C1-C6 alkoxy substituted C1-C6 alkyl group

(wherein, on the furan ring, at least one C1-C6 alkoxycarbonyl group may be substituted);
(12) a tetrazolyl C1-C6 alkoxy substituted C1-C6 alkyl group (wherein, on the tetrazole ring, at least one selected from the group consisting of a phenyl group

(wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a phenyl C1-C6 alkyl group,
and a C3-C8 cycloalkyl C1-C6 alkyl group, may be substituted);
(13) an isoxazolyl C1-C6 alkoxy substituted C1-C6 alkyl group (wherein, on the isoxazole ring, at least one C1-C6 alkyl group may be substituted);
(14) a benzothienyl C1-C6 alkoxy substituted C1-C6 alkyl group (wherein, on the benzothiophene ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted);
(15) a 1,3,4-oxadiazolyl C1-C6 alkoxy substituted C1-C6 alkyl group (wherein, on the 1,3,4-oxadiazole ring, a phenyl group may be substituted [wherein, on the phenyl
ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted));

(16) a C2-C6 alkynyl oxy substituted C1-C6 alkyl group;
(17) a naphthyl C1-C6 alkoxy substituted C1-C6 alkyl group;
(18) a 1,2,4-oxadiazoIyl C1-C6 alkoxy substituted C1-C6 alkyl group [wherein, on the 1,2,4-oxadiazole ring, a phenyl group may be substituted];
(19) a pyridyl C1-C6 alkoxy substituted C1-C6 alkyl group [wherein, on the pyridine ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted];
(20) a thiazolyl C1-C6 alkoxy substituted C1-C6 alkyl group [wherein, on the thiazole ring, at least one selected from the group consisting of a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)] and a C1-C6 alkyl group may be substituted);
(21) a 1,2,3,4-tetrahydronaphthyl C1-C6 alkoxy substituted C1-C6 alkyl group [wherein, on the 1,2,3,4-
tetrahydronaphthalene ring, at least one C1-C6 alkyl group may be substituted;  
(22) a carbamoyl C1-C6 alkoxy substituted C1-C6 alkyl group [wherein, on the amino group, at least one selected from the group consisting of a C3-C8 cycloalkyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted) may be substituted];  
(23) a benzofuryl C1-C6 alkoxy substituted C1-C6 alkyl group [wherein, on the benzofuran ring, at least one cyano group may be substituted];  
(24) a benzofuryl C1-C6 alkyl group [wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted];  
(25) a phenoxy group [wherein, on the phenyl ring, at least one selected from the group consisting of a phenyl C1-C6 alkoxy group, a C3-C8 cycloalkyl group, a C7-C10 alkoxy group, and a phenoxy group, is substituted];  
(26) a naphthyl group;  
(27) a 2,3-dihydrobenzofuryloxy group [wherein, on the 2,3-dihydrobenzofuran ring, at least one oxo group may
be substituted);

(28) a benzothiazolyloxy group [wherein, on the benzothiazole ring, at least one C1-C6 alkyl group may be substituted];

(29) a 1,2,3,4-tetrahydronaphthoxyloxy group [wherein, on the 1,2,3,4-tetrahydronaphthalene ring, at least one oxo group may be substituted];

(30) a dibenzofuryloxy group;

(31) a quinolyloxy group;

(32) a furyl C1-C6 alkoxy group [wherein, on the furan ring, at least one C1-C6 alkoxy carbonyl group may be substituted];

(33) a tetrazolyl C1-C6 alkoxy group [wherein, on the tetrazole ring, at least one selected from the group consisting of a phenyl C1-C6 alkyl group and a C3-C8 cycloalkyl C1-C6 alkyl group may be substituted];

(34) a 1,2,4-oxadiazolyl C1-C6 alkoxy group [wherein, on the 1,2,4-oxadiazole ring, a phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)];

(35) a benzothienyl C1-C6 alkoxy group [wherein, on the benzothiophene ring, at least one halogen atom may be substituted];

(36) an isoxazolyl C1-C6 alkoxy group [wherein, on the isoxazole ring, at least one C1-C6 alkyl group may be
substituted];
(37) a 1,3,4-oxadiazolyl Cl-C6 alkoxy group (wherein, 
on the 1,3,4-oxadiazole ring, at least one phenyl group 
may be substituted (wherein, on the phenyl ring, at 
least one Cl-C6 alkyl group may be substituted)];
(38) a naphthyl Cl-C6 alkoxy group;
(39) a pyridyl Cl-C6 alkoxy group (wherein, on the 
pyridine ring, at least one halogen substituted or 
unsubstituted Cl-C6 alkyl group may be substituted);
(40) a thiazolyl Cl-C6 alkoxy group (wherein, on the 
thiazole ring, at least one phenyl group may be 
substituted (wherein, on the phenyl ring, at least one 
selected from the group consisting of a halogen atom, a 
halogen substituted or unsubstituted Cl-C6 alkyl group, 
and a halogen substituted or unsubstituted Cl-C6 alkoxy 
group, may be substituted)];
(41) a 1,2,3,4-tetrahydronaphthyl Cl-C6 alkoxy group 
(wherein, on the 1,2,3,4-tetrahydronaphthalene ring, at 
least one Cl-C6 alkyl group may be substituted);
(42) a phenoxy Cl-C6 alkoxy group (wherein, on the 
phenyl ring, at least one selected from the group 
consisting of a halogen atom, a halogen substituted or 
unsubstituted Cl-C6 alkyl group, and a halogen 
substituted or unsubstituted Cl-C6 alkoxy group, may be 
substituted);
(43) a carbamoyl Cl-C6 alkoxy group (wherein, on the 
amino group, at least one selected from the group 
consisting of a C3-C8 cycloalkyl group and a phenyl
group (wherein, or the phenyl ring, at least one
selected from the group consisting of a halogen atom, a
halogen substituted or unsubstituted C1-C6 alkyl group,
and a halogen substituted or unsubstituted C1-C6 alkoxy
5 group, may be substituted) may be substituted];
(44) a benzofuryl C1-C6 alkoxy group (wherein, on the
benzofuran ring, at least one cyano group may be
substituted);
(45) a naphthoxyloxy C1-C6 alkyl group (wherein, on the
naphthalene ring, at least one C1-C6 alkoxy group may
10 be substituted);
(46) a benzothiazolyloxy C1-C6 alkyl group (wherein, on
the benzothiazole ring, at least one C1-C6 alkyl group
may be substituted);
(47) a quinolyloxy C1-C6 alkyl group (wherein, on the
quinoline ring, at least one C1-C6 alkyl group may be
15 substituted);
(48) a 2,3-dihydrobenzofuryloxy C1-C6 alkyl group
(wherein, on the 2,3-dihydrobenzofuran ring, at least
one selected from the group consisting of a C1-C6 alkyl
group and an oxo group may be substituted);  
(49) a 1,2,3,4-tetrahydronaphthoxyloxy C1-C6 alkyl group
(wherein, on the 1,2,3,4-tetrahydronaphthalene ring, at least
20 one oxo group may be substituted);
(50) a 2,3-dihydro-1H-indenyloxy C1-C6 alkyl group
(wherein, on the 2,2-dihydro-1H-indene ring, at least
one oxo group may be substituted);
(51) a benzoxathiolanyloxy C1-C6 alkyl group (wherein,
on the benzoxathiolane ring, at least one oxo group may be substituted);

(52) an isoquinolyloxy C1-C6 alkyl group;

(53) a pyridyloxy C1-C6 alkyl group;

(54) a dibenzofuryloxy C1-C6 alkyl group;

(55) a 2H-1-benzopyranloxy C1-C6 alkyl group (wherein, on the 2H-1-benzopyran ring, at least one oxo group may be substituted);

(56) a benzoisoaxazolyloxy C1-C6 alkyl group;

(57) a benzofurazanyloxy C1-C6 alkyl group;

(58) a quinoxalyloxy C1-C6 alkyl group;

(59) a C1-C6 alkoxy C1-C6 alkoxy substituted C1-C6 alkyl group;

(60) a thienyl C1-C6 alkoxy substituted C1-C6 alkyl group (wherein, on the thiophene ring, at least one halogen atom may be substituted);

(61) a phenyl C2-C6 alkenyloxy substituted C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted);

(62) a quinolyl C1-C6 alkoxy substituted C1-C6 alkyl group; and

(63) a piperidylcarbonyl C1-C6 alkoxy substituted C1-C6 alkyl group,

and further, \( R^1 \) and \( R^2 \) together may form a group \( =\mathrm{C}(\mathrm{R}^{29})(\mathrm{R}^{10}) \), wherein \( R^{10} \) and \( R^{29} \) each identically or
differently represent a hydrogen atom, Cl-C6 alkyl group, or phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]); (iii) a group represented by the following chemical formula (36):

\[ -(\text{W})_3 N - \bigcirc - N - R^{13} \]  

(Wherein \( \text{W} \) and \( o \) are the same as above, and \( R^{13} \) represents: a 2,3-dihydro-1H-indenyl group; a benzothienyl group; a phenyl C2-C10 alkenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a Cl-C4 alkylenedioxy group, a Cl-C6 alkylthio group, a benzyol group, a cyano group, a nitro group, a C2-C6 alkanoyloxy group, an amino group that may have a Cl-C6 alkyl group as a substituent, a hydroxyl group, a phenyl Cl-C6 alkoxy group, a phenoxy group, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]; a naphthyl C2-C6 alkenyl group; a benzofuryl Cl-C6 alkyl group [wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen...
substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a benzothienyl C2-C6 alkenyl group; a benzothiazolyl C2-C6 alkenyl group (wherein, on the benzothiazole ring, at least one C1-C6 alkyl group may be substituted); a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the following group is substituted: a piperidinyl group (on the piperidine ring, at least one phenoxy group may be substituted) {wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted}), a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, is substituted); and a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted}); a diphenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted}); a benzoyl C1-C6 alkyl group
(wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); an amino group wherein at least one selected from the following group may be substituted: a C1-C6 alkyl group, a C1-C6 alkoxy carbonyl group, and a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); an amino C1-C6 alkyl group wherein at least one selected from the group consisting of a C1-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted) may be substituted; a benzofuryl C2-C6 alkenyl group (wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted
Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted; a piperidyl group (wherein, on the piperidine ring, at least one phenyl C2-C6 alkenyl group may be substituted) (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted); a ferrocene substituted Cl-C6 alkyl group; an indolyl Cl-C6 alkyl group (wherein, on the indole ring, at least one halogen atom may be substituted); a phenyl C2-C6 alkynyl group; a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a Cl-C4 alkylenedioxy group, a phenyl group, a Cl-C6 alkoxy carbonyl group, a hydroxyl group, and a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted), is substituted); a benzofuranyl group (wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom and a Cl-C6 alkyl group may be substituted); a benzothiazoliny1 group (wherein, on the benzothiazoline ring, at least one oxo group may be substituted); a benzothiienyl group (wherein, on the benzothiophene ring, at least one halogen atom may be substituted)
substituted); a naphthyl group; a 1,2,3,4-tetrahydroquinolyl group [wherein, on the 1,2,3,4-tetrahydroquinoline ring, at least one selected from the group consisting of an oxo group and a C1-C6 alkyl group may be substituted]; a benzoisoxazolyl group; a 2,3-dihydrobenzofuryl group; a 1,2-dihydroquinolyl group [wherein, on the 1,2-dihydroquinoline ring, at least one oxo group may be substituted]; a 1,2,3,4-tetrahydroquinazolyl group [wherein, on the 1,2,3,4-tetrahydroquinazoline ring, at least one selected from the group consisting of an oxo group and a C1-C6 alkyl group may be substituted]; a benzocycloheptyl group; a phenoxy C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]; a benzothienyl substituted C1-C6 alkyl group [wherein, on the benzothiophene ring, at least one halogen atom may be substituted]; a naphthyl substituted C1-C6 alkyl group [wherein, on the naphthalene ring, at least one C1-C6 alkoxy group may be substituted]; a pyridyl substituted C1-C6 alkyl group [wherein, on the pyridine ring, at least one halogen atom may be substituted]; a furyl substituted C1-C6 alkyl group [wherein, on the furan ring, at least one nitro group may be substituted]; a thienyl substituted C1-C6 alkyl group [wherein, on the thiophene ring, at least one halogen
atom may be substituted]; a thiazolyl substituted C1-C6 alkyl group [wherein, on the thiazole ring, at least one selected from the group consisting of a C1-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom and a halogen substituted or unsubstituted C1-C6 alkyl group may be substituted); a tetrazolyl substituted C1-C6 alkyl group [wherein, on the tetrazole ring, at least one C1-C6 alkyl group may be substituted]; an isoxazolyl substituted C1-C6 alkyl group [wherein, on the isoxazole ring, at least one C1-C6 alkyl group may be substituted]; a 1,2,4-oxadiazolyl substituted C1-C6 alkyl group [wherein, on the 1,2,4-oxadiazole ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, a C1-C6 alkyl group may be substituted)]; or a benzofurazanyl substituted C1-C6 alkyl group];

(iv) a group represented by the following chemical formula (37):

\[
\text{-R}^{14}
\]  

(37)

(wherein \(R^{14}\) represents: a phenylamino group [wherein, at the N-position of the phenylamino group, a C1-C6 alkyl group may be substituted, and on the phenyl ring of the phenylamino group, at least one halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted].)
substituted); a piperidyl group (wherein, on the piperidine ring, at least one selected from the group consisting of a phenoxy group (wherein, on the phenyl ring, a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) and an amino group (wherein, on the amino group, at least one selected from the group consisting of a C1-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted) may be substituted as a substituent) may be substituted); a piperazinyl group (wherein, on the piperazine ring, at least one selected from the following group may be substituted: a C1-C6 alkoxy carbonyl group, a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), and a benzoyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen...
substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a homopiperazinyl group (wherein, on the homopiperazine ring, at least one selected from the group consisting of a C1-C6 alkoxy carbonyl group and a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted) may be substituted); or a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen substituted or unsubstituted C1-C6 alkoxy group and a phenoxy substituted phenyl group (wherein, on the phenyl ring, at least one halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), may be substituted));
(v) a group represented by the following chemical formula (38):
(wherein \( R^3 \) is the same as above, and a dotted line represents that the bond may be a double bond):

(vi) a homopiperazinyl group (wherein, on the homopiperazine ring, at least one selected from the following group may be substituted: a C1-C6 alkoxy carbonyl group; a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a phenyl C1-C6 alkoxy carbonyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a phenylcarbamoyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a
halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]; and a benzoyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]);

(vii) a group represented by the following chemical formula (39):

\[
\begin{align*}
&\text{N} - R^{19} \\
&\text{R}^{20}
\end{align*}
\]  

(39)

(wherin R\textsuperscript{19} represents a C1-C6 alkoxy group, and R\textsuperscript{20} represents a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]);

(viii) a group -CHR\textsuperscript{22}R\textsuperscript{21} (wherein R\textsuperscript{20} is the same as above, and R\textsuperscript{22} represents an amino group that may have a C1-C6 alkyl group as a substituent);

(ix) a 1,2,3,4-tetrahydroisoquinolyl group (wherein, on the 1,2,3,4-tetrahydroisoquinoline ring, at least one amino group may be substituted [wherein, on the amino group, at least one selected from the group consisting of a phenyl C1-C6 alkyl group (wherein, on the phenyl
ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted) and a Cl-C6 alkyl group may be substituted];

(x) an oxazolyl group (wherein, on the oxazole ring, at least one selected from the following group may be substituted: a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted], a Cl-C6 alkyl group, and a piperidyl group [wherein, on the piperidine ring, at least one phenoxy group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]);

(xi) an isoindoliny1 group (wherein, on the isoindoline ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted);

(xii) a thiazolyl group (wherein, on the thiazole ring,
at least one selected from the following group may be substituted: a phenoxy Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted); a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted); a group -\{(W)\}ONR\(^{31}R^{32}\) [wherein W, and v are the same as above, and R\(^{31}\) and R\(^{32}\) each identically or differently represent a hydrogen atom, Cl-C6 alkyl group, phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted); or phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a piperazinyl group (wherein, on the piperazine ring, at least one phenyl group may be substituted) (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a piperidyl group (wherein, on the piperidine ring, at least one selected from the group consisting of a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted) and a phenyl C1-C6 alkyl group may be substituted); and a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted));

(xiii) a hydroxyl group substituted C1-C6 alkyl group;
(xiv) an oxazolyl C1-C6 alkyl group (wherein, on the oxazole ring, at least one phenyl group may be substituted) (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group).
group, may be substituted)];

(xv) an isoxazolyl group (wherein, on the isoxazoline ring, at least one phenyl ring may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted)];

(xvi) a benoxazolyl group (wherein, on the benzoxazole ring, at least one halogen atom may be substituted);

(xvii) a phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted);

(xviii) a benzoimidazolyl group (wherein, on the benzoimidazole ring, at least one selected from the group consisting of a halogen atom and a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted) may be substituted);

(xiv) a pyrrolidinyl group (wherein, on the pyrrolidine ring, at least one amino group is substituted (wherein, on the amino group, at least one selected from the group consisting of a Cl-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, at least one
selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted);]

5 (xx) a phenylsulfonyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted);

(xx) an imidazolyl group (wherein, on the imidazole ring, at least one phenyl group is substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted); and

(xxii) a phenylsulfinyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted));

(s) an imidazolyl group (wherein, on the imidazole ring, at least one selected from the group consisting of a halogen atom and a nitro group may be substituted);

(t) an isoindolinyloxy group (wherein, on
the isoindoline ring, at least one selected from the following group may be substituted: a C1-C6 alkoxy carbonyl group, a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a benzofuryl group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a furyl C1-C6 alkyl group (wherein, on the furan ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)), a pyridyl C1-C6 alkyl group (wherein, on the pyridine ring, at least one selected from the group consisting of a furyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a benzofuryl C1-C6 alkyl group (wherein,
on the benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted), a benzothienyl Cl-C6 alkyl group (wherein, on the benzothiophene ring, at least one halogen atom may be substituted), a benzofuryl C2-C6 alkenyl group (wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted), a thiazolyl group (wherein, on the thiazole ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted)), and a phenoxy Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted));

(u) a benzothiazolidinylxyloxy group (wherein, on the benzothiazolidine ring, at least one selected from the group consisting of an oxo group and a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at
least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted],

(v) an indolyl group [wherein, on the indole ring, at least one phenyl Cl-C6 alkyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted)];

(w) a pyrroolidinyl group [wherein, on the pyrroolidine ring, at least one amino group is substituted (wherein, on the amino group, at least one selected from the group consisting of a Cl-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted)];

(x) an indolyl group [wherein, on the indoline ring, at least one halogen atom may be substituted]; and

(y) an indolinyloxy group [wherein, on the indoline ring, at least one selected from the group consisting of a phenyl Cl-C6 alkyl group (wherein, on
the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted; and an oxo group may be substituted).

The present invention provides 2,3-dihydro-6-nitroimidazol[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (I), wherein R² represents a group described in any one of (a) to (c), (e) to (h), (j) to (q), and (s) to (y).

The present invention provides 2,3-dihydro-6-nitroimidazol[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (I), wherein R² represents the group described in (d).

The present invention provides 2,3-dihydro-6-nitroimidazol[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (I), wherein R² represents the group described in (i).

The present invention provides 2,3-dihydro-6-nitroimidazol[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general
formula (1), wherein R³ represents the group described in (r).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (1), wherein R¹ represents a hydrogen atom.

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (1), wherein R¹ represents a C1-C6 alkyl group.

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (1), wherein R¹ and -(CH₂)ₙR² may bind to each other to form a spiro ring together with the carbon atom adjacent thereto, represented by the following formula (30):

![spiro ring formula](image)

wherein RRR represents a piperidyl group wherein, on the piperidine ring, at least one phenoxy group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group,
and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (i), wherein R' represents a hydrogen atom or a C1-C6 alkyl group and R' represents the group described in (i).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (i), wherein R' represents a hydrogen atom or a C1-C6 alkyl group and R' represents the group described in (ii).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (i), wherein R' represents a hydrogen atom or a C1-C6 alkyl group and R' represents the group described in (iii).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (i), wherein R' represents a hydrogen atom or a
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C1-C6 alkyl group and R² represents the group described in (iv).

The present invention provides 2,3-dihydro-6-nitroimidazol[2,1-b]oxazole compound, an optically
5 active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (1), wherein R¹ represents a hydrogen atom or a C1-C6 alkyl group and R² represents the group described in (v).

10 The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (1), wherein R¹ represents a hydrogen atom or a C1-C6 alkyl group and R² represents the group described in (vi).

15 The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (1), wherein R¹ represents a hydrogen atom or a C1-C6 alkyl group and R² represents the group described in (vii).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically
20 active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (1), wherein R¹ represents a hydrogen atom or a C1-C6 alkyl group and R² represents the group described in (viii).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically
25 active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (1), wherein R¹ represents a hydrogen atom or a
C1-C6 alkyl group and R³ represents the group described in (viii).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (I), wherein R¹ represents a hydrogen atom or a C1-C6 alkyl group and R³ represents the group described in (ix).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (I), wherein R¹ represents a hydrogen atom or a C1-C6 alkyl group and R³ represents the group described in (x).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (I), wherein R¹ represents a hydrogen atom or a C1-C6 alkyl group and R³ represents the group described in (xi).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (I), wherein R¹ represents a hydrogen atom or a
C1-C6 alkyl group and R² represents the group described in (xii).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (1), wherein R¹ represents a hydrogen atom or a C1-C6 alkyl group and R² represents the group described in (xiii).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (1), wherein R¹ represents a hydrogen atom or a C1-C6 alkyl group and R² represents the group described in (xiv).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (1), wherein R¹ represents a hydrogen atom or a C1-C6 alkyl group and R² represents the group described in (xv).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (1), wherein R¹ represents a hydrogen atom or a
C1-C6 alkyl group and R' represents the group described in (xvi).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (I), wherein R' represents a hydrogen atom or a C1-C6 alkyl group and R'' represents the group described in (xvii).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (I), wherein R' represents a hydrogen atom or a C1-C6 alkyl group and R'' represents the group described in (xviii).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (I), wherein R' represents a hydrogen atom or a C1-C6 alkyl group and R'' represents the group described in (xix).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (I), wherein R' represents a hydrogen atom or a
Cl-C6 alkyl group and R' represents the group described in (xx).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (I), wherein R' represents a hydrogen atom or a Cl-C6 alkyl group and R' represents the group described in (xxi).

The present invention provides 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to the above-mentioned general formula (I), wherein R' represents a hydrogen atom or a Cl-C6 alkyl group and R' represents the group described in (xxii).

In the compounds represented by the formula (1) of the present invention, particularly preferred are as follows:

2-methyl-6-nitro-2-[4-(4-trifluoromethylbenzyloxymethyl)piperidin-1-yl]phenoxyethyl]-2,3-dihydroimidazo[2,1-b]oxazole,

(R)-2-methyl-6-nitro-2-[4-(4-(4-trifluoromethylbenzyloxymethyl)piperidin-1-yl]phenoxyethyl]-2,3-dihydroimidazo[2,1-b]oxazole,

(S)-2-methyl-6-nitro-2-[4-(4-(4-trifluoromethylbenzyloxymethyl)piperidin-1-yl]phenoxyethyl]-2,3-dihydroimidazo[2,1-b]oxazole,
2-methyl-6-nitro-2-{4-[4-(4-chlorophenoxy)methyl)piperidin-1-yl]phenoxy)methyl}-2,3-dihydropyrimidazo[2,1-b]oxazole,

(R)-2-methyl-6-nitro-2-{4-[4-(4-chlorophenoxy)methyl)piperidin-1-yl]phenoxy)methyl}-2,3-dihydropyrimidazo[2,1-b]oxazole,

(S)-2-methyl-6-nitro-2-{4-[4-(4-chlorophenoxy)methyl)piperidin-1-yl]phenoxy)methyl}-2,3-dihydropyrimidazo[2,1-b]oxazole,

2-methyl-6-nitro-2-{4-[4-(4-trifluoromethyl)cinnamyl)piperazin-1-yl]phenoxy)methyl}-2,3-dihydropyrimidazo[2,1-b]oxazole,

(R)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethyl)cinnamyl)piperazin-1-yl]phenoxy)methyl}-2,3-dihydropyrimidazo[2,1-b]oxazole,

(S)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethyl)cinnamyl)piperazin-1-yl]phenoxy)methyl}-2,3-dihydropyrimidazo[2,1-b]oxazole,

2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxy)cinnamyl)piperazin-1-yl]phenoxy)methyl}-2,3-dihydropyrimidazo[2,1-b]oxazole,

(R)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxy)cinnamyl)piperazin-1-yl]phenoxy)methyl}-2,3-dihydropyrimidazo[2,1-b]oxazole,

(S)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxy)cinnamyl)piperazin-1-yl]phenoxy)methyl}-2,3-dihydropyrimidazo[2,1-b]oxazole,
trifluoromethylphenoxy)methyl)piperidin-1-ylphenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole,

(R)-2-methyl-6-nitro-2-(4-[(4-(trifluoromethylphenoxy)methyl)piperidin-1-yl]phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole,

(S)-2-methyl-6-nitro-2-(4-[(4-(trifluoromethylphenoxy)methyl)piperidin-1-yl]phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole,

6-nitro-2-(4-(4-

trifluoromethoxybenzyl)oxy)piperidin-1-yl]phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole,

(R)-6-nitro-2-(4-(4-(trifluoromethoxybenzyl)oxy)piperidin-1-yl]phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole,

(S)-6-nitro-2-(4-(4-(trifluoromethoxybenzyl)oxy)piperidin-1-yl]phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole,

6-nitro-2-(4-(4-(trifluoromethoxyphenoxy)methyl)piperidin-1-yl]phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole,

(R)-6-nitro-2-(4-(4-(trifluoromethoxyphenoxy)methyl)piperidin-1-yl]phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole,

(S)-6-nitro-2-(4-(4-(trifluoromethoxybenzyl)piperidin-1-yl]phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole,
2,3-dihydroimidazo[2,1-b]oxazole,
(R)-6-nitro-2-{4-[4-(4-
trifluoromethoxybenzyl)piperidin-1-yl]phenoxyethyl}-
2,3-dihydroimidazo[2,1-b]oxazole,
(S)-6-nitro-2-{4-[4-(4-
trifluoromethoxybenzyl)piperidin-1-yl]phenoxyethyl}-
2,3-dihydroimidazo[2,1-b]oxazole,
2-methyl-6-nitro-2-{4-[4-(4-
trifluoromethoxybenzyl)piperidin-1-yl]phenoxyethyl}-
2,3-dihydroimidazo[2,1-b]oxazole,
2,3-dihydroimidazo[2,1-b]oxazole,
(R)-2-methyl-6-nitro-2-{4-[4-(4-
trifluoromethoxybenzyl)piperidin-1-yl]phenoxyethyl}-
2,3-dihydroimidazo[2,1-b]oxazole,
(S)-2-methyl-6-nitro-2-{4-[4-(4-
trifluoromethoxybenzyl)piperidin-1-yl]phenoxyethyl}-
2,3-dihydroimidazo[2,1-b]oxazole,
2-methyl-6-nitro-2-{4-[4-[4-(4-
trifluoromethoxybenzyl)piperidin-1-yl]phenoxyethyl]-
2,3-dihydroimidazo[2,1-b]oxazole,
2-methyl-6-nitro-2-{4-[4-[4-(4-
trifluoromethoxybenzyl)piperidin-1-yl]phenoxyethyl]-
2,3-dihydroimidazo[2,1-b]oxazole,
(R)-2-methyl-6-nitro-2-[4-4-[4-4-
trifluoromethoxyphenoxy)benzyl)piperazin-1-
yl]phenoxy)methyl]-2,3-dihydroimidazo[2,1-b]oxazole,
(S)-2-methyl-6-nitro-2-[4-4-[4-
trifluoromethoxyphenoxy)benzyl)piperazin-1-
yl]phenoxy)methyl]-2,3-dihydroimidazo[2,1-b]oxazole,
6-nitro-2-[4-4-[3-(4-
trifluoromethoxyphenyl)propyl]piperidin-1-
yl]phenoxy)methyl]-2,3-dihydroimidazo[2,1-b]oxazole,
(3)-6-nitro-2-[4-4-[3-(4-
trifluoromethoxyphenyl)propyl]piperidin-1-
yl]phenoxy)methyl]-2,3-dihydroimidazo[2,1-b]oxazole,
(S)-6-nitro-2-[4-4-[3-(4-
trifluoromethoxyphenyl)propyl]piperidin-1-
yl]phenoxy)methyl]-2,3-dihydroimidazo[2,1-b]oxazole,
2-methyl-6-nitro-2-[4-4-
trifluoromethoxyphenyl]oxazol-4-yl]phenoxy)methyl]-2,3-
dihydroimidazo[2,1-b]oxazole,
(R)-2-methyl-6-nitro-2-[4-4-
trifluoromethoxyphenyl]oxazol-4-yl]phenoxy)methyl]-2,3-
dihydroimidazo[2,1-b]oxazole,
(S)-2-methyl-6-nitro-2-[4-4-
trifluoromethoxyphenyl]oxazol-4-yl]phenoxy)methyl]-2,3-
dihydroimidazo[2,1-b]oxazole,
6-nitro-2-[4-4-[4-
chlorophenoxy)methyl)propyl]piperidin-1-yl]phenoxy)methyl]-2,3-
dihydroimidazo[2,1-b]oxazole,
(R)-6-nitro-2-[4-4-[4-
chlorophenoxy)methyl)piperidin-1-yl)phenoxy)methyl]-2,3-
dihydroimidazo[2,1-b]oxazole,

(S)-6-nitro-2-{4-[4-(4-
chlorophenoxy)methyl)piperidin-1-yl)phenoxy)methyl]-2,3-
dihydroimidazo[2,1-b]oxazole,

2-methyl-6-nitro-2-{4-[4-(5-
trifluoromethyl)benzofuran-2-yl)methyl)piperidin-1-
yl)phenoxy)methyl]-2,3-dihydroimidazo[2,1-b]oxazole,

(R)-2-methyl-6-nitro-2-{4-[4-(5-
trifluoromethyl)benzofuran-2-yl)methyl)piperidin-1-
yl)phenoxy)methyl]-2,3-dihydroimidazo[2,1-b]oxazole,

2-methyl-6-nitro-2-{4-[2-(4-
chlorophenyl)oxazol-4-yl)phenoxy)methyl]-2,3-
dihydroimidazo[2,1-b]oxazole,

(R)-2-methyl-6-nitro-2-{4-[2-(4-
chlorophenyl)oxazol-4-yl)phenoxy)methyl]-2,3-
dihydroimidazo[2,1-b]oxazole,

(S)-2-methyl-6-nitro-2-{4-[2-(4-
chlorophenyl)oxazol-4-yl)phenoxy)methyl]-2,3-
dihydroimidazo[2,1-b]oxazole,
yl]phenoxy)methyl]2,3-dihydroimidazo[2,1-b]oxazole,
(S)-6-nitro-2-{4-[4-(4-
trifluoromethylphenoxy)methyl)piperidin-1-
yl]phenoxy)methyl]2,3-dihydroimidazo[2,1-b]oxazole,
2-methyl-6-nitro-2-{4-(4-
bromocinnamyl)piperazin-1-yl]phenoxy)methyl]2,3-
dihydroimidazo[2,1-b]oxazole,
(R)-2-methyl-6-nitro-2-{4-(4-
bromocinnamyl)piperazin-1-yl]phenoxy)methyl]2,3-
dihydroimidazo[2,1-b]oxazole,
(S)-2-methyl-6-nitro-2-{4-[4-(4-
bromocinnamyl)piperazin-1-yl]phenoxy)methyl]2,3-
dihydroimidazo[2,1-b]oxazole,
2-methyl-6-nitro-2-{2-(4-
trifluoromethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-
6-yloxy)methyl]2,3-dihydroimidazo[2,1-b]oxazole,
(R)-2-methyl-6-nitro-2-{2-(4-
trifluoromethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-
6-yloxy)methyl]2,3-dihydroimidazo[2,1-b]oxazole, and
(S)-2-methyl-6-nitro-2-{2-(4-
trifluoromethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-
6-yloxy)methyl]2,3-dihydroimidazo[2,1-b]oxazole.

The present invention provides a pharmaceutical composition which is an antitubercular agent
comprising, as an active ingredient, the 2,3-dihydro-6-
nitroimidazo[2,1-b]oxazole compound, optically active
form thereof, or pharmacologically acceptable salt
thereof represented by general formula (1).
In particular, the present invention provides a pharmaceutical composition which is an antitubercular agent comprising, as an active ingredient, at least one compound selected from the 2,3-dihydro-6-nitroimidazo-[2,1-b]oxazole compounds that are preferred compound listed above.

The present invention provides a method for producing a compound represented by general formula (1):

\[
\begin{align*}
&\text{R}^1 \quad \text{N} \quad \text{CH}_2 \text{R}^2 \quad \text{O}_2 \text{N} \\
\text{O}_2 \text{N} \\
\end{align*}
\]  
(1)

(wherin \( R^1, R^2, \) and \( n \) have the same definitions as described above),

said method comprising:

a reaction of a 4-nitroimidazole compound represented by the following general formula (2):

\[
\begin{align*}
&\text{N} \\
\text{O}_2 \text{N} \\
\end{align*}
\]  
(2)

(wherin \( X_4 \) represents a halogen atom or a nitro group),

with an epoxy compound represented by the following general formula (3a):
(wherein \( R^1, R^2 \) and \( n \) have the same definitions as described above), to obtain a compound represented by the following general formula (4a):

(4a)

(wherein \( R^1, R^2 \) and \( n \) have the same definitions as described above, and \( x^1 \) represents a halogen atom or a nitro group); and a subsequent ring closure of the obtained compound represented by the above general formula (4a).

The present invention provides a method for producing a compound represented by the following general formula (1w):

(1w)

(wherein \( R^{2a} \) represents a hydrogen atom, or a C1-C6 alkyl group, \( R^{2a} \) represents a group described in any one of (a) to (y) as defined above, and \( n \) represents an integer between 0 and 6).
said method comprising:
a reaction of a compound represented by the
following general formula (3b):

(3b)

(wherein \( R^{2\alpha} \) is the same as described above, and \( X' \)
represents a halogen atom or nitro group),
with a compound \( R^{2\alpha}H:5 \) or a salt thereof (wherein \( R^{2\alpha} \)
represents a group described in any one of (a) to (y)
as defined above), to obtain a compound represented by
the following general formula (4c):

(4c)

(wherein \( R^1 \) has the same definition as described above,
\( R^{2\alpha} \) represents a group described in any one of (a) to
(y) as defined above, and \( X' \) represents a halogen atom
or a nitro group); and a subsequent ring closure of the
obtained compound represented by the above general
formula (4c).

The present invention provides a method for
producing a compound represented by the following
general formula (1w):
(wherein $R^{1A}$, $R^{nA}$, and $n$ have the same definitions as described above),

said method comprising:

a reaction of a compound represented by the following general formula (6):

![Chemical structure](image)

(6)

((wherein $R^{1A}$ and $n$ have the same definitions as described above, and $R^{13}$ represents a Cl-C6 alkylsulfonyl group or a benzenesulfonyl group wherein a Cl-C6 alkyl group may be substituted),

with a compound $R^{25}H(5)$ or a salt thereof (wherein $R^{1A}$ represents a group described in any one of (a) to (y) as defined above).

**BEST MODE FOR CARRYING OUT THE INVENTION**

In the compounds of the present invention,

25 particularly preferred groups of $R^1$, $R^2$, $R^3$ are as follows. $R^1$ is preferably a hydrogen atom or Cl-C6 alkyl group. $R^2$ is preferably a group (d), (i) or (r)
as defined above. \( R^3 \) is preferably a group (ii), (iii) or (x) as defined above. \( R^3 \) is preferably a group (1), (2), (4), (5), (8), (24) or (25) as defined above. \( R^{13} \) is preferably a phenyl C2-C10 alkenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a C1-C4 alkylenedioxy group, a Cl-C6 alkylthio group, a benzoyl group, a cyano group, a nitro group, a C2-C6 alkanoyloxy group, an amino group which may have Cl-C6 alkyl group as substituent(s), a hydroxyl group, a phenyl Cl-C6 alkoxy group, a phenoxy group, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted] or a phenyl Cl-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a piperidinyl group [wherein, on the piperidine ring, at least one phenoxy group may be substituted [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]], a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted] and a phenoxy group (wherein, on the
phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group, may be
substituted), may be substituted).

In this specification, each group represented
by R', R", R' or the like is specifically as follows:
Examples of halogen atoms are fluorine atom,
chlorine atom, bromine atom and iodine atom.

A C1-C6 alkyl group is a straight or branched
alkyl group containing 1 to 6 carbon atoms, examples of
which include a methyl group, ethyl group, n-propyl
group, isopropyl group, n-butyl group, isobutyl group,
tert-butyl group, sec-butyl group, n-pentyl group,
neopentyl group, n-hexyl group, isohexyl group, 3-
methylpentyl group or the like.

A C1-C6 alkoxy group is a group containing a
C1-C6 alkyl group as defined above and an oxygen atom,
examples of which include a methoxy group, ethoxy
group, n-propoxy group, isopropoxy group, n-butoxy
group, isobutoxy group, tert-butoxy group, sec-butoxy
group, n-pentoxy group, neopentoxy group, n-hexyloxy
group, isohexyloxy group, 3-methylpentoxy group or the
like.

A halogen substituted or unsubstituted C1-C6
alkyl group is a straight or branched alkyl group
containing 1 to 6 carbon atoms as defined above and
optionally substituted by 1 to 7 halogen atoms,
examples of which include a methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, tert-butyl group, sec-butyl group, n-pentyl group, neopentyl group, n-hexyl group, iso-hexyl group, 3-methylpentyl group, fluoromethyl group, difluoromethyl group, trifluoromethyl group, chloromethyl group, dichloromethyl group, trichloromethyl group, bromomethyl group, dibromomethyl group, dichlorofluoromethyl group, 2,2,2-trifluoroethyl group, pentafluoroethyl group, 2-chloroethyl group, 3,3,3-trifluoropropyl group, heptafluoropropyl group, heptafluoroisopropyl group, 3-chloropropyl group, 2-chloropropyl group, 3-bromopropyl group, 4,4,4-trifluorobutyl group, 4,4,4,3,3-pentafluorobutyl group, 4-chlorobutyl group, 4-bromobutyl group, 2-chlorobutyl group, 5,5,5-trifluoropentyl group, 3-chloropentyl group, 6,6,6-trifluorohexyl group, 6-chlorohexyl group or the like.

A halogen substituted or unsubstituted C1-C6 alkoxy group is a C1-C6 alkoxy group as defined above and an alkoxy group substituted by 1 to 7 halogen atoms, examples of which include a methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, isobutoxy group, tert-butoxy group, sec-butoxy group, n-pentox group, neopentox group, n-hexyloxy group, iso-hexyloxy group, 3-methypentox group, fluoromethoxy group, difluoromethoxy group, trifluoromethoxy group, chloromethoxy group.
dichloromethoxy group, trichloromethoxy group,
bromomethoxy group, dibromomethoxy group, dichloro-
fluoromethoxy group, 2,2,2-trifluoroethoxy group,
pentafluoroethoxy group, 2-chloroethoxy group, 3,3,3-
5 trifluoroproproxy group, heptafluoroproproxy group,
heptafluoroisoproproxy group, 3-chloroproproxy group, 2-
chloroproproxy group, 3-bromoproproxy group, 4,4,4-
trifluorobutoxy group, 4,4,4,3,3-pentafluorobutoxy
group, 4-chlorobutoxy group, 4-bromobutoxy group, 2-
10 chlorobutoxy group, 5,5,5-trifluoropentoxy group, 5-
chloropentoxy group, 5,6,6-trifluorohexyloxy group, 6-
chlorohexyloxy group or the like.

A phenoxy group (wherein, on the phenyl ring,
at least one selected from the group consisting of a
15 halogen atom, a halogen substituted or unsubstituted
C1-C6 alkyl group and a halogen substituted or
unsubstituted C1-C6 alkoxy group, may be substituted)
includes a phenoxy group (wherein, on the phenyl ring,
1 to 5, preferably 1 to 3 groups selected from the
group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group and a
halogen substituted or unsubstituted C1-C6 alkoxy
group, may be substituted), for example, a phenoxy
group, 2-fluorophenoxy group, 3-fluorophenoxy group, 4-
25 fluorophenoxy group, 2-chlorophenoxy group, 3-
chlorophenoxy group, 4-chlorophenoxy group, 2-
bromophenoxy group, 3-bromophenoxy group, 4-
bromophenoxy group, 2,3-dichlorophenoxy group, 3,4-
dichlorophenoxy group, 2,4-dichlorophenoxy group, 3,4,5-trichlorophenoxy group, 2,4,6-trichlorophenoxy group, 2,3,4,5,6-pentafluorophenoxy group, 2-methylphenoxy group, 3-methylphenoxy group, 4-methylphenoxy group, 2-ethylphenoxy group, 3-ethylphenoxy group, 4-ethylphenoxy group, 4-n-propylphenoxy group, 4-tert-butylphenoxy group, 4-n-butylphenoxy group, 2-trifluoromethylphenoxy group, 3-trifluoromethylphenoxy group, 4-trifluoromethylphenoxy group, 2-pentafluoroethylphenoxy group, 3-pentafluoroethylphenoxy group, 2,3-dimethylphenoxy group, 3,4,5-trimethylphenoxy group, 4-n-pentylphenoxy group, 4-n-hexylphenoxy group, 2-methoxyphenoxy group, 3-methoxyphenoxy group, 4-methoxyphenoxy group, 2-ethoxyphenoxy group, 3-ethoxyphenoxy group, 4-ethoxyphenoxy group, 4-n-propoxyphenoxy group, 4-tert-butoxyphenoxy group, 4-n-butoxyphenoxy group, 2-trifluoromethoxyphenoxy group, 3-trifluoromethoxyphenoxy group, 4-trifluoromethoxyphenoxy group, 2-pentafluoroethoxyphenoxy group, 3-pentafluoroethoxyphenoxy group, 2,3-dimethoxyphenoxy group, 3,4,5-trimethoxyphenoxy group, 4-n-pentyloxyphenoxy group, 4-n-hexyloxyphenoxy group or the like.

A piperidyl group [wherein, on the piperidine ring, at least one phenoxy group may be substituted (wherein, on the phenyl ring, at least one selected
from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted) includes a piperidyl group

5 wherein, on the piperidine ring, 1 to 3 phenoxy groups may be substituted (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen

10 substituted or unsubstituted Cl-C6 alkoxy group, may be substituted; for example, a 1-piperidyl group, 2-piperidyl group, 3-piperidyl group, 4-piperidyl group, 4-phenoxy-1-piperidyl group, 2,4-diphenoxy-1-piperidyl group, 2,4,6-triphenoxy-1-piperidyl group, 2-(2-fluorophenoxy)-1-piperidyl group, 3-(3-fluorophenoxy)-2-piperidyl group, 4-(4-fluorophenoxy)-3-piperidyl group, 2-(2-chlorophenoxy)-4-piperidyl group, 3-(3-chlorophenoxy)-5-piperidyl group, 4-(4-chlorophenoxy)-2-piperidyl group, 5-(2-bromophenoxy)-2-piperidyl group, 6-(3-bromophenoxy)-3-piperidyl group, 4-(4-bromophenoxy)-1-piperidyl group, 3-(2,3-dichlorophenoxy)-2-piperidyl group, 4-(3,4-dichlorophenoxy)-3-piperidyl group, 3-(2,4-dichlorophenoxy)-4-piperidyl group, 2-(3,4,5-trichlorophenoxy)-3-piperidyl group, 6-(2,4,6-trichlorophenoxy)-2-piperidyl group, 3-(2,3,4,5,6-pentafluorophenoxy)-1-piperidyl group, 4-(2-methylphenoxy)-1-piperidyl group, 5-(3-methylphenoxy)-
2-piperidyl group, 6-(4-methylphenoxy)-3-piperidyl group, 1-(2-ethylphenoxy)-4-piperidyl group, 2-(3-ethylphenoxy)-1-piperidyl group, 3-(4-ethylphenoxy)-2-piperidyl group, 4-(4-n-propylphenoxy)-3-piperidyl group, 3-(4-tert-butylphenoxy)-4-piperidyl group, 2-(4-n-butylphenoxy)-3-piperidyl group, 1-(2-trifluoromethylphenoxy)-2-piperidyl group, 2-(3-trifluoromethylphenoxy)-1-piperidyl group, 3-(4-trifluoromethylphenoxy)-1-piperidyl group, 1-(2-pentafluoroethylphenoxy)-4-piperidyl group, 1-(3-pentafluoroethylphenoxy)-4-piperidyl group, 4-(2,3-dimethylphenoxy)-1-piperidyl group, 1-(3,4,5-trimethylphenoxy)-4-piperidyl group, 1-(4-n-pentylphenoxy)-4-piperidyl group, 4-(4-n-hexylphenoxy)-1-piperidyl group, 4-(2-methoxyphenoxy)-1-piperidyl group, 1-(3-methoxyphenoxy)-4-piperidyl group, 1-(4-methoxyphenoxy)-4-piperidyl group, 2-(2-ethoxyphenoxy)-3-piperidyl group, 3-(3-ethoxyphenoxy)-4-piperidyl group, 4-(4-ethoxyphenoxy)-3-piperidyl group, 3-(4-n-propoxyphenoxy)-2-piperidyl group, 2-(4-tert-butoxyphenoxy)-1-piperidyl group, 1-(4-n-butoxyphenoxy)-2-piperidyl group, 2-(2-trifluoromethoxyphenoxy)-3-piperidyl group, 3-(3-trifluoromethoxyphenoxy)-4-piperidyl group, 4-(4-trifluoromethoxyphenoxy)-3-piperidyl group, 3-(2-pentafluoroethoxyphenoxy)-2-piperidyl group, 2-(4-pentafluoroethoxyphenoxy)-1-piperidyl group, 1-(2,3-dimethoxyphenoxy)-4-piperidyl group, 4-(3,4,5-
trimethoxyphenoxy)-1-piperidyl group, 4-(4-n-pentyloxyphenoxy)-1-piperidyl group, 4-(4-n-hexyloxyphenoxy)-1-piperidyl group or the like.

A phenyl group (wherein, on the phenyl ring, at least one piperidyl group may be substituted (wherein, on the piperidine ring, at least one phenoxy group may be substituted (wherein, on the phenyl group, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted)) includes a phenyl group (wherein, on the phenyl ring, 1 to 3 piperidyl groups may be substituted (wherein, on the piperidine ring, 1 to 3 phenoxy groups may be substituted (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted))); for example, a phenyl group, 4-(1-piperidyl)phenyl group, 2,4-di(1-piperidyl)phenyl group, 2,4,6-tri(1-piperidyl)phenyl group, 3-(4-piperidyl)phenyl group, 2-(2-piperidyl)phenyl group, 4-(3-piperidyl)phenyl group, 3-(4-phenoxy-1-piperidyl)phenyl group, 2-(2,4-diphtenoxy-1-piperidyl)phenyl group, 4-(2,4,6-triphtenoxy-1-piperidyl)phenyl group, 3-[2-(2-fluorophenoxy)-1-piperidyl]phenyl group, 2-[3-(3-fluorophenoxy)-2-piperidyl]phenyl group, 2-[3-(3-fluorophenoxy)-2-...
piperidyl]phenyl group, 4-[4-(4-fluorophenoxy)-3-piperidyl]phenyl group, 3-[2-(2-chlorophenoxy)-4-piperidyl]phenyl group, 2-[3-(3-chlorophenoxy)-5-piperidyl]phenyl group, 4-[4-(4-chlorophenoxy)-2-piperidyl]phenyl group, 3-[5-(2-bromophenoxy)-2-piperidyl]phenyl group, 2-[6-(3-bromophenoxy)-3-piperidyl]phenyl group, 4-[4-(4-bromophenoxy)-1-piperidyl]phenyl group, 3-[3-(2,3-dichlorophenoxy)-2-piperidyl]phenyl group, 2-[4-(3,4-dichlorophenoxy)-3-piperidyl]phenyl group, 4-[3-(2,4-dichlorophenoxy)-4-piperidyl]phenyl group, 3-[2-(3,4,5-trichlorophenoxy)-3-piperidyl]phenyl group, 2-[6-(2,4,6-trichlorophenoxy)-2-piperidyl]phenyl group, 4-[3-(2,3,4,5,6-pentafluorophenoxy)-1-piperidyl]phenyl group, 3-[4-(2-methylphenoxy)-1-piperidyl]phenyl group, 2-[5-(3-methylphenoxy)-2-piperidyl]phenyl group, 4-[6-(4-methylphenoxy)-3-piperidyl]phenyl group, 3-[1-(2-ethylphenoxy)-4-piperidyl]phenyl group, 2-[2-(2-ethylphenoxy)-1-piperidyl]phenyl group, 4-[3-(4-ethylphenoxy)-2-piperidyl]phenyl group, 3-[4-(4-n-propylphenoxy)-3-piperidyl]phenyl group, 2-[3-(4-tert-butylphenoxy)-4-piperidyl]phenyl group, 4-[2-(4-n-butylphenoxy)-3-piperidyl]phenyl group, 3-[1-(2-trifluoromethylphenoxy)-2-piperidyl]phenyl group, 2-[2-(3-trifluoromethylphenoxy)-1-piperidyl]phenyl group, 4-[3-(4-trifluoromethylphenoxy)-1-piperidyl]phenyl group, 3-[1-(2-pentafluoroethylphenoxy)-4-piperidyl]phenyl group, 2-[1-(3-pentafluoroethylphenoxy)-4-
piperidyl]phenyl group, 4-(4-(2,3-dimethylphenoxy)-1-piperidyl]phenyl group, 3-[1-(3,4,5-trimethylphenoxy)-4-piperidyl]phenyl group, 2-[1-(4-n-pentylphenoxy)-4-piperidyl]phenyl group, 4-(4-(4-n-hexylphenoxy)-1-piperidyl]phenyl group, 3-[4-(2-methoxyphenoxy)-1-piperidyl]phenyl group, 2-[1-(3-methoxyphenoxy)-4-piperidyl]phenyl group, 4-[1-(4-methoxyphenoxy)-4-piperidyl]phenyl group, 3-[2-(2-ethoxyphenoxy)-3-piperidyl]phenyl group, 2-[3-(3-ethoxyphenoxy)-4-piperidyl]phenyl group, 4-[4-(4-ethoxyphenoxy)-3-piperidyl]phenyl group, 3-[3-(4-n-propoxyphenoxy)-2-piperidyl]phenyl group, 2-[2-(4-tert-butoxyphenoxy)-1-piperidyl]phenyl group, 4-[1-(4-n-butoxyphenoxy)-2-piperidyl]phenyl group, 3-[2-(2-trifluoromethoxyphenoxy)-3-piperidyl]phenyl group, 2-[3-(3-trifluoromethoxyphenoxy)-4-piperidyl]phenyl group, 4-[4-(4-trifluoromethoxyphenoxy)-1-piperidyl]phenyl group, 3-[3-(2-pentafluoroethoxyphenoxy)-2-piperidyl]phenyl group, 2-[2-(4-pentafluoroethoxyphenoxy)-1-piperidyl]phenyl group, 4-[1-(2,3-dimethoxyphenoxy)-4-piperidyl]phenyl group, 3-[4-(3,4,5-trimethoxyphenoxy)-1-piperidyl]phenyl group, 2-[4-(4-n-pentylphenoxy)-1-piperidyl]phenyl group, 4-[4-(4-n-hexylphenoxy)-1-piperidyl]phenyl group or the like.

A phenyl group wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted
C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted; includes a phenyl group unsubstituted or substituted by 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group, as defined above, examples of which include a phenyl group, 2-fluorophenyl group, 3-fluorophenyl group, 4-fluorophenyl group, 2-chlorophenyl group, 3-chlorophenyl group, 4-chlorophenyl group, 2-bromophenyl group, 3-bromophenyl group, 4-bromophenyl group, 2-iodophenyl group, 3-iodophenyl group, 4-iodophenyl group, 2,3-difluorophenyl group, 3,4-difluorophenyl group, 3,5-difluorophenyl group, 2,4-difluorophenyl group, 2,6-difluorophenyl group, 2,3-dichlorophenyl group, 3,4-dichlorophenyl group, 3,5-dichlorophenyl group, 2,4-dichlorophenyl group, 2,6-dichlorophenyl group, 3,4,5-trifluorophenyl group, 3,4,5-trichlorophenyl group, 2,4,6-trifluorophenyl group, 2,4,6-trichlorophenyl group, 2-fluoro-4-bromophenyl group, 4-chloro-3-fluorophenyl group, 2,3,4-trichlorophenyl group, 2,3,4,5,6-pentafluorophenyl group, 2,4,6-trimethylphenyl group, 4-n-butylphenyl group, 2,4-dimethylphenyl group, 2,3-dimethylphenyl group, 2,6-dimethylphenyl group, 3,5-dimethylphenyl group, 3,5-dimethylphenyl group, 3,5-dimethylphenyl group, 4-n-butoxyphenyl group, 2,4-dimethoxyphenyl group.
group, 2,3-dimethoxyphenyl group, 2,6-dimethoxyphenyl group, 3,5-dimethoxyphenyl group, 2,5-dimethoxyphenyl group, 2,4,6-trimethoxyphenyl group, 3,5-ditrifluoromethoxyphenyl group, 3-chloro-4-methoxyphenyl group, 2-chloro-4-trifluoromethoxyphenyl group, 3-methyl-4-fluorophenyl group, 4-bromo-3-trifluoromethylphenyl group, 2-methylphenyl group, 3-methylphenyl group, 4-methylphenyl group, 2-methyl-3-chlorophenyl group, 3-methyl-4-chlorophenyl group, 2-chloro-4-methylphenyl group, 2-methyl-3-fluorophenyl group, 2-trifluoromethylphenyl group, 3-trifluoromethylphenyl group, 4-trifluoromethylphenyl group, 2-pentafluoroethylphenyl group, 3-pentafluoroethylphenyl group, 4-pentafluoroethylphenyl group, 2-isopropylphenyl group, 3-isopropylphenyl group, 4-isopropylphenyl group, 2-tert-butylphenyl group, 3-tert-butylphenyl group, 4-tert-butylphenyl group, 2-sec-butylphenyl group, 3-sec-butylphenyl group, 4-sec-butylphenyl group, 2-n-heptafluoropropylphenyl group, 3-n-heptafluoropropylphenyl group, 4-n-heptafluoropropylphenyl group, 4-pentylphenyl group, 4-hexylphenyl group, 2-methoxyphenyl group, 3-methoxyphenyl group, 4-methoxyphenyl group, 3-chloro-2-methoxyphenyl group, 2-fluoro-3-methoxyphenyl group, 2-fluoro-4-methoxyphenyl group, 2,3,4-trifluorophenyl group, 2-trifluoromethoxyphenyl group, 3-trifluoromethoxyphenyl group, 4-trifluoromethoxyphenyl group, 5-fluoro-2-trifluoromethoxyphenyl group, 2-fluoro-3-
trifluoromethoxyphenyl group, 3-fluoro-4-
trifluoromethoxyphenyl group, 3-chloro-2-
trifluoromethoxyphenyl group, 2-chloro-3-
trifluoromethoxyphenyl group, 3-chloro-4-trifluoro-
methoxyphenyl group, 2-pentafluoroethoxyphenyl group,
3-pentafluoroethoxyphenyl group, 4-pentafluoroethoxy-
phenyl group, 3-chloro-2-pentafluoroethoxyphenyl group,
2-chloro-3-pentafluoroethoxyphenyl group, 3-chloro-4-
pentafluoroethoxyphenyl group, 2-isopropoxyphenyl
group, 3-isopropoxyphenyl group, 4-isopropoxyphenyl
group, 2-tert-butoxyphenyl group, 3-tert-butoxyphenyl
group, 4-tert-butoxyphenyl group, 2-sec-butoxyphenyl
group, 3-sec-butoxyphenyl group, 4-sec-butoxyphenyl
group, 2-n-heptafluoropropoxyphenyl group, 3-n-
heptafluoropropoxyphenyl group, 4-n-heptafluoropropoxy-
phenyl group, 4-n-pentoxypenyl group, 4-n-hexyloxy-
phenyl group or the like.

Examples of a phenyl C1-C6 alkyl group
include a benzyl group, 1-phenethyl group, 2-phenethyl
group, 3-phenylpropyl group, 2-phenylpropyl group, 4-
phenylbutyl group, 5-phenylpentyl group, 4-phenylpentyl
group, 6-phenylhexyl group, 2-methyl-3-phenylpropyl
group, 1,1-dimethyl-2-phenylethyl group or the like.

A phenyl C1-C6 alkyl group (wherein, on the
phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group, may be
substituted) includes a phenyl C1-C6 alkyl group
unsubstituted or substituted on the phenyl ring by 1 to
5, preferably 1 to 3 substituents selected from the
group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group and a
halogen substituted or unsubstituted C1-C6 alkoxy
group, examples of which include a benzyl group, 1-
phenethyl group, 2-phenethyl group, 3-phenylpropyl
group, 2-phenylpropyl group, 4-phenylbutyl group, 5-
phenylpentyl group, 4-phenylpentyl group, 6-phenylhexyl
group, 2-fluorobenzyl group, 3-fluorobenzyl group, 6-
fluorobenzyl group, 2-chlorobenzyl group, 3-
chlorobenzyl group, 4-chlorobenzyl group, 2-bromobenzyl
group, 3-bromobenzyl group, 4-bromobenzyl group, 2-
iodobenzyl group, 3-iodobenzyl group, 4-iodobenzyl
group, 2,3-difluorobenzyl group, 3,4-difluorobenzyl
group, 3,5-difluorobenzyl group, 2,4-difluorobenzyl
group, 2,6-difluorobenzyl group, 2,3-dichlorobenzyl
group, 3,4-dichlorobenzyl group, 3,5-dichlorobenzyl
group, 2,4-dichlorobenzyl group, 2,6-dichlorobenzyl
group, 2-fluoro-4-bromobenzyl group, 4-chloro-3-
fluorobenzyl group, 2,3,4-trichlorobenzyl group, 3,4,5-
trifluorobenzyl group, 2,4,6-trichlorobenzyl group, 4-
isopropylbenzyl group, 4-n-butylbenzyl group, 4-
methylbenzyl group, 2-methylbenzyl group, 3-
methylbenzyl group, 2,4-dimethylbenzyl group, 2,3-
dimethylbenzyl group, 2,6-dimethylbenzyl group, 3,5-
dimethylbenzyl group, 2,5-dimethylbenzyl group, 2,4,
6-trimethylbenzyl group, 3,5-ditrifluoromethylbenzyl group, 2,3,4,5,6-pentafluorobenzyl group, 4-isopropoxybenzyl group, 4-n-butoxybenzyl group, 4-methoxybenzyl group, 2-methoxybenzyl group, 3-methoxybenzyl group, 2,4-dimethoxybenzyl group, 2,3-dimethoxybenzyl group, 2,6-dimethoxybenzyl group, 3,5-dimethoxybenzyl group, 2,5-dimethoxybenzyl group, 2,4,6-trimethoxybenzyl group, 3,5-ditrifluoromethoxybenzyl group, 2-isopropoxybenzyl group, 3-chloro-4-methoxybenzyl group, 2-chloro-4-trifluoromethoxybenzyl group, 3-methyl-4-fluorobenzyl group, 4-bromo-3-trifluoromethylbenzyl group, 2-trifluoromethylbenzyl group, 3-trifluoromethylbenzyl group, 4-trifluoromethylbenzyl group, 2-pentafluoroethylbenzyl group, 3-pentafluoroethylbenzyl group, 4-pentafluoroethylbenzyl group, 2-trifluoromethoxybenzyl group, 3-trifluoromethoxybenzyl group, 4-trifluoromethoxybenzyl group, 2-pentafluoroethoxybenzyl group, 3-pentafluoroethoxybenzyl group, 4-pentafluoroethoxybenzyl group, 2-(2-trifluoromethylphenyl)ethyl group, 2-(3-trifluoromethylphenyl)ethyl group, 2-(4-trifluoromethylphenyl)ethyl group, 2-(2-trifluoromethoxyphenyl)ethyl group, 2-(3-(trifluoromethoxyphenyl)ethyl group, 2-(4-trifluoromethoxyphenyl)ethyl group, 2-(2-pentafluoroethoxyphenyl)ethyl group, 2-(3-pentafluoroethoxyphenyl)ethyl group, 2-(4-pentafluoroethoxyphenyl)ethyl group, 3-(2-trifluoromethylphenyl)propyl group, 3-(3-trifluoromethylphenyl)propyl group, 3-(4-
trifluoromethylphenyl)propyl group, 3-(2-trifluoromethoxyphenyl)propyl group, 3-(3-trifluoromethoxyphenyl)propyl group, 3-(4-trifluoromethoxyphenyl)propyl group, 3-(3-pentafluoroethoxyphenyl)propyl group, 3-(4-pentafluoroethoxyphenyl)propyl group, 4-(3-pentafluoroethoxyphenyl)butyl group, 5-(4-trifluoromethylphenyl)-pentyl group, 4-(4-trifluoromethylphenyl)pentyl group, 4-(4-trifluoromethoxyphenyl)pentyl group, 6-(3-trifluoromethylphenyl)hexyl group, 6-(4-trifluoromethoxyphenyl)hexyl group or the like.

A phenyl Cl-C6 alkyl group [wherein, on the phenyl group, at least one selected from the group consisting of a halogen atom, a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted), a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group (may be substituted) includes a phenyl alkyl group wherein the alkyl moiety is a straight or branched alkyl group containing 1 to 6 carbon atoms (wherein, on the phenyl group, 1 to 5, preferably 1 to 3 groups selected from the group consisting of a halogen atom, a phenyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 groups selected from the group consisting of a halogen.
atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], examples of which include a 4-(4-trifluoromethylphenyl)benzyl group, 4-(4-trifluoromethoxyphenyl)benzyl group, 4-(4-chlorophenyl)benzyl group, 4-(4-trifluoromethylphenyl)-benzyl group, 4-phenylbenzyl group, 3-phenylbenzyl group, 3,4-diphenylbenzyl group, 3,4,5-triphenylbenzyl group, 4-nitro-3-trifluoromethylbenzyl group, 4-trifluoromethoxy-3-phenylbenzyl group or the like, in addition to the above-mentioned phenyl C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted].

A piperazinyl group [wherein, on the piperazine ring, at least one phenyl C1-C6 alkyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)] includes a piperazinyl group [wherein, on the piperidine ring, 1 to 3 phenyl C1-C6 alkyl groups may
be substituted (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted), for example, 1-piperazinyl group, 2-piperazinyl group, 3,4-dibenzyl-1-piperazinyl group, 2,3,4-tribenzyl-1-piperazinyl group, 4-benzyl-1-piperazinyl group, 4-(2-phenethyl)-1-piperazinyl group, 4-(3-phenylpropyl)-1-piperazinyl group, 4-(4-phenylbutyl)-1-piperazinyl group, 4-(5-phenylpentyl)-1-piperazinyl group, 4-(6-phenylhexyl)-1-piperazinyl group, 4-(2-fluorobenzyl)-1-piperazinyl group, 4-(3-fluorobenzyl)-1-piperazinyl group, 4-(4-fluorobenzyl)-1-piperazinyl group, 4-(2-chlorobenzyl)-1-piperazinyl group, 4-(3-chlorobenzyl)-1-piperazinyl group, 4-(4-chlorobenzyl)-1-piperazinyl group, 4-(2,3-dichlorobenzyl)-1-piperazinyl group, 4-(2,4-dichlorobenzyl)-1-piperazinyl group, 4-(3,4-dichlorobenzyl)-1-piperazinyl group, 4-(3,5-dichlorobenzyl)-1-piperazinyl group, 4-(3,4,5-trichlorobenzyl)-1-piperazinyl group, 4-(2,3,4,5,6-pentafluorobenzyl)-1-piperazinyl group, 4-(2-trifluoromethylbenzyl)-1-piperazinyl group, 4-(3-trifluoromethylbenzyl)-1-piperazinyl group, 4-(4-trifluoromethylbenzyl)-1-piperazinyl group, 4-(4-methylbenzyl)-1-piperazinyl group, 4-(3,4-dimethylbenzyl)-1-piperazinyl group, 4-(2,4,6-
trimethylbenzyl)-1-piperazinyl group, 4-(2-
pentafluoroethylbenzyl)-1-piperazinyl group, 4-(3-
pentafluoroethylbenzyl)-1-piperazinyl group, 4-(4-
pentafluoroethylbenzyl)-1-piperazinyl group, 4-(2-
trifluoromethoxybenzyl)-1-piperazinyl group, 4-(3-
trifluoromethoxybenzyl)-1-piperazinyl group, 4-(4-
trifluoromethoxybenzyl)-1-piperazinyl group, 4-(4-
methoxybenzyl)-1-piperazinyl group, 4-(3,4-
dimethoxybenzyl)-1-piperazinyl group, 4-(2,4,6-
trimethoxybenzyl)-1-piperazinyl group, 4-(2-
pentafluoroethoxybenzyl)-1-piperazinyl group, 4-(3-
pentafluoroethoxybenzyl)-1-piperazinyl group, 4-(4-
pentafluoroethoxybenzyl)-1-piperazinyl group, 4-(2-(4-
trifluoromethoxyphenyl)ethyl)-1-piperazinyl group, 4-
[3-(4-trifluoromethoxyphenyl)propyl]-1-piperazinyl
group, 4-[4-(4-trifluoromethoxyphenyl)butyl]-1-
piperazinyl group, 4-[5-(4-trifluoromethoxyphenyl)-pentyl]-1-piperazinyl group, 4-[6-(4-
trifluoromethoxyphenyl)hexyl]-1-piperazinyl group, 4-
[2-(4-trifluoromethylphenyl)ethyl]-1-piperazinyl group, 4-(3-(4-trifluoromethylphenyl)propyl)-1-piperazinyl
group, 4-[4-(4-trifluoromethoxyphenyl)butyl]-1-
piperazinyl group, 4-[5-(4-trifluoromethylphenyl)-pentyl]-1-piperazinyl group, 4-[6-(4-
trifluoromethylphenyl)hexyl]-1-piperazinyl group or the
like.

A piperidyl group (wherein, on the piperidine
ring, at least one selected from the group consisting
of an amino group (wherein, on the amino group, at least one selected from the group consisting of a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted] and a C1-C6 alkyl group, may be substituted), a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted) and a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one group selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), may be substituted] includes a piperidyl group (wherein, on the piperidine ring, 1 to 3 substituents selected from the group consisting of an amino group (wherein, on the amino group, 1 or 2 substituents selected from the group consisting of a phenyl group [wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted] and a C1-C6 alkyl group, may
be substituted), a phenoxy group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted) and a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted), for example, a 1-piperidyl group, 2-piperidyl group, 3-piperidyl group, 4-piperidyl group, 2,4-diamino-1-piperidyl group, 2,4,6-triamino-1-piperidyl group, 2-amino-1-piperidyl group, 3-amino-1-piperidyl group, 4-amino-1-piperidyl group, 4-methylamino-1-piperidyl group, 4-ethylamino-1-piperidyl group, 4-n-propylamino-1-piperidyl group, 4-dimethylamino-1-piperidyl group, 4-diethylamino-1-piperidyl group, 4-di-n-propylamino-1-piperidyl group, 4-phenylamino-1-piperidyl group, 4-(N-phenyl-N-methylamino)-1-piperidyl group, 4-(2-fluorophenylamino)-1-piperidyl group, 4-(3-fluorophenylamino)-1-piperidyl group, 4-(4-fluorophenylamino)-1-piperidyl group, 4-(2-chlorophenylamino)-1-piperidyl group, 4-(3-chlorophenylamino)-1-piperidyl group, 4-(4-chlorophenylamino)-1-piperidyl group, 4-(2,3-
dichlorophenylamino)-1-piperidyl group, 4-(2,4,6-trifluorophenylamino)-1-piperidyl group, 4-(2,4-dichlorophenylamino)-1-piperidyl group, 4-(3,4-dichlorophenylamino)-1-piperidyl group, 4-(3,5-dichlorophenylamino)-1-piperidyl group, 4-(2,3,4,5,6-pentafluorophenylamino)-1-piperidyl group, 4-(2-trifluoromethylphenylamino)-1-piperidyl group, 4-(2-methylphenylamino)-1-piperidyl group, 4-(2,3-dimethylphenylamino)-1-piperidyl group, 4-(2-trifluoromethylphenylamino)-1-piperidyl group, 4-(2,4,6-trimethylphenylamino)-1-piperidyl group, 4-(4-trifluoromethylphenylamino)-1-piperidyl group, 4-(2-pentafluoroethylphenylamino)-1-piperidyl group, 4-(3-pentafluoroethylphenylamino)-1-piperidyl group, 4-(4-pentafluoroethylphenylamino)-1-piperidyl group, 4-(2-trifluoromethoxyphenylamino)-1-piperidyl group, 4-(2-methoxyphenylamino)-1-piperidyl group, 4-(2,3-dimethoxyphenylamino)-1-piperidyl group, 4-(2,4,6-trimethoxyphenylamino)-1-piperidyl group, 4-(N-methyl-N-(2,4,6-trimethoxyphenylamino))-1-piperidyl group, 4-[(N-methyl-N-(3,4-dimethylphenylamino))-1-piperidyl group, 4-(3-trifluoromethoxyphenylamino)-1-piperidyl group, 4-(4-trifluoromethoxyphenylamino)-1-piperidyl group, 4-(2-pentafluoroethoxyphenylamino)-1-piperidyl group, 4-(3-pentafluoroethoxyphenylamino)-1-piperidyl group, 4-(4-pentafluoroethoxyphenylamino)-1-piperidyl group, 4-phenoxy-1-piperidyl group, 2,4-diphenoxy-1-piperidyl group, 2,4,6-triphenoxy-1-piperidyl group, 2-
(2-fluorophenoxy)-1-piperidyl group, 5-(3-fluorophenoxy)-2-piperidyl group, 4-(4-fluorophenoxy)-3-piperidyl group, 2-(2-chlorophenoxy)-4-piperidyl group, 3-(3-chlorophenoxy)-5-piperidyl group, 4-(4-chlorophenoxy)-2-piperidyl group, 5-(2-bromophenoxy)-2-piperidyl group, 6-(3-bromophenoxy)-3-piperidyl group, 4-(4-bromophenoxy)-1-piperidyl group, 3-(2,3-dichlorophenoxy)-2-piperidyl group, 4-(3,4-dichlorophenoxy)-3-piperidyl group, 3-(2,4-dichlorophenoxy)-4-piperidyl group, 2-(3,4,5-trichlorophenoxy)-3-piperidyl group, 6-(2,4,6-trichlorophenoxy)-2-piperidyl group, 3-(2,3,4,5,6-pentafluorophenoxy)-1-piperidyl group, 4-(2-methylphenoxy)-1-piperidyl group, 5-(3-methylphenoxy)-2-piperidyl group, 6-(4-methylphenoxy)-3-piperidyl group, 1-(2-ethylphenoxy)-4-piperidyl group, 2-(3-ethylphenoxy)-1-piperidyl group, 3-(4-ethylphenoxy)-2-piperidyl group, 4-(4-n-propylphenoxy)-3-piperidyl group, 3-(4-tert-butylphenoxy)-4-piperidyl group, 2-(4-n-butylphenoxy)-3-piperidyl group, 1-(2-trifluoromethylphenoxy)-2-piperidyl group, 2-(3-trifluoromethylphenoxy)-1-piperidyl group, 3-(4-trifluoromethylphenoxy)-1-piperidyl group, 1-(2-pentafluoroethylphenoxy)-4-piperidyl group, 1-(3-pentafluoroethylphenoxy)-4-piperidyl group, 4-(2,3-dimethylphenoxy)-1-piperidyl group, 3-(3,4,5-trimethylphenoxy)-4-piperidyl group, 1-(4-n-pentylphenoxy)-4-piperidyl group, 4-(4-n-hexylphenoxy)-
1-piperidyl group, 4-(2-methoxyphenoxy)-1-piperidyl group, 1-(3-methoxyphenoxy)-4-piperidyl group, 1-(4-methoxyphenoxy)-4-piperidyl group, 2-(2-ethoxyphenoxy)-3-piperidyl group, 3-(3-ethoxyphenoxy)-4-piperidyl group, 4-(4-ethoxyphenoxy)-3-piperidyl group, 3-(4-n-propoxyphenoxy)-2-piperidyl group, 2-(4-tert-butoxyphenoxy)-1-piperidyl group, 1-(4-n-butoxyphenoxy)-2-piperidyl group, 2-(2-trifluoromethoxyphenoxy)-3-piperidyl group, 3-(3-trifluoromethoxyphenoxy)-4-piperidyl group, 4-(4-trifluoromethoxyphenoxy)-3-piperidyl group, 3-(2-pentafluoroethoxyphenoxy)-2-piperidyl group, 2-(4-pentafluoroethoxyphenoxy)-1-piperidyl group, 1-(2,3-dimethoxyphenoxy)-4-piperidyl group, 4-(3,4,5-trimethoxyphenoxy)-1-piperidyl group, 4-(4-n-pentyloxyphenoxy)-1-piperidyl group, 4-(4-n-hexyloxyphenoxy)-1-piperidyl group, 4-benzyl-1-piperidyl group, 2,4-dibenzyl-1-piperidyl group, 2,4,6-tribenzyl-1-piperidyl group, 2-(2-fluorobenzyl)-1-piperidyl group, 3-[2-(3-fluorophenyl)ethyl]-2-piperidyl group, 4-[1-(4-fluorophenyl)ethyl]-3-piperidyl group, 2-[3-(2-chlorophenyl)propyl]-4-piperidyl group, 3-[4-(3-chlorophenyl)butyl]-5-piperidyl group, 4-[5-(4-chlorophenyl)pentyl]-2-piperidyl group, 5-[6-(2-bromophenyl)hexyl]-2-piperidyl group, 6-(3-bromobenzyl)-3-piperidyl group, 4-(4-bromobenzyl)-1-piperidyl group, 3-(2,3-dichlorobenzyl)-2-piperidyl group, 4-(3,4-dichlorobenzyl)-3-piperidyl group.
group, 3-(2,4-dichlorobenzyl)-4-piperidyl group, 2-
(3,4,5-trichlorobenzyl)-3-piperidyl group, 6-(2,4,6-
trichlorobenzyl)-2-piperidyl group, 3-(2,3,4,5,6-
pentafluorobenzyl)-1-piperidyl group, 4-(2-
methylbenzyl)-1-piperidyl group, 5-{2-(3-
methylphenyl)ethyl}-2-piperidyl group, 6-[3-(4-
methylphenyl)propyl]-3-piperidyl group, 1-[4-(2-
ethylphenyl)butyl]-4-piperidyl group, 2-[5-(3-
ethylphenyl)pentyl]-1-piperidyl group, 3-[6-(4-
ethylphenyl)hexyl]-2-piperidyl group, 4-(4-n-
propylbenzyl)-3-piperidyl group, 3-(4-tert-
butylbenzyl)-4-piperidyl group, 2-(4-n-butylbenzyl)-3-
piperidyl group, 1-(2-trifluoromethylbenzyl)-2-
piperidyl group; 2-(3-trifluoromethylbenzyl)-1-
piperidyl group, 3-(4-trifluoromethylbenzyl)-1-
piperidyl group, 1-(2-pentafluoroethylbenzyl)-4-
piperidyl group, 1-(3-pentafluoroethylbenzyl)-4-
piperidyl group, 4-(2,3-dimethylbenzyl)-1-piperidyl
group, 1-(3,4,5-trimethylbenzyl)-4-piperidyl group, 1-
(4-n-pentylbenzyl)-4-piperidyl group, 4-(4-n-
hexylbenzyl)-1-piperidyl group, 4-(2-methoxybenzyl)-1-
piperidyl group, 1-[2-(3-methoxyphenyl)ethyl]-4-
piperidyl group, 1-[1-(4-methoxyphenyl)ethyl]-4-
piperidyl group, 2-[3-(2-ethoxyphenyl)propyl]-3-
piperidyl group, 3-[4-(3-ethoxyphenyl)butyl]-4-
piperidyl group, 4-[5-(4-ethoxyphenyl)pentyl]-3-
piperidyl group, 3-[6-(4-n-propoxyphenyl)hexyl]-2-
piperidyl group, 2-(4-tert-butoxybenzyl)-1-piperidyl
group, 1-(4-n-butoxybenzyl)-2-piperidyl group, 2-(2-
trifluoromethoxybenzyl)-3-piperidyl group, 3-(3-
trifluoromethoxybenzyl)-4-piperidyl group, 4-(4-
trifluoromethoxybenzyl)-3-piperidyl group, 3-(2-
pentafluoroethoxybenzyl)-2-piperidyl group, 2-(4-
pentafluoroethoxybenzyl)-1-piperidyl group, 1-(2,3-
dimethoxybenzyl)-4-piperidyl group, 4-(3,4,5-
dimethoxybenzyl)-1-piperidyl group, 4-(4-n-
pytloxybenzyl)-1-piperidyl group, 4-(4-n-
hexyloxybenzyl)-1-piperidyl group, 4-benzyl-3-phenoxy-
1-piperidyl group, 4-phenoxy-2-methylamino-1-piperidyl

group or the like.

A C1-C6 alkoxy C1-C6 alkoxy substituted C1-C6
alkyl group includes an alkoxyalkoxyalkyl group having
a straight or branched alkoxy group containing 1 to 6
carbon atoms on the alkoxy part and a straight or
branched alkyl group containing 1 to 6 carbon atoms on
the alkyl part, for example, a methoxymethoxymethyl
group, 2-(methoxymethoxy)ethyl group, 1-(2-
methoxyethoxy)ethyl group, 1-(methoxymethoxy)ethyl
group, 2-(3-propoxy)propoxyethyl group, 3-(2-
ethoxyisopropoxy)propyl group, 4-(4-butoxybutoxy)butyl
group, 5-(5-pentyloxypropoxy)pentyl group, 6-(6-
hexyloxyhexyloxy)hexyl group, 1,1-dimethyl-2-
(ethoxymethoxy)ethyl group, 2-methyl-3-(methoxymethoxy)-
propyl or 3-(propoxymethoxy)propyl group or the like.

A thienyl C1-C6 alkoxy substituted C1-C6
alkyl group (wherein, on the thiophene ring, at least
one halogen atom may be substituted) includes an thierylalkoxyalkyl group having a straight or branched alkoxy group containing 1 to 6 carbon atoms on the alkoxy part and a straight or branched alkyl group containing 1 to 6 carbon atoms on the alkyl part (wherein, on the thiophene ring, 1 to 3 halogen atoms may be substituted as a substituent group), for example, a 2-thieny1methoxymethyl group, 3-thienylmethoxymethyl group, 2-(2-(2-

10 thieryl)ethoxy)ethyl group, 3-(3-(2-thienyl)propoxy)propyl group, 4-(4-(2-thienyl)butoxy)butyl group, 4-(4-(3-thienyl)butoxy)butyl group, 5-(5-(2-thienyl)pentyloxy)pentyl group, 5-(5-(3-thienyl)pentyloxy)pentyl group, 6-(6-(2-thienyl)hexyloxy)hexyl group, 6-(6-(3-thienyl)hexyloxy)hexyl group, (5-chloro-2-thienylmethoxy)methyl group, (5-chloro-3-thienylmethoxy)methyl group, 2-(2-(4-bromo-2-

20 thieryl)ethoxy)ethyl group, 3-(3-(3-fluoro-2-thienyl)propoxy)propyl group, 4-(4-(5-iodo-2-thienyl)butoxy)butyl group, 4-(4-(4-chloro-3-thienyl)butoxy)butyl group, 5-(5-(3-chloro-2-thienyl)pentyloxy)pentyl group, 5-(2-chloro-3-thienyl)methoxy)pentyl group, 6-(2-(3-chloro-2-thienyl)ethoxy)hexyl group, 6-(6-(5-chloro-3-thienyl)hexyloxy)hexyl group, (2-(4,5-dichloro-2-thienyl)ethoxy)methyl group, ((2,4,5-trichloro-3-
thienyl)methoxy)methyl or the like.

A phenyl C2-C6 alkenyloxy substituted C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) is a group composed of a phenyl group unsubstituted or substituted by 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted straight or branched alkyl group containing 1 to 6 halogen carbon atoms and a halogen substituted or unsubstituted straight or branched alkoxy group containing 1 to 6 carbon atoms and an alkenyl group containing 2 to 6 carbon atoms and having at least 1 to 3 double bonds. The phenyl C2-C6 alkenyloxy group includes both trans and cis forms. Such a phenyl C2-C6 alkenyloxy C1-C6 alkyl group includes a (2-phenylvinloxy)methyl group, (3-phenyl-2-propenyloxy)methyl group, 2-(4-phenyl-2-butenyloxy)ethyl group, 1-(4-phenyl-3-butenyloxy)ethyl group, 3-(4-phenyl-1,3-butaadienyloxy)propyl group, 4-(5-phenyl-1,3,5-hexatrienyloxy)butyl group, 5-(3-(2-fluorophenyl)-2-propenyloxy)pentyl group, 6-(3-(3-fluorophenyl)-2-propenyloxy)hexyl group, (3-(4-fluorophenyl)-2-propenyloxy)methyl group, 2-(3-(2,3-difluorophenyl)-2-propenyloxy)ethyl group, 3-(3-(2,3,4,5,6-pentafluorophenyl)-2-propenyloxy)propyl group.
group, 4-(3-(2,4-difluorophenyl)-2-propenyl)oxy)butyl group, 5-(3-(3,4-difluorophenyl)-2-propenyl)oxy)pentyl group, 6-(3-(3,5-difluorophenyl)-2-propenyl)oxy)hexyl group, (3-(2-chlorophenyl)-2-propenyl)oxy)methyl group, 2-(3-(3-chlorophenyl)-2-propenyl)oxy)ethyl group, 3-(3-(4-chlorophenyl)-2-propenyl)oxy)propyl group, 4-(3-(2,3-dichlorophenyl)-2-propenyl)oxy)butyl group, 5-(3-(2,4-dichlorophenyl)-2-propenyl)oxy)pentyl group, 6-(3-(3,4-dichlorophenyl)-2-propenyl)oxy)hexyl group, (3-(3,5-dichlorophenyl)-2-propenyl)oxy)methyl group, 2-(3-(2-bromophenyl)-2-propenyl)oxy)ethyl group, 3-(3-(3-bromophenyl)-2-propenyl)oxy)propyl group, 4-(3-(4-bromophenyl)-2-propenyl)oxy)butyl group, 5-(3-(2-methylphenyl)-2-propenyl)oxy)pentyl group, 6-(3-(3-methylphenyl)-2-propenyl)oxy)hexyl group, (3-(4-methylphenyl)-2-propenyl)oxy)methyl group, 2-(3-(2-trifluoromethyl)phenyl)-2-propenyl)oxy)ethyl group, 3-(3-(2-fluoro-4-bromophenyl)-2-propenyl)oxy)propyl group, 4-(3-(4-chloro-3-fluorophenyl)-2-propenyl)oxy)butyl group, 5-(3-(2,3,4-trichlorophenyl)-2-propenyl)oxy)pentyl group, 6-(3-(2,4,6-trichlorophenyl)-2-propenyl)oxy)hexyl group, (3-(4-isopropylphenyl)-2-propenyl)oxy)methyl group, 2-(3-(4-n-butylphenyl)-2-propenyl)oxy)ethyl group, 1-(3-(2,4-dimethyl)phenyl)-2-propenyl)oxy)ethyl group, 3-(3-(2,3-dimethylphenyl)-2-propenyl)oxy)propyl group, (2,6-dimethylphenyl)-2-propenyl)oxy)methyl group, 5-(3-(3,5-dimethylphenyl)-2-propenyl)oxy)pentyl group, 6-(3-(2,5-dimethylphenyl)-2-propenyl)oxy)hexyl group.
group, (3-(2,4,6-trimethylphenyl)-2-propenyloxy)methyl group, (3-(3,5-ditrifluoromethylphenyl)-2-propenyloxy)methyl group, (3-(4-n-butoxyphenyl)-2-propenyloxy)methyl group, (3-(2,4-dimethoxyphenyl)-2-propenyloxy)methyl group, (3-(2,3-dimethoxyphenyl)-2-propenyloxy)methyl group, (3-(2,6-dimethoxyphenyl)-2-propenyloxy)methyl group, (3-(3,5-dimethoxyphenyl)-2-propenyloxy)methyl group, (3-(2,5-dimethoxyphenyl)-2-propenyloxy)methyl group, (3-(3,5-ditrifluoromethoxyphenyl)-2-propenyloxy)methyl group, (3-(3-chloro-4-methoxyphenyl)-2-propenyloxy)methyl group, (3-(2-chloro-4-trifluoromethoxyphenyl)-2-propenyloxy)methyl group, (3-(3-methyl-4-fluorophenyl)-2-propenyloxy)methyl group, (3-(4-bromo-3-trifluoromethylphenyl)-2-propenyloxy)methyl group, (3-(3-trifluoromethylphenyl)-2-propenyloxy)methyl group, (3-(4-trifluoromethoxyphenyl)-2-propenyloxy)methyl group, (3-(2-trifluoromethoxyphenyl)-2-propenyloxy)methyl group, (3-(3-trifluoromethoxyphenyl)-2-propenyloxy)methyl group, (3-(4-trifluoromethoxyphenyl)-2-propenyloxy)methyl group, (3-(2-methoxyphenyl)-2-propenyloxy)methyl group, (3-(3-methoxyphenyl)-2-propenyloxy)methyl group, (3-(4-methoxyphenyl)-2-propenyloxy)methyl group, (3-(3,4-dimethoxyphenyl)-2-propenyloxy)methyl group, (3-(3,5-dimethoxyphenyl)-2-propenyloxy)methyl group, (4-(4-chlorophenyl)-2-butenyloxy)methyl group, (4-(4-chlorophenyl)-3-butenyloxy)methyl group, 15-(4-
chlorophenyl)-2-pentenyloxy)methyl group, (5-(4-
chlorophenyl)-4-pentenyloxy)methyl group, (5-(4-
chlorophenyl)-3-pentenyloxy)methyl group, (6-(4-
chlorophenyl)-5-hexenyloxy)methyl group, (6-(4-
chlorophenyl)-4-hexenyloxy)methyl group, (6-(4-
chlorophenyl)-3-hexenyloxy)methyl group, (6-(4-
chlorophenyl)-3-hexenyloxy)methyl group or the like.

A quinolyl C1-C6 alkoxy substituted C1-C6 alkyl group includes a quinolylalkoxyalkyl group having a straight or branched alkoxy group containing 1 to 6 carbon atoms on the alkoxy part and a straight or branched alkyl group containing 1 to 6 carbon atoms on the alkyl part, for example, a (2-, 3-, 4-, 5-, 6-, 7- or 8-)quinolylmethoxyethylmethyl group, 2-(2-(2-, 3-, 4-, 5-, 6-, 7- or 8-)quinolylmethoxyethyl group, 3-(3-
(2-, 3-, 4-, 5-, 6-, 7- or 8-)quinolylpropoxy)propyl group, 4-(4-(2-, 3-, 4-, 5-, 6-, 7- or 8-)quinolyl:-butoxy)butyl group, 5-(5-(2-, 3-, 4-, 5-, 6-, 7- or 8-)quinolyl)pentyloxy)penty1 group, 6-(6-(2-, 3-, 4-, 5-, 6-, 7- or 8-)quinolyl)hexyloxy)hexyl group or the like.

A piperidylcarbonyl C1-C6 alkoxy substituted C1-C6 alkyl group includes a piperidylcarbonylalkoxyalkyl group having a straight or branched alkoxy group containing 1 to 6 carbon atoms on the alkoxy part and a straight or branched alkyl group containing 1 to 6 carbon atoms on the alkyl part, for example, (1-, 2- or 3-)piperidylcarbonylmethoxymethyl
group, 2-:2-((1-, 2- or 3-):piperidylcarbonyl)-ethoxy:ethyl group, 3-((1-, 2- or 3-):piperidyl-
carbonyl):propoxy):propyl group, 4-((1-, 2- or 3-):piperidyl-
carbonyl):butoxy):butyl group, 5-((1-, 2- or
3-):piperidyl:carbonyl):pentyloxy):penty1 group, 6-((1-, 2- or 3-):piperidyl:carbonyl):hexyloxy):hexyl group or the
like.

A phenyl C1-C6 alkyl group [wherein, on the
phenyl ring, at least one phenyl group (wherein, on the
phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group is
substituted] is substituted) includes a phenyl:alkyl
group having a straight or branched alkyl group
containing 1 to 6 carbon atoms on the alkyl part
[wherein, on the phenyl ring, 1 to 3 phenyl groups
(wherein, on the phenyl ring, 1 to 5, preferably 1 to 3
substituents selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted
straight or branched C1-C6 alkyl group and a halogen
substituted or unsubstituted straight or branched C1-C6
alkoxy group are substituted), for example,
a 2-(2-fluorophenyl):benzyl group, 5-(3-
fluorophenyl):benzyl group, 4-(4-fluorophenyl):benzyl
group, 2-(2-chlorophenyl):benzyl group, 3-(3-
chlorophenyl):benzyl group, 4-(4-chlorophenyl):benzyl
group, 2-(2-bromophenyl)benzyl group, 3-(3-
bromophenyl)benzyl group, 4-(4-bromophenyl)benzyl group,
2-(2-iodophenyl)benzyl group, 3-(3-iodophenyl)benzyl
5 group, 4-(4-iodophenyl)benzyl group, 4-(2,3-
difluorophenyl)benzyl group, 3-(3,4-
difluorophenyl)benzyl group, 2-(3,5-
dichlorophenyl)benzyl group, 4-(2,4-
difluorophenyl)benzyl group, 3-(2,6-
dichlorophenyl)benzyl group, 2-(2,3-
dichlorophenyl)benzyl group, 4-(3,4-
dichlorophenyl)benzyl group, 3-(3,5-
dichlorophenyl)benzyl group, 2-(2,4-
dichlorophenyl)benzyl group, 4-(2,6-
dichlorophenyl)benzyl group, 3-(2-fluoro-4-
bromophenyl)benzyl group, 2-(4-chloro-3-
fluorophenyl)benzyl group, 4-(2,3,4-
trichlorophenyl)benzyl group, 3-(3,4,5-
trifluorophenyl)benzyl group, 2-(2,4,6-
trichlorophenyl)benzyl group, 4-(4-
isopropylphenyl)benzyl group, 3-(4-n-butylphenyl)benzyl
group, 2-(4-methylphenyl)benzyl group, 4-(2-
methylphenyl)benzyl group, 3-(3-methylphenyl)benzyl
group, 2-(2,4-dimethylphenyl)benzyl group, 4-(2,3-
dimethylphenyl)benzyl group, 3-(2,6-
dimethylphenyl)benzyl group, 2-(3,5-
dimethylphenyl)benzyl group, 4-(2,5-
dimethylphenyl)benzyl group, 3-(2,4,6-
trimethylphenyl)benzyl group, 2-(3,5-
ditrifluoromethylphenyl)benzyl group, 4-(2,3,4,5,6-pentafluorophenyl)benzyl group, 3-(4-isopropoxyphenyl)benzyl group, 2-(4-n-butoxyphenyl)benzyl group, 4-(4-methoxyphenyl)benzyl group, 3-(2-methoxyphenyl)benzyl group, 2-(3-methoxyphenyl)benzyl group, 4-(2,4-dimethoxyphenyl)benzyl group, 3-(2,3-dimethoxyphenyl)benzyl group, 2-(2,6-dimethoxyphenyl)benzyl group, 2-(3,5-dimethoxyphenyl)benzyl group, 4-(2,5-dimethoxyphenyl)benzyl group, 3-(2,4,6-trimethoxyphenyl)benzyl group, 2-(3,5,5-ditrifluoromethoxyphenyl)benzyl group, 4-(2-isopropoxyphenyl)benzyl group, 3-(3-chloro-4-methoxyphenyl)benzyl group, 2-(2-chloro-4-trifluoromethoxyphenyl)benzyl group, 4-(3-methyl-4-fluorophenyl)benzyl group, 3-(4-bromo-3-trifluoromethylphenyl)benzyl group, 4-(2-trifluoromethylphenyl)benzyl group, 3-(3-trifluoromethylphenyl)benzyl group, 4-(4-trifluoromethylphenyl)benzyl group, 2-(2-pentafluoroethylphenyl)benzyl group, 3-(3-pentafluoroethylphenyl)benzyl group, 2-(4-pentafluoroethylphenyl)benzyl group, 4-(2-trifluoromethoxyphenyl)benzyl group, 3-(3-trifluoromethoxyphenyl)benzyl group, 4-(4-trifluoromethoxyphenyl)benzyl group, 4-(2-pentafluoroethoxyphenyl)benzyl group, 3-(3-
pentafluoroethoxyphenyl)benzyl group, 2-(4-
pentafluoroethoxyphenyl)benzyl group, 2-(4-(2-
trifluoromethylphenyl)phenyl)ethyl group, 2-(3-(3-
trifluoromethylphenyl)phenyl)ethyl group, 2-(2-(4-
trifluoromethylphenyl)phenyl)ethyl group, 2-(4-(2-
trifluoromethoxyphenyl)phenyl)ethyl group, 2-(3-(3-
trifluoromethoxyphenyl)phenyl)propyl group, 2-(2-(4-
trifluoromethoxyphenyl)phenyl)propyl group, 2-(4-(2-
pentafluoroethoxyphenyl)phenyl)ethyl group, 2-(3-(3-
pentafluoroethoxyphenyl)phenyl)ethyl group, 3-(4-(2-
trifluoromethylphenyl)phenyl)propyl group, 3-(3-(3-
trifluoromethylphenyl)phenyl)propyl group, 3-(2-(4-
trifluoromethylphenyl)phenyl)propyl group, 3-(4-(2-
trifluoromethoxyphenyl)phenyl)propyl group, 3-(3-(3-
trifluoromethoxyphenyl)phenyl)propyl group, 3-(2-(4-
trifluoromethoxyphenyl)phenyl)propyl group, 3-(4-(2-
pentafluoroethoxyphenyl)phenyl)propyl group, 4-(2-(3-
pentafluoroethoxyphenyl)phenyl)butyl group, 5-(4-(4-
trifluoromethylphenyl)phenyl)pentyl group, 4-(3-(4-
trifluoromethylphenyl)phenyl)pentyl group, 4-(2-(4-
trifluoromethoxyphenyl)phenyl)pentyl group, 6-(4-(3-
trifluoromethylphenyl)phenyl)hexyl group, 6-(3-(4-
trifluoromethylphenyl)phenyl)hexyl group, 6-(2-(4-
trifluoromethylphenyl)phenyl)hexyl group, 2,4-di(4-
trifluoromethylphenyl)benzyl group, 2,4,6-tri(4-
trifluoromethoxyphenyl)benzyl group or the like.
A benzoyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) is a benzoyl C1-C6 alkyl group unsubstituted or substituted on the phenyl ring constituting the group by 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted straight or branched C1-C6 alkyl group and a halogen substituted or unsubstituted straight or branched C1-C6 alkoxy group, examples of which include a benzoylmethyl group, 1-benzoylethyl group, 2-benzoylethyl group, 3-benzoylpropyl group, 2-benzoylpropyl group, 4-benzoylbutyl group, 5-benzoylpentyl group, 4-benzoylpentyl group, 6-benzoylhexyl group, 2-fluorobenzoylmethyl group, 3-fluorobenzoylmethyl group, 4-fluorobenzoylmethyl group, 2-chlorobenzoylmethyl group, 3-chlorobenzoylmethyl group, 4-chlorobenzoylmethyl group, 2-bromobenzoylmethyl group, 3-bromobenzoylmethyl group, 4-bromobenzoylmethyl group, 2-iodobenzoylmethyl group, 3-iodobenzoylmethyl group, 4-iodobenzoylmethyl group, 2,3-difluorobenzoylmethyl group, 3,4-difluorobenzoylmethyl group, 3,5-difluorobenzoylmethyl group, 2,4-difluorobenzoylmethyl group, 2,6-difluorobenzoylmethyl group, 2,3-dichlorobenzoylmethyl group, 3,4-dichlorobenzoylmethyl group.
group, 3,5-dichlorobenzoylmethyl group, 2,4-
dichlorobenzoylmethyl group, 2,6-dichlorobenzoylmethyl
group, 2-fluoro-4-bromobenzoylmethyl group, 4-chloro-3-
fluorobenzoylmethyl group, 2,3,4-trichlorobenzoylmethyl
group, 3,4,5-trifluorobenzoylmethyl group, 2,4,6-
trichlorobenzoylmethyl group, 4-isopropylbenzoylmethyl
group, 4-n-butylbenzoylmethyl group, 4-
methylbenzoylmethyl group, 2-methylbenzoylmethyl group,
3-methylbenzoylmethyl group, 2,4-dimethylbenzoylmethyl
group, 2,3-dimethylbenzoylmethyl group, 2,6-
dimethylbenzoylmethyl group, 3,5-dimethylbenzoylmethyl
group, 2,5-dimethylbenzoylmethyl group, 2,4,6-
trimethylbenzoylmethyl group, 3,5-
ditrifluoromethylenzoylmethyl group, 2,3,4,5,6-
pentafluorobenzoylmethyl group, 4-
isoproxybenzoylmethyl group, 4-n-butoxybenzoylmethyl
group, 4-methoxybenzoylmethyl group, 2-
methoxybenzoylmethyl group, 3-methoxybenzoylmethyl
group, 2,4-dimethoxybenzoylmethyl group, 2,3-
dimethoxybenzoylmethyl group, 2,6-
dimethoxybenzoylmethyl group, 3,5-
dimethoxybenzoylmethyl group, 2,5-
dimethoxybenzoylmethyl group, 2,4,6-
trimethoxybenzoylmethyl group, 3,5-
ditrifluoromethoxybenzoylmethyl group, 2-
isoproxybenzoylmethyl group, 3-chloro-4-
methoxybenzoylmethyl group, 2-chloro-4-
ditrifluoromethoxybenzoylmethyl group, 3-methyl-4-
fluorobenzoylmethyl group, 4-bromo-3-
trifluoromethylbenzoylmethyl group, 2-
trifluoromethylbenzoylmethyl group, 3-
trifluoromethylbenzoylmethyl group, 4-

5 trifluoromethylbenzoylmethyl group, 2-
pentafluoroethylbenzoylmethyl group, 3-
pentafluoroethylbenzoylmethyl group, 4-
pentafluoroethylbenzoylmethyl group, 2-
trifluoromethoxybenzoylmethyl group, 3-

10 trifluoromethoxybenzoylmethyl group, 4-
trifluoromethoxybenzoylmethyl group, 2-
pentafluoroethoxybenzoylmethyl group, 3-
pentafluoroethoxybenzoylmethyl group, 4-
pentafluoroethoxybenzoylmethyl group, 2-(2-

15 trifluoromethylbenzoyl)ethyl group, 2-(3-
trifluoromethylbenzoyl)ethyl group, 2-(4-
trifluoromethylbenzoyl)ethyl group, 2-(2-
trifluoromethoxybenzoyl)ethyl group, 2-(3-
trifluoromethoxybenzoyl)ethyl group, 2-(4-

20 trifluoromethoxybenzoyl)ethyl group, 2-(2-
pentafluoroethoxybenzoyl)ethyl group, 2-(3-
pentafluoroethoxybenzoyl)ethyl group, 2-(4-
pentafluoroethoxybenzoyl)ethyl group, 3-(2-
trifluoromethylbenzoyl)propyl group, 3-(3-

25 trifluoromethyl benzoyl)propyl group, 3-(4-
trifluoromethylbenzoyl)propyl group, 3-(2-
trifluoromethoxybenzoyl)propyl group, 3-(3-
trifluoromethoxybenzoyl)propyl group, 3-(4-
trifluoromethoxybenzoyl) propyl group, 3-(3-
pentafluorooethoxybenzoyl) propyl group, 3-(4-
pentafluorooethoxybenzoyl) propyl group, 4-(3-
pentafluorooethoxybenzoyl) butyl group, 5-(4-
trifluoromethylbenzoyl) penty1 group, 4-(4-
trifluoromethylbenzoyl) penty1 group, 4-(4-
trifluoromethoxybenzoyl) penty1 group, 6-(3-
trifluoromethylbenzoyl) hexyl group, 6-(4-
trifluoromethylbenzoyl) hexyl group, 6-(4-
trifluoromethoxybenzoyl) hexyl group or the like.

An amino group which may be substituted by at
least one selected from the group consisting of a Cl-C6
alkyl group, a Cl-C6 alkoxy carbonyl group and a phenyl
Cl-C6 alkyl group [wherein, on the phenyl ring, at
least one selected from the group consisting of a
phenyl group (wherein, on the phenyl ring, at least one
selected from the group consisting of a halogen atom, a
halogen substituted or unsubstituted Cl-C6 alkyl group
and a halogen substituted or unsubstituted Cl-C6 alkoxy
group may be substituted), a halogen atom, a halogen
substituted or unsubstituted Cl-C6 alkyl group and a
halogen substituted or unsubstituted Cl-C6 alkoxy group
may be substituted] includes an amino group which may
be substituted by 1 or 2 substituents selected from the
group consisting of a straight or branched alkyl group
containing 1 to 6 carbon atoms as described above or
later, a straight or branched alkoxy carbonyl group
containing 1 to 6 carbon atoms, and a phenyl alkyl group
having a straight or branched alkyl group containing 1 to 6 carbon atoms on the alkyl part (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a phenyl group (wherein, on the phenyl group, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 straight or branched alkyl group and a halogen substituted or unsubstituted C1-C6 straight or branched alkoxy group may be substituted), a halogen atom, a halogen substituted or unsubstituted C1-C6 straight or branched alkyl group and a halogen substituted or unsubstituted C1-C6 straight or branched alkoxy group may be substituted), for example, an amino group, tert-butoxycarbonylamino group, methylamino group, benzylamino group, (4-trifluoromethoxybenzyl)amino group, (4-trifluoromethylbenzyl)amino group, (4-chlorobenzyl)amino group, (4-(4-trifluoromethoxyphenyl)benzyl)amino group, (4-(4-trifluoromethylphenyl)benzyl)amino group, (4-(4-chlorophenyl)benzyl)amino group, N-methyl-N-benzylamino group, N-methyl-N-(4-trifluoromethoxybenzyl)amino group, N-methyl-N-(4-trifluoromethylbenzyl)amino group, N-methyl-N-(4-chlorobenzyl)amino group, N-methyl-N-(4-(4-trifluoromethoxyphenyl)benzyl)amino group, N-methyl-N-(4-(4-chlorophenyl)benzyl)amino group, N-methoxycarbonyl-N-benzylamino group, N-ethoxycarbonyl-
N-(4-trifluoromethoxybenzyl)amino group, N-propoxycarbonyl-N-(4-trifluoromethylbenzyl)amino group, N-n-butoxycarbonyl-N-(4-chlorobenzyl)amino group, N-n-pentyloxy carbonyl-N-(4-(4-trifluoromethoxyphenyl)benzyl)amino group, N-n-hexyloxy carbonyl-N-(4-(4-trifluoromethylphenyl)benzyl)amino group, N-ethoxycarbonyl-N-(4-(4-chlorophenyl)benzyl)amino group, N,N-dimethylamino group, N-methyl-N-ethylamino group or the like.

An amino C1-C6 alkyl group which may be substituted by at least one selected from the group consisting of a C1-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) includes an amino alkyl group having a straight or branched alkyl group containing 1 to 6 carbon atoms on the alkyl part, which may be substituted by 1 or 2 substituents selected from the group consisting of a straight or branched alkyl group containing 1 to 6 carbon atoms and a phenyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 straight or branched alkyl group and a halogen substituted or unsubstituted C1-C6 straight or branched
alkoxy group may be substituted), for example, an aminomethyl group, 2-aminoethyl group, 1-aminoethyl group, 3-aminopropyl group, 4-aminobutyl group, 5-aminopentyl group, 6-aminohexyl group, 2-methyl-3-aminopropyl group, 1,1-dimethyl-2-aminoethyl group, ethylaminomethyl group, 1-(propylamino)ethyl group, 2-(methylamino)ethyl group, 3-(isopropylamino)propyl group, 4-(n-butyramino)butyl group, 5-(n-pentylamino)pentyl group, 6-(n-hexylamino)hexyl group, dimethylaminomethyl group, (N-ethyl-N-propylamino)methyl group, 2-(N-methyl-N-n-hexylamino)ethyl group, phenylaminomethyl group, 1-(phenylamino)ethyl group, 2-(4-chloroanilino)ethyl group, 2-(4-trifluoromethoxyanilino)ethyl group, 2-(4-trifluoromethylanilino)ethyl group, 3-(4-fluoroanilino)propyl group, 4-(3,4-difluoroanilino)butyl group, 5-(3,4,6-trifluoroanilino)pentyl group, 6-(4-methylanilino)hexyl group, (3-methoxyanilino)methyl group, (2,3,4-trimethoxyanilino)methyl group, (3,4-dimethylanilino)methyl group, (2,4,6-trimethylanilino)methyl group, (N-ethyl-N-(3,4-dimethoxyanilino))methyl group, 2-(N-methyl-N-(4-chloroanilino))ethyl group, 2-(N-methyl-N-(4-trifluoromethoxyanilino))ethyl group or the like.

A benzofuryl C2-C6 alkenyl group (wherein, on the benzofuran ring, at least one selected from the
group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted] includes a benzofurylalkenyl group having a straight or branched alkenyl group containing 2 to 6 carbon atoms on the alkenyl part and having 1 to 3 double bonds and including both trans and cis forms wherein, on the benzofuran ring, 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 straight or branched alkyl group and a halogen substituted or unsubstituted Cl-C6 straight or branched alkoxy group may be substituted], for example, a 2-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)vinyl group, 3-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)-2-propenyl group, 3-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)-2-methyl-2-propenyl group, 4-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)-2-butenyl group, 4-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)-3-butene group, 4-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)-1,3-butadienyl group, 5-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)-1,3,5-hexatrienyl group, 5-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)-2,4-hexadienyl group, 5-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)-3-pentenyl group, 3-(5-trifluoromethyl-(2-, 3-, 4-, 6- or 7-)benzofuryl)-2-propenyl group, 3-(6-trifluoromethoxy-(2-, 3-, 4-, 5- or 7-)benzofuryl)2-propenyl group, 3-(6-trifluoromethyl-(2-, 3-, 4-, 5- or 7-)benzofuryl)-2-propenyl group, 3-(4-chloro-(2-, 3-, 5-, 6-, or
7-(4,5-dimethoxy-2-, 3-, 6- or 7-benzofuranyl)-2-propenyl group, 3-(4,5-dimethoxy-2-, 3-, 6- or 7-benzofuranyl)-2-propenyl group, 3-(3,4,5-trimethyl-2-, 6- or 7-benzofuranyl)-2-propenyl group, 3-(3-methyl-5-methoxy-2-, 4-, 6- or 7-benzofuranyl)-2-propenyl or the like, which includes a benzofuranylalkenyl group (wherein, on the benzofuran ring, 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 straight or branched alkyl group and a halogen substituted or unsubstituted Cl-C6 straight or branched alkoxy group may be substituted) including both trans or cis forms.

A piperidyl group (wherein, on the piperidine ring, at least one phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted; may be substituted) includes a piperidyl group (wherein, on the piperidine ring, 1 to 3 phenylalkenyl groups having a straight or branched alkenyl group containing 2 to 6 carbon atoms on the alkenyl part as described above and having 1 to 3 double bonds and including both trans and cis forms (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 straight or branched alkyl group and a halogen...
substituted or unsubstituted C1-C6 straight or branched alkoxy group may be substituted), for example, a (1-, 2-, 3- or 4-)piperidyl group, 1-(3-phenyl-2-propenyl)-(2-, 3- or 4-)piperidyl group, 1,3-di(3-phenyl-2-propenyl)-(2-, 4-, 5- or 6-)piperidyl group, 1,2,4-tri(3-phenyl-2-propenyl)-(3-, 5- or 6-)piperidyl group, 1-(3-(4-trifluoromethoxyphenyl)-2-propenyl)-(2-, 3- or 4-)piperidyl group, 1-(3-(4-trifluoromethylphenyl)-2-propenyl)-(2-, 3- or 4-)piperidyl group, 1-(3-(4-chlorophenyl)-2-propenyl)-(2-, 3- or 4-)piperidyl group, 1-(3-(3,4-dimethoxyphenyl)-2-propenyl)-(2-, 3- or 4-)piperidyl group, 1-(3-(2,4,6-trimethylphenyl)-2-propenyl)-2(2-, 3- or 4-)piperidyl group or the like.

A ferrocene substituted C1-C6 alkyl group includes a ferrocenealkyl group having a straight or branched alkyl group containing 1 to 6 carbon atoms on the alkyl part, for example, a ferrocenemethyl group, 1-ferroceneethyl group, 2-ferroceneethyl group, 3-ferrocenepropyl group, 2-ferrocenepropyl group, 4-ferrocenebutyl group, 5-ferrocenepentyl group, 4-ferrocenepentyl group, 6-ferrocenehexyl group, 1,1-dimethyl-2-ferroceneethyl group, 2-methyl-3-ferrocenepropyl group or the like.

An indolyl C1-C6 alkyl group (wherein, on the indole ring, at least one halogen atom may be substituted) includes an indolylalkyl group having a straight or branched alkyl group containing 1 to 6
carbon atoms on the alkyl part (wherein, on the indole ring, 1 to 3 halogen atoms may be substituted), for example, \((1-, 2-, 3-, 4-, 5-, 6-\ or\ 7-)\text{indolyl\text{methyl}}\) group, \(1-(1-, 2-, 3-, 4-, 5-, 6-\ or\ 7-)\text{indolyl\text{ethyl}}\) group, \(2-(1-, 2-, 3-, 4-, 5-, 6-\ or\ 7-)\text{indolyl\text{propyl}}\) group, \(3-(1-, 2-, 3-, 4-, 5-, 6-\ or\ 7-)\text{indolyl\text{butyl}}\) group, \(4-(1-, 2-, 3-, 4-, 5-, 6-\ or\ 7-)\text{indolyl\text{pentyl}}\) group, \(5-(1-, 2-, 3-, 4-, 5-, 6-\ or\ 7-)\text{indolyl\text{hexyl}}\) group, \(1,1\text{-dimethyl-2-}(1-, 2-, 3-, 4-, 5-, 6-\ or\ 7-)\text{indolyl\text{ethyl}}\) group, \(2\text{-methyl-3-}(1-, 2-, 3-, 4-, 5-, 6-\ or\ 7-)\text{indolyl\text{propyl}}\) group, \(5\text{-chloro-(1-, 2-, 3-, 4-, 5-, 6-\ or\ 7-)indolyl\text{methyl}}\) group, \(5,6\text{-difluoro-(1-, 2-, 3-, 4-\ or\ 7-)indolyl\text{methyl}}\) group, \(3,5,6\text{-tribromo-(1-, 2-, 4-\ or\ 7-)indolyl\text{methyl}}\) group or the like.

A phenyl C2-C6 alkynyl group includes a phenylalkenyl group having a straight or branched alkynyl group containing 2 to 6 carbon atoms on the alkynyl part, for example, a 2-phenylethynyl group, 3-phenyl-2-propynyl group, 3-phenyl-1-methyl-2-propynyl group, 4-phenyl-2-butynyl group, 4-phenyl-1-butynyl group, 5-phenyl-2-pentynyl group, 6-phenyl-2-hexynyl group or the like.

A naphthyl substituted C1-C6 alkyl group (wherein, on the naphthalene ring, at least one C1-C6 alkoxy group may be substituted) includes a naphthyl
substituted alkyl group having a straight or branched alkyl group containing 1 to 6 carbon atoms on the alkyl part (wherein, on the naphthalene ring, 1 to 3 straight or branched alkoxy groups containing 1 to 6 carbon atoms as described above may be substituted), for example, 1-(1- or 2-)naphthyl)methyl group, 1-((1- or 2-)naphthyl)ethyl group, 2-((1- or 2-)naphthyl)ethyl group, 3-((1- or 2-)naphthyl)propyl group, 2-((1- or 2-)naphthyl)propyl group, 4-((1- or 2-)naphthyl)butyl group, 5-((1- or 2-)naphthyl)pentyl group, 4-((1- or 2-)naphthyl)pentyl group, 5-((1- or 2-)naphthyl)hexyl group, 1,1-dimethyl-2-((1- or 2-)naphthyl)ethyl group, 2-methyl-3-((1- or 2-)naphthyl)propyl group, 6-methoxy-((1- or 2- or 3- or 4- or 5- or 7- or 8-)naphthyl)methyl group, 5,6-dimethoxy-(1-, 2-, 3-, 4-, 7- or 8-)-naphthyl)methyl group, (5,6,7-trimethoxy-1-, 2-, 3-, 4- or 8-)-naphthyl)methyl group or the like.

A benzothiazolyloxy group (wherein, on the benzothiazole ring, at least one selected from the group consisting of a (b-1)phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a (b-2)piperadiny1 group (wherein, on the piperidine ring, at least one selected from the group consisting of a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group...
consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), (b-3)piperidyl group wherein, on the piperidine ring, at least one selected from the group consisting of an amino group (wherein, on the amino group, at least one selected from the group consisting of a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted).
substituted) and a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), a (b-4)pyrrolyl group (wherein, on the pyrrole ring, at least one selected from the group consisting of a Cl-C6 alkyl group and a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) may be substituted] and a (b-5)phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) may be substituted) includes a benzothiazolyl alkoxy group (wherein, on the benzothiazole ring, 1 to 3 substituents selected from the group consisting of a (b-1)phenyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), a (b-2)piperadinyi group (wherein, on the piperidine
ring, 1 to 3 substituents selected from the group consisting of a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a phenyl C2-C6 alkenyl group having a straight or branched alkenyl group containing 2 to 6 carbon atoms on the alkenyl part and having 1 to 3 double bonds as described later and including both trans and cis forms (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) and a phenyl group as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted), a (b-3)piperidyl group (wherein, on the piperidine ring, 1 to 3 substituents selected from the group consisting of an amino group (wherein, on the amino group, 1 or 2 groups selected from the group consisting of a phenyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted] and 1 or 2 groups selected from the group consisting of Cl-C6 alkyl groups may be substituted], a phenoxy group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) and a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) may be constituted], a (b-4)pyrrolyl group as described later [wherein, on the pyrrole ring, 1 to 3 substituents selected from the group consisting of a Cl-C6 alkyl group and a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted] may be substituted] and a (b-5)phenylthio group as described later (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), for example, a 2-benzothiazoleoxy group, 4-benzothiazoleoxy group, 5-benzothiazoleoxy group, 6-benzothiazoleoxy group, 7-benzothiazoleoxy group, 2-(1-piperidinyl)-4-benzothiazoleoxy group, 2-(4-benzyl-1-piperidinyl)-4-benzothiazoleoxy group, 2-(3,4-dibenzyl-1-piperidinyl)-4-benzothiazoleoxy group, 5-(2,3,4-tribenzyl-1-piperidinyl)-2-benzothiazoleoxy group, 4-(4-(2-phenethyl)-1-piperidinyl)-2-benzothiazoleoxy group, 4-(4-(3-phenylpropyl)-1-piperidinyl)-5-benzothiazoleoxy group, 4-(4-(4-phenylbutyl)-1-piperidinyl)-6-benzothiazoleoxy group, 4-(4-(5-phenylpenty1)-1-piperidinyl)-7-benzothiazoleoxy group, 2-(4-(6-phenylhexyl)-1-piperidinyl)-4-benzothiazoleoxy group, 4-(4-(2-fluorobenzyl)-1-piperidinyl)-2-benzothiazoleoxy group, 2-(4-(3-fluorobenzyl)-1-piperidinyl)-4-benzothiazoleoxy group, 2-(4-(4-fluorobenzyl)-1-piperidinyl)-5-benzothiazoleoxy group, 2-(4-(2-chlorobenzyl)-1-piperidinyl)-6-benzothiazoleoxy group, 2-(4-(3-chlorobenzyl)-1-piperazinyl)-7-benzothiazoleoxy group, 5-(4-(4-chlorobenzyl)-1-piperazinyl)-4-benzothiazoleoxy group, 6-(4-(2,3-dichlorobenzyl)-1-piperazinyl)-4-benzothiazoleoxy group, 7-(4-(2,4-dichlorobenzyl)-1-piperazinyl)-4-benzothiazoleoxy group, 2-(4-(3,4-dichlorobenzyl)-1-piperazinyl)-4-benzothiazoleoxy group.
group, 4-(4-(3,5-dichlorobenzyl)-1-piperidinyl)-2-benzothiazolylloxoy group, 4-(4-(3,4,5-trichlorobenzyl)-1-piperidinyl)-5-benzothiazolylloxoy group, 4-(4-(2,3,4,5,6-pentafluorobenzyl)-1-piperidinyl)-2-benzothiazolylloxoy group, 4-(4-(2-trifluoromethylbenzyl)-1-piperidinyl)-6-benzothiazolylloxoy group, 4-(4-(3-trifluoromethylbenzyl)-1-piperidinyl)-7-benzothiazolylloxoy group, 2-(4-(4-trifluoromethylbenzyl)-1-piperidinyl)-4-benzothiazolylloxoy group, 5-(4-(4-methylbenzyl)-1-piperidinyl)-4-benzothiazolylloxoy group, 6-(4-(3,4-dimethylbenzyl)-1-piperidinyl)-4-benzothiazolylloxoy group, 7-(4-(2,4,6-trimethylbenzyl)-1-piperidinyl)-4-benzothiazolylloxoy group, 4-(4-(2-pentafluoroethylbenzyl)-1-piperidinyl)-2-benzothiazolylloxoy group, 4-(4-(3-pentafluoroethylbenzyl)-1-piperidinyl)-5-benzothiazolylloxoy group, 4-(4-(4-pentafluoroethylbenzyl)-1-piperidinyl)-6-benzothiazolylloxoy group, 4-(4-(2-trifluoromethoxybenzyl)-1-piperidinyl)-7-benzothiazolylloxoy group, 5-(4-(3-trifluoromethoxybenzyl)-1-piperidinyl)-4-benzothiazolylloxoy group, 6-(4-(4-trifluoromethoxybenzyl)-1-piperidinyl)-5-benzothiazolylloxoy group, 7-(4-(4-methoxybenzyl)-1-piperidinyl)-5-benzothiazolylloxoy group, 6-(4-(3,4-
dimethoxybenzyl)-1-piperadiny1)-4-benzothiazoloyloxy
group, 7-(4-(4-(2,4,6-trimethoxybenzyl)-1-piperadiny1)-4-
benzothiazoloyloxy group, 5-(4-(2-
pentafluorothoxybenzyl)-1-piperadiny1)-4-
benzothiazoloyloxy group, 4-(4-(3-
pentafluorothoxybenzyl)-1-piperadiny1)-2-
benzothiazoloyloxy group, 6-(4-(4-
pentafluorothoxybenzyl)-1-piperadiny1)-4-
benzothiazoloyloxy group, 4-(4-(2-(4-
trifluoromethoxyphenyl)ethyl)-1-piperadiny1)-2-
benzothiazoloyloxy group, 4-(4-(3-(4-
trifluoromethoxyphenyl)propyl)-1-piperadiny1)-2-
benzothiazoloyloxy group, 4-(4-(4-(4-
trifluoromethoxyphenyl)butyl)-1-piperadiny1)-2-
benzothiazoloyloxy group, 4-(4-(5-(4-
trifluoromethoxyphenyl)pentyl)-1-piperadiny1)-2-
benzothiazoloyloxy group, 4-(4-(6-(4-
trifluoromethoxyphenyl)hexyl)-1-piperadiny1)-2-
benzothiazoloyloxy group, 4-(4-(2-(4-
trifluoromethylphenyl)ethyl)-1-piperadiny1)-2-
benzothiazoloyloxy group, 5-(4-(3-(4-
trifluoromethylphenyl)propyl)-1-piperadiny1)-2-
benzothiazoloyloxy group, 6-(4-(4-(4-
trifluoromethylphenyl)butyl)-1-piperadiny1)-2-
benzothiazoloyloxy group, 7-(4-(5-(4-
trifluoromethylphenyl)pentyl)-1-piperadiny1)-2-
benzothiazoloyloxy group, 5-(4-(6-(4-
trifluoromethylphenyl)hexyl)-1-piperadiny1)-2-
benzothiazolylloxy group, 2-((4-(trifluoromethoxyphenoxyl-1-piperidyl))-6-benzothiazolylloxy group, 2-((4-
(trifluoromethoxybenzyl-1-piperidyl))-6-
benzothiazolylloxy group, 2-((4-(N-ethyl-N-(4-
chlorophenyl)amino)-1-piperidyl))-6-benzothiazolylloxy group, 2-phenyl-5-benzothiazolylloxy group, 2-((4-
chlorophenyl))-5-benzothiazolylloxy group, 2-((4-
trifluoromethoxyphenyl))-6-benzothiazolylloxy group, 2-
(3-trifluoromethylphenyl))-5-benzothiazolylloxy group, 2-
(1-piperidyl))-4-benzothiazolylloxy group, 2-((4-benzyl-1-
piperidyl))-4-benzothiazolylloxy group, 2-(3,4-dibenzyl-
1-piperidyl))-4-benzothiazolylloxy group, 5-(2,3,4-
tribenzyl-1-piperidyl))-2-benzothiazolylloxy group, 4-(4-
(2-phenethyl)-1-piperidyl))-2-benzothiazolylloxy group,
4-(4-(3-phenylpropyl)-1-piperidyl))-5-benzothiazolylloxy group, 4-(4-(4-phenylbutyl)-1-piperidyl))-6-
benzothiazolylloxy group, 4-(4-(5-phenylpentyl)-1-
piperidyl))-7-benzothiazolylloxy group, 2-(4-(6-
phenylhexyl)-1-piperidyl))-4-benzothiazolylloxy group, 4-
(4-(2-fluorobenzyl)-1-piperidyl))-2-benzothiazolylloxy group, 2-(4-(3-fluorobenzyl)-1-piperidyl))-4-
benzothiazolylloxy group, 2-(4-(4-fluorobenzyl)-1-
piperidinyl))-5-benzothiazolylloxy group, 2-(4-(4-
chlorobenzyl)-1-piperidyl))-6-benzothiazolylloxy group,
2-(4-(3-chlorobenzyl)-1-piperidyl))-7-benzothiazolylloxy group,
5-(4-(4-chlorobenzyl)-1-piperidyl))-4-benzothiazolylloxy group, 6-(4-(2,3-dichlorobenzyl-1-piperidyl))-4-

benzothiazolyloxy group, 7-(4-(2,4-dichlorobenzyl)-1-piperidyl)-4-benzothiazolyloxy group, 2-(4-(3,4-dichlorobenzyl)-1-piperidyl)-4-benzothiazolyloxy group, 4-(4-(3,5-dichlorobenzyl)-1-piperidyl)-2-benzothiazolyloxy group, 4-(4-(3,4,5-trichlorobenzyl)-1-piperidyl)-5-benzothiazolyloxy group, 4-(4-(2,3,4,5,6-pentafluorobenzyl)-1-piperidyl)-2-benzothiazolyloxy group, 4-(4-(2-trifluoromethylbenzyl)-1-piperidyl)-6-benzothiazolyloxy group, 4-(4-(3-trifluoromethylbenzyl)-1-piperidyl)-7-benzothiazolyloxy group, 2-(4-(4-trifluoromethylbenzyl)-1-piperidyl)-4-benzothiazolyloxy group, 5-(4-(4-methylbenzyl)-1-piperidyl)-4-benzothiazolyloxy group, 6-(4-(3,4-dimethylbenzyl)-1-piperidyl)-4-benzothiazolyloxy group, 7-(4-(2,4,6-trimethylbenzyl)-1-piperidyl)-4-benzothiazolyloxy group, 4-(4-(2-pentafluoroethylbenzyl)-1-piperidyl)-2-benzothiazolyloxy group, 4-(4-(3-pentafluoroethylbenzyl)-1-piperidyl)-5-benzothiazolyloxy group, 4-(4-(4-pentafluoroethylbenzyl)-1-piperidyl)-6-benzothiazolyloxy group, 4-(4-(2-trifluoromethoxybenzyl)-1-piperidyl)-7-benzothiazolyloxy group, 5-(4-(3-trifluoromethoxybenzyl)-1-piperidyl)-4-benzothiazolyloxy group, 6-(4-(4-trifluoromethoxybenzyl)-1-piperidyl)-5-benzothiazolyloxy group, 7-(4-(4-methoxybenzyl)-1-benzo
piperidyl)-5-benzo[4,5]-thiazol-2-yl)oxy group, 6-\{(4-\{(3,4-
dimethoxybenzyl)-1-piperidyl\)-4-benzo[4,5]-thiazol-2-yl)oxy group, 7-\{(4-\{(2,4,6-trimethoxybenzyl)-1-piperidyl\)-4-
benzo[4,5]-thiazol-2-yl)oxy group, 5-\{(4-\{(2-
pentafluoroethoxybenzyl)-1-piperidyl\)-4-benzo[4,5]-
thiazol-2-yl)oxy group, 4-\{(3-
pentafluoroethoxybenzyl)-1-piperidyl\)-2-
benzo[4,5]-thiazol-2-yl)oxy group, 6-\{(4-
pentafluoroethoxybenzyl)-1-piperidyl\)-4-
benzo[4,5]-thiazol-2-yl)oxy group, 4-\{(2-
trifluoromethoxyphenyl)ethyl\)-1-piperidyl\)-2-
benzo[4,5]-thiazol-2-yl)oxy group, 4-\{(3-
trifluoromethoxyphenyl)propyl\)-1-piperidyl\)-2-
benzo[4,5]-thiazol-2-yl)oxy group, 4-\{(4-
trifluoromethoxyphenyl)butyl\)-1-piperidyl\)-2-
benzo[4,5]-thiazol-2-yl)oxy group, 4-\{(5-
trifluoromethoxyphenyl)pentyl\)-1-piperidyl\)-2-
benzo[4,5]-thiazol-2-yl)oxy group, 4-\{(6-
trifluoromethoxyphenyl)hexyl\)-1-piperidyl\)-2-
benzo[4,5]-thiazol-2-yl)oxy group, 4-\{(2-
trifluoromethylphenyl)ethyl\)-1-piperidyl\)-2-
benzo[4,5]-thiazol-2-yl)oxy group, 5-\{(4-
trifluoromethylphenyl)propyl\)-1-piperidyl\)-2-
benzo[4,5]-thiazol-2-yl)oxy group, 6-\{(4-
trifluoromethylphenyl)butyl\)-1-piperidyl\)-2-
benzo[4,5]-thiazol-2-yl)oxy group, 7-\{(5-
trifluoromethylphenyl)pentyl\)-1-piperidyl\)-2-
benzo[4,5]-thiazol-2-yl)oxy group, 5-\{(6-
6-\{(4-
...
trifluoromethylphenyl)hexyl)-1-piperidyl)-2-benzothiazolylloxy group, 2-(4-phenoxy-1-piperidyl)-4-benzothiazolylloxy group, 2-(3,4-diphenoxo-1-piperidyl)-4-benzothiazolylloxy group, 5-(2,3,4-triphenoxo-1-piperidyl)-2-benzothiazolylloxy group, 4-(4-(2-fluorophenoxy)-1-piperidyl)-2-benzothiazolylloxy group, 2-(4-(3-fluorophenoxy)-1-piperidyl)-4-benzothiazolylloxy group, 2-(4-(4-fluorophenoxy)-1-piperidyl)-5-benzothiazolylloxy group, 2-(4-(2-chlorophenoxy)-1-piperidyl)-6-benzothiazolylloxy group, 2-(4-(3-chlorophenoxy)-1-piperidyl)-7-benzothiazolylloxy group, 5-(4-(4-chlorophenoxy)-1-piperidyl)-4-benzothiazolylloxy group, 6-(4-(2,3-dichlorophenoxy)-1-piperidyl)-4-benzothiazolylloxy group, 7-(4-(2,4-dichlorophenoxy)-1-piperidyl)-4-benzothiazolylloxy group, 2-(4-(3,4-dichlorophenoxy)-1-piperidyl)-4-benzothiazolylloxy group, 4-(4-(3,5-dichlorophenoxy)-1-piperidyl)-2-benzothiazolylloxy group, 4-(4-(3,4,5-trichlorophenoxy)-1-piperidyl)-5-benzothiazolylloxy group, 2-(2,3,4,5,6-pentafluorophenoxy)-1-piperidyl)-2-benzothiazolylloxy group, 4-(4-(2-trifluoromethylphenoxy)-1-piperidyl)-6-benzothiazolylloxy group, 4-(4-(3-trifluoromethylphenoxy)-1-piperidyl)-7-benzothiazolylloxy group, 2-(4-(4-trifluoromethylphenoxy)-1-piperidyl)-4-benzothiazolylloxy group, 5-(4-(4-methylphenoxy)-1-piperidyl)-4-benzothiazolylloxy group, 6-(4-(3,4-
dimethylphenoxy)-1-piperidyl)-4-benzothiazolylloxy group, 7-(4-(2,4,6-trimethylphenoxy)-1-piperidyl)-4-
benzothiazolylloxy group, 4-(4-(2-
pentafluoroethoxyphenoxy)-1-piperidyl)-2-
benzothiazolylloxy group, 4-(4-(3-
pentafluoroethoxyphenoxy)-1-piperidyl)-5-
benzothiazolylloxy group, 4-(4-(4-
pentafluoroethoxyphenoxy)-1-piperidyl)-6-
benzothiazolylloxy group, 4-(4-(2-
trifluoromethoxyphenoxy)-1-piperidyl)-7-
benzothiazolylloxy group, 5-(4-(3-
trifluoromethoxyphenoxy)-1-piperidyl)-4-
benzothiazolylloxy group, 6-(4-(4-
trifluoromethoxyphenoxy)-1-piperidyl)-5-
benzothiazolylloxy group, 7-(4-(4-methoxyphenoxy)-1-
piperidyl)-5-benzothiazolylloxy group, 6-(4-(3,4-
dimethoxyphenoxy)-1-piperidyl)-4-benzothiazolylloxy group, 7-(4-(2,4,6-trimethoxyphenoxy)-1-piperidyl)-4-
benzothiazolylloxy group, 5-(4-(2-
pentafluoroethoxyphenoxy)-1-piperidyl)-4-
benzothiazolylloxy group, 4-(4-(3-
pentafluoroethoxyphenoxy)-1-piperidyl)-2-
benzothiazolylloxy group, 6-(4-(4-
pentafluoroethoxyphenoxy)-1-piperidyl)-4-
benzothiazolylloxy group, 2,5,6-triphenyl-7-
benzothiazolylloxy group, 2-(4-amino-1-piperidyl)-6-
benzothiazolylloxy group, 4-(2,4-diamino-1-piperidyl)-2-
benzothiazolylloxy group, 5-(2,4,6-triamino-1-
piperidyl)-4-benzothiazolyloxy group, 6-(2-amino-1-piperidyl)-5-benzothiazolyloxy group, 7-(3-amino-1-piperidyl)-6-benzothiazolyloxy group, 2-(4-methylamino-1-piperidyl)-4-benzothiazolyloxy group, 2-(4-ethylamino-1-piperidyl)-5-benzothiazolyloxy group, 2-(4-n-propylamino-1-piperidyl)-6-benzothiazolyloxy group, 2-(4-dimethylamino-1-piperidyl)-7-benzothiazolyloxy group, 2-(4-diethylamino-1-piperidyl)-4-benzothiazolyloxy group, 2-(4-di-n-propylamino-1-piperidyl)-5-benzothiazolyloxy group, 2-(4-phenylamino-1-piperidyl)-6-benzothiazolyloxy group, 2-(4-(N-phenyl-N-methylamino)-1-piperidyl)-7-benzothiazolyloxy group, 2-(4-(2-fluorophenylamino)-1-piperidyl)-4-benzothiazolyloxy group, 2-(4-(3-fluorophenylamino)-1-piperidyl)-5-benzothiazolyloxy group, 2-(4-(4-fluorophenylamino)-1-piperidyl)-6-benzothiazolyloxy group, 2-(4-(2-chlorophenylamino)-1-piperidyl)-7-benzothiazolyloxy group, 2-(4-(3-chlorophenylamino)-1-piperidyl)-4-benzothiazolyloxy group, 2-(4-(4-chlorophenylamino)-1-piperidyl)-5-benzothiazolyloxy group, 2-(4-(2,3-dichlorophenylamino)-1-piperidyl)-6-benzothiazolyloxy group, 2-(4-(2,4,6-trifluorophenylamino)-1-piperidyl)-7-benzothiazolyloxy group, 2-(4-(2,4,6-dichlorophenylamino)-1-piperidyl)-4-benzothiazolyloxy group, 2-(4-(3,4-dichlorophenylamino)-1-piperidyl)-6-benzothiazolyloxy group, 4-(3,5-dichlorophenylamino)-1-piperidyl)-5-benzothiazolyloxy group, 2-(4-(2,3,4,5,6-
pentafluorophenylamino)-1-piperidyl)-6-benzothiazolyl oxy group, 2-{4-(2-trifluoromethylphenylamino)-1-piperidyl)-7-benzothiazolyl oxy group, 2-{4-(2-methylphenylamino)-1-piperidyl)-4-benzothiazolyl oxy group, 2-{4-(2,3-dimethylphenylamino)-1-piperidyl)-5-benzothiazolyl oxy group, 2-{4-(2-trifluoromethylphenylamino)-1-piperidyl)-6-benzothiazolyl oxy group, 2-{4-(2,4,6-trimethylphenylamino)-1-piperidyl)-7-benzothiazolyl oxy group, 2-{4-(2,4-trifluoromethylphenylamino)-1-piperidyl)-4-benzothiazolyl oxy group, 2-{4-(2-pentafluoroethylphenylamino)-1-piperidyl)-5-benzothiazolyl oxy group, 2-{4-(3-pentafluoroethylphenylamino)-1-piperidyl)-5-benzothiazolyl oxy group, 2-{4-(4-pentafluoroethylphenylamino)-1-piperidyl)-6-benzothiazolyl oxy group, 2-{4-(2-trifluoromethoxyphenylamino)-1-piperidyl)-7-benzothiazolyl oxy group, 2-{4-(2-methoxyphenylamino)-1-piperidyl)-4-benzothiazolyl oxy group, 2-{4-(2,3-dimethoxyphenylamino)-1-piperidyl)-5-benzothiazolyl oxy group, 2-{4-(2,4,6-trimethoxyphenylamino)-1-piperidyl)-6-benzothiazolyl oxy group, 2-{4-(N-methyl-N-(2,4,6-trimethoxyphenylamino))-1-piperidyl)-7-benzothiazolyl oxy group, 2-{4-(N-methyl-N-(3,4-dimethylphenylamino))-1-piperidyl)-4-benzothiazolyl oxy group, 2-{4-(3-trifluoromethoxyphenylamino)-1-piperidyl)-5-benzothiazolyl oxy group, 2-{4-(4-
trifluoromethoxyphenylamino)-1-piperidyl)-6-
benzothiazolylloxy group, 2-(4-(2-pentafluoroethoxyphenylamino)-1-piperidyl)-7-
benzothiazolylloxy group, 2-(4-(3-
pentafluoroethoxyphenylamino)-1-piperidyl)-4-
benzothiazolylloxy group, 2-(4-(4-
pentafluoroethoxyphenylamino)-1-piperidyl)-5-
benzothiazolylloxy group, 2-(4-(2-fluorophenylamino)-1-
piperidyl)-5-benzothiazolylloxy group, 4-(3-
fluorophenylamino)-1-piperidyl)-6-benzothiazolylloxy
group, 2-(4-(4-fluorophenylamino)-1-piperidyl)-7-
benzothiazolylloxy group, 2-phenyl-5-(4-phenoxy-1-
piperidyl)-7-benzothiazolylloxy group, 2-(1-(4-
trifluoromethoxyphenyl)-2- or 3-)pyrrolyl)-(4-, 5-, 6-, or 7-)benzothiazolylloxy group, 2-(1-methyl-(2- or 3-)pyrrolyl)-(4-, 5-, 6- or 7-)benzothiazolylloxy group, 2-(4-(3-(4-trifluoromethylphenyl)-3-propenyl)-(1-, 2- or 3-)piperadiny)-(4-, 5-, 6- or 7-)benzothiazolylloxy group, 2-(4-(4-trifluoromethoxyphenyl))(4-, 2- or 3-)piperadiny)-(4-, 5-, 6- or 7-)benzothiazolylloxy group, 2-(4-(4-trifluoromethylphenyl))(1-, 2- or 3-)piperadiny)-(4-, 5-, 6- or 7-)benzothiazolylloxy group, 2-(4-chlorophenylthio)-(4-, 5-, 6- or 7-)benzothiazolylloxy group or the like.

A phenyl C1-C6 alkylidene group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be substituted) includes a phenyl C1-C6 alkylidene group (or the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), for example, benzylidene group, 1-phenylethylidene group, 2-phenylethylidene group, 3-phenylpropylidene group, 2-phenylpropylidene group, 4-phenylbutylidene group, 5-phenylpentylidene group, 4-phenylpentylidene group, 6-phenylhexylidene group, 2-fluorobenzylidene group, 3-fluorobenzylidene group, 4-fluorobenzylidene group, 2-chlorobenzylidene group, 3-chlorobenzylidene group, 4-chlorobenzylidene group, 2-bromobenzylidene group, 3-bromobenzylidene group, 4-bromobenzylidene group, 2-iodobenzylidene group, 3-iodobenzylidene group, 4-iodobenzylidene group, 2,3-difluorobenzylidene group, 3,4-difluorobenzylidene group, 3,5-difluorobenzylidene group, 2,4-difluorobenzylidene group, 2,6-difluorobenzylidene group, 2,3-dichlorobenzylidene group, 3,4-dichlorobenzylidene group, 3,5-dichlorobenzylidene group, 2,4-dichlorobenzylidene group, 2,6-dichlorobenzylidene group, 2-fluoro-4-bromobenzylidene group, 4-chloro-3-fluorobenzylidene group, 2,3,4-trichlorobenzylidene group, 3,4,5-trifluorobenzylidene group, 2,4,6-trichlorobenzylidene group, 4-isopropylbenzylidene
group, 4-n-butylenylbenzylidene group, 4-methylbenzylidene group, 2-methylbenzylidene group, 3-methylbenzylidene group, 2,4-dimethylbenzylidene group, 2,3-dimethylbenzylidene group, 2,6-dimethylbenzylidene group, 5,5-dimethylbenzylidene group, 2,5-dimethylbenzylidene group, 2,4,6-trimethylbenzylidene group, 3,5-difluoromethylbenzylidene group, 2,3,4,5,6-pentafluorobenzylidene group, 4-isopropoxybenzylidene group, 4-n-butoxybenzylidene group, 4-methoxybenzylidene group, 2-methoxybenzylidene group, 3-methoxybenzylidene group, 2,4-dimethoxybenzylidene group, 2,3-dimethoxybenzylidene group, 2,6-dimethoxybenzylidene group, 3,5-dimethoxybenzylidene group, 2,5-dimethoxybenzylidene group, 2,4,5-trimethoxybenzylidene group, 3,5-difluoromethoxybenzylidene group, 2-isopropoxybenzylidene group, 3-chloro-4-methoxybenzylidene group, 2-chloro-4-trifluoromethoxybenzylidene group, 3-methyl-4-fluorobenzylidene group, 4-bromo-3-trifluoromethylbenzylidene group, 2-trifluoromethylbenzylidene group, 3-trifluoromethylbenzylidene group, 4-trifluoromethylbenzylidene group, 2-pentafluoroethylbenzylidene group, 3-pentafluoroethylbenzylidene group, 4-pentafluoroethylbenzylidene group, 2-trifluoromethoxybenzylidene group, 3-
trifluoromethoxybenzylidene group, 4-
trifluoromethoxybenzylidene group, 2-
pentafluoroethoxybenzylidene group, 3-
pentafluoroethoxybenzylidene group, 4-
pentafluoroethoxybenzylidene group, 2-(2-
trifluoromethylphenyl)ethylidene group, 2-(3-
trifluoromethylphenyl)ethylidene group, 2-(4-
trifluoromethylphenyl)ethylidene group, 2-(2-
trifluoromethoxyphenyl)ethylidene group, 2-(3-
trifluoromethoxyphenyl)ethylidene group, 2-(4-
trifluoromethoxyphenyl)ethylidene group, 3-(2-
trifluoromethylphenyl)propylidine group, 3-(3-
trifluoromethylphenyl)propylidine group, 3-(4-
trifluoromethylphenyl)propylidine group, 3-(2-
trifluoromethoxyphenyl)propylidine group, 3-(3-
trifluoromethoxyphenyl)propylidine group, 3-(4-
trifluoromethoxyphenyl)propylidine group, 3-(3-
pentafluoroethoxyphenyl)propylidine group, 3-(4-
pentafluoroethoxyphenyl)propylidine group, 4-(3-
pentafluoroethoxyphenyl)butylidene group, 5-(4-
trifluoromethylphenyl)pentylidene group, 4-(4-
trifluoromethylphenyl)pentylidene group, 4-(4-
trifluoromethoxyphenyl)pentylidene group, 6-(3-
trifluoromethylphenyl)hexylidene group, 6-(4-
trifluoromethoxyphenyl)hexylidene group, 6-(4-
trifluoromethoxyphenyl)hexylidene group or the like.

A piperidyl group [wherein, on the piperidine ring, at least one selected from the group consisting of an amino group (wherein, on the amino group, at least one selected from the group consisting of a phenyl group [wherein, on the phenyl group, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyi group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] and a C1-C6 alkyl group may be substituted); a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted); a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a C1-C4 alkenyenedioxy group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted]; a phenyl C1-C6 alkoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted]; a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting
of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted); a naphthyl C1-C6 alkyl group; and a phenyl C1-C6 alkylidene group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted) includes a piperidyl group (wherein, on the piperidine ring, 1 to 3 substituents selected from the group consisting of an amino group (wherein, on the amino group, 1 or 2 groups selected from the group consisting of a phenyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) and a C1-C6 alkyl group may be substituted); a phenoxy group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted); a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a straight or
branched C1-C4 alkylenedioxy group containing 1 to 4 carbon atoms, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted); a phenyl C1-C6 alkoxy group as described later (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted); a phenyl group as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted); a naphthyl C1-C6 alkyl group having a straight or branched alkyl group containing 1 to 6 carbon atoms on the alkyl part as described later; and a phenyl C1-C6 alkylidene group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted], for example, a 1-piperidyl group, 2-piperidyl group, 3-piperidyl group, 4-piperidyl group, 2,4-diamino-1-piperidyl group, 2,4,6-triamino-1-piperidyl group, 2-amino-1-piperidyl
group, 3-amino-1-piperidyl group, 4-amino-1-piperidyl group, 4-methylamino-1-piperidyl group, 4-ethylamino-1-piperidyl group, 4-n-propylamino-1-piperidyl group, 4-dimethylamino-1-piperidyl group, 4-diethylamino-1-piperidyl group, 4-di-n-propylamino-1-piperidyl group, 4-phenylamino-1-piperidyl group, 4-(N-phenyl-N-methylamino)-1-piperidyl group, 4-(2-fluorophenylamino)-1-piperidyl group, 4-(3-fluorophenylamino)-1-piperidyl group, 4-(4-fluorophenylamino)-1-piperidyl group, 4-(2-chlorophenylamino)-1-piperidyl group, 4-(3-chlorophenylamino)-1-piperidyl group, 4-(4-chlorophenylamino)-1-piperidyl group, 4-(2,3-dichlorophenylamino)-1-piperidyl group, 4-(2,4,6-trifluorophenylamino)-1-piperidyl group, 4-(2,4-dichlorophenylamino)-1-piperidyl group, 4-(3,4-dichlorophenylamino)-1-piperidyl group, 4-(3,5-dichlorophenylamino)-1-piperidyl group, 4-(2,3,4,5,6-pentafluorophenylamino)-1-piperidyl group, 4-(2-trifluoromethylphenylamino)-1-piperidyl group, 4-(2-methylphenylamino)-1-piperidyl group, 4-(2,3-dimethylphenylamino)-1-piperidyl group, 4-(3-trifluoromethylphenylamino)-1-piperidyl group, 4-(2,4,6-trimethylphenylamino)-1-piperidyl group, 4-(4-trifluoromethylphenylamino)-1-piperidyl group, 4-(2-pentafluoroethylphenylamino)-1-piperidyl group, 4-(3-pentafluoroethylphenylamino)-1-piperidyl group, 4-(4-pentafluoroethylphenylamino)-1-piperidyl group, 4-(2-
trifluoromethoxyphenylamino)-1-piperidyl group, 4-(2-methoxyphenylamino)-1-piperidyl group, 4-(2,3-dimethoxyphenylamino)-1-piperidyl group, 4-(2,4,6-trimethoxyphenylamino)-1-piperidyl group, 4-(N-methyl-N-(2,4,6-trimethoxyphenylamino))-1-piperidyl group, 4-(N-methyl-N-(3,4-dimethylphenylamino))-1-piperidyl group, 4-(N-ethyl-N-(4-chlorophenylamino))-1-piperidyl group, 4-(3-trifluoromethoxyphenylamino)-1-piperidyl group, 4-(4-trifluoromethoxyphenylamino)-1-piperidyl group, 4-(2-pentafluoroethoxyphenylamino)-1-piperidyl group, 4-(3-pentafluoroethoxyphenylamino)-1-piperidyl group, 4-(4-pentafluoroethoxyphenylamino)-1-piperidyl group, 4-(N-methyl-N-(2-fluorophenyl)amino)-1-piperidyl group, 4-(N-methyl-N-(3-fluorophenyl)amino)-1-piperidyl group, 4-(N-methyl-N-(4-fluorophenyl)amino)-1-piperidyl group, 4-phenoxy-1-piperidyl group, 2,4-diphenoxy-1-piperidyl group, 2,4,6-triphenoxy-1-piperidyl group, 2-(2-fluorophenoxy)-1-piperidyl group, 3-(3-fluorophenoxy)-2-piperidyl group, 4-(4-fluorophenoxy)-3-piperidyl group, 2-(2-chlorophenoxy)-4-piperidyl group, 3-(3-chlorophenoxy)-5-piperidyl group, 4-(4-calorophenoxy)-5-piperidyl group, 5-(2-bromophenoxy)-2-piperidyl group, 6-(3-bromophenoxy)-3-piperidyl group, 4-(4-bromophenoxy)-1-piperidyl group, 3-(2,3-dichlorophenoxy)-2-piperidyl group, 4-(3,4-dichlorophenoxy)-3-piperidyl group, 3-(2,4-dichlorophenoxy)-4-piperidyl group, 2-(3,4,5-trichlorophenoxy)-3-piperidyl group, 6-(2,4,6-
trichlorophenoxy)-2-piperidyl group, 3-(4,5,6-
pentafluorophenoxy)-1-piperidyl group, 4-(2-
methylphenoxy)-1-piperidyl group, 5-(3-methylphenoxy)-
2-piperidyl group, 6-(4-methylphenoxy)-3-piperidyl
5 group, 4-(2-ethylphenoxy)-1-piperidyl group, 2-(3-
ethylphenoxy)-1-piperidyl group, 3-(4-ethylphenoxy)-2-
piperidyl group, 4-(4-n-propylphenoxy)-3-piperidyl
group, 3-(4-tert-butylphenoxy)-4-piperidyl group, 2-(4-
n-butylphenoxy)-3-piperidyl group, 1-(2-
10 trifluoromethylphenoxy)-2-piperidyl group, 2-(3-
trifluoromethylphenoxy)-1-piperidyl group, 4-(4-
trifluoromethylphenoxy)-1-piperidyl group, 1-(2-
pentafluoroethylphenoxy)-4-piperidyl group, 4-(3-
pentafluoroethylphenoxy)-1-piperidyl group, 4-(2,3-
dimethylphenoxy)-1-piperidyl group, 4-(3,4,5-
trimethylphenoxy)-1-piperidyl group, 4-(4-n-
pentylphenoxy)-1-piperidyl group, 4-(4-n-hexylphenoxy)-
1-piperidyl group, 4-(2-methoxyphenoxy)-1-piperidyl
group, 4-(3-methoxyphenoxy)-1-piperidyl group, 4-(4-
20 methoxyphenoxy)-1-piperidyl group, 2-(2-ethoxyphenoxy)-
3-piperidyl group, 3-(3-ethoxyphenoxy)-4-piperidyl
group, 4-(4-ethoxyphenoxy)-3-piperidyl group, 3-(4-n-
propoxyphenoxy)-2-piperidyl group, 2-(4-tert-
butoxyphenoxy)-1-piperidyl group, 4-(4-n-
butoxyphenoxy)-2-piperidyl group, 2-(2-
trifluoromethoxyphenoxy)-3-piperidyl group, 3-(3-
trifluoromethoxyphenoxy)-4-piperidyl group, 4-(4-
trifluoromethoxyphenoxy)-3-piperidyl group, 3-(2-
pentafluoroethoxyphenoxy)-2-piperidyl group, 2-(4-
pentafluoroethoxyphenoxy)-1-piperidyl group, 4-(2,3-
dimethoxyphenoxy)-14-piperidyl group, 4-(3,4,5-
trimethoxyphenoxy)-1-piperidyl group, 4-(4-n-
pentyl)oxyphenoxy)-1-piperidyl group, 4-(4-n-
hexyl)oxyphenoxy)-1-piperidyl group, 4-benzyl-1-
piperidyl group, 2,4-dibenzyl-1-piperidyl group, 2,4,6-
tribenzyl-1-piperidyl group, 2-(2-fluorobenzyl)-1-
piperidyl group, 3-(2-(3-fluorophenyl)ethyl)-2-
piperidyl group, 4-(1-(4-fluorophenyl)ethyl)-3-
piperidyl group, 2-(3-(2-chlorophenyl)propyl)-4-
piperidyl group, 3-(4-(3-chlorophenyl)butyl)-5-
piperidyl group, 4-(5-(4-chlorophenyl)pentyl)-2-
piperidyl group, 5-(6-(2-bromophenyl)hexyl)-2-piperidyl 
group, 6-(3-bromobenzyl)-3-piperidyl group, 4-(4-
bromobenzyl)-1-piperidyl group, 3-(2,3-dichlorobenzyl)-
2-piperidyl group, 4-(3,4-dichlorobenzyl)-3-piperidyl 
group, 3-(2,4-dichlorobenzyl)-4-piperidyl group, 2-
(3,4,5-trichlorobenzyl)-3-piperidyl group, 6-(2,4,6-
trichlorobenzyl)-2-piperidyl group, 3-(2,3,4,5,6-
pentafluorobenzyl)-1-piperidyl group, 4-(2-
methylbenzyl)-1-piperidyl group, 5-(2-(3-
methylphenyl)ethyl)-2-piperidyl group, 6-(3-(4-
methylphenyl)propyl)-3-piperidyl group, 1-(4-(2-
ethylphenyl)butyl)-4-piperidyl group, 2-(5-(3-
ethylphenyl)pentyl)-1-piperidyl group, 3-(6-(4-
ethylphenyl)hexyl)-2-piperidyl group, 4-(4-n-
propylbenzyl)-3-piperidyl group, 3-(4-tert-
butylbenzyl)-4-piperidyl group, 2-(4-n-butylbenzyl)-3-piperidyl group, 1-(2-trifluoromethylbenzyl)-2-piperidyl group, 2-(3-trifluoromethylbenzyl)-1-piperidyl group, 4-(4-trifluoromethylbenzyl)-1-piperidyl group, 1-(2-pentafluorostyrylbenzyl)-4-piperidyl group, 1-(3-pentafluorostyrylbenzyl)-4-piperidyl group, 4-(2,3-dimethylbenzyl)-1-piperidyl group, 1-(3,4,5-trimethylbenzyl)-4-piperidyl group, 1-(4-n-pentylbenzyl)-4-piperidyl group, 4-(4-n-hexylbenzyl)-1-piperidyl group, 4-(2-methoxybenzyl)-1-piperidyl group, 1-(2-(3-methoxyphenyl)ethyl)-4-piperidyl group, 1-(1-(4-methoxyphenyl)ethyl)-4-piperidyl group, 2-(3-(2-ethoxyphenyl)propyl)-3-piperidyl group, 3-(4-(3-ethoxyphenyl)butyl)-4-piperidyl group, 4-(5-(4-ethoxyphenyl)pentyl)-3-piperidyl group, 3-(6-(4-n-propoxyphenyl)hexyl)-2-piperidyl group, 2-(4-tert-butoxybenzyl)-1-piperidyl group, 1-(4-n-butoxybenzyl)-2-piperidyl group, 2-(2-trifluoromethoxybenzyl)-3-piperidyl group, 3-(3-trifluoromethoxybenzyl)-4-piperidyl group, 4-(4-trifluoromethoxybenzyl)-1-piperidyl group, 3-(2-pentafluorothoxybenzyl)-2-piperidyl group, 2-(4-pentafluorothoxybenzyl)-1-piperidyl group, 1-(2,3-dimethoxybenzyl)-4-piperidyl group, 4-(3,4,5-trimethoxybenzyl)-1-piperidyl group, 4-(4-n-pentylbenzyl)-1-piperidyl group, 4-(4-n-hexylbenzyl)-1-piperidyl group, 4-(4-n-hexylbenzyl)-1-piperidyl group, 4-(benzyl-3-phenoxy-1-piperidyl group, 4-phenoxy-2-methylamino-1-piperidyl
group, 4-(4-trifluoromethoxybenzylidene)-1-piperidyl group, 4-(4-chlorobenzylidene)-1-piperidyl group, 4-(4-trifluoromethylbenzylidene)-1-piperidyl group, 4-(3,4-dichlorobenzoyloxy)-(1-, 2- or 3-)piperidyl group, 4-(4-methylbenzoyloxy)-(1-, 2- or 3-)piperidyl group, 4-(4-trifluoromethoxybenzoyloxy)-(1-, 2- or 3-)piperidyl group, 4-(4-methoxyphenyl)-(1-, 2- or 3-)piperidyl group, 4-(3,4-dichlorophenyl)-(1-, 2- or 3-)piperidyl group, 4-[(1- or 2-)napthylmethyl]-(1-, 2- or 3-)piperidyl group, 4-(3,4-methylenedioxyphenyl)-(1-, 2- or 3-)piperidyl group, 4-(4-chlorobenzoyloxy)-(1-, 2- or 3-)piperidyl group or the like.

A quinolyloxy group (wherein, on the quinoline ring, at least one selected from the group consisting of a (c-1)halogen atom, a (c-2)phenoxy group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted], a (c-3)piperadinyll group [wherein, on the piperadine ring, at least one selected from the group consisting of a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted], a phenyl group [wherein, on the phenyl ring, at least one selected from the group
consisting of a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) and a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted) and a (c-4)piperidyl group (wherein, on the piperidine ring, at least one selected from the group consisting of an amino group (wherein, on the amino group, at least one selected from the group consisting of a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) and a C1-C6 alkyl group may be substituted); a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be
substituted); a phenyl Cl-C6 alkyl group (wherein, on
the phenyl ring, at least one selected from the group
consisting of a Cl-C4 alkylenedioxy group, a halogen
atom, a halogen substituted or unsubstituted Cl-C6
alkyl group and a halogen substituted or unsubstituted
Cl-C6 alkoxy group may be substituted); a phenyl Cl-C6
alkoxy group (wherein, on the phenyl ring, at least one
selected from the group consisting of a halogen atom, a
halogen substituted or unsubstituted Cl-C6 alkyl group
and a halogen substituted or unsubstituted Cl-C6 alkoxy
group may be substituted); a phenyl group (wherein, on
the phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted Cl-C6 alkyl group and a halogen
substituted or unsubstituted Cl-C6 alkoxy group may be
substituted); a naphthyl Cl-C6 alkyl group; and a
phenyl Cl-C6 alkylidene group (wherein, on the phenyl
ring, at least one selected from the group consisting
of a halogen atom, a halogen substituted or
unsubstituted Cl-C6 alkyl group and a halogen
substituted or unsubstituted Cl-C6 alkoxy group may be
substituted; may be substituted) may be substituted)
includes an quinolyloxy group (wherein, on the
quinoline ring, 1 to 3 substituents selected from the
group consisting of a (c-1) halogen atom, a (c-2)
phenoxy group (wherein, on the phenyl ring, 1 to 5,
preferably 1 to 3 substituents selected from the group
consisting of a halogen atom, a halogen substituted or

unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), (c-3) a piperadiny1 group [wherein, on the piperidine ring, 1 to 5, preferably 1 to 3 groups selected from the group consisting of a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a phenyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 groups selected from the group consisting of a phenoxy group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a phenylalkenyl group, containing a C2-C6 alkenyl group having at least 1 to 3 double bonds, wherein each double bond contains both of a trans-form and a cis-form (wherein, on the phenyl ring, at least one group selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be
substituted) may be substituted] and a (C-4) piperidyl group (wherein, on the piperidine ring, 1 to 3 substituents selected from the group consisting of an amino group (wherein, on the amino group, 1 or 2 groups selected from the group consisting of a phenyl group [wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted] and a Cl-C6 alkyl group may be substituted); a phenoxy group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted); a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a straight or branched Cl-C4 alkylenedioxy group, a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted); a phenylalkoxy group in which the alkoxy moiety is a straight or branched Cl-C6 alkoxy group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a phenyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen

substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a naphthylalkyl group in which the alkyl moiety is a straight or branched C1-C6 alkyl group; and a phenyl C1-C6 alkylidene group

(wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), for example, a 2-quinolyloxy group, 3-quinolyloxy group, 4-quinolyloxy group, 5-quinolyloxy group, 6-quinolyloxy group, 7-quinolyloxy group, 8-quinolyloxy group, 4-(1-piperadiny1)-2-quinolyloxy group, 3-(2-piperadiny1)-4-quinolyloxy group, 4-(1-piperadiny1)-3-quinolyloxy group, 5-(1-piperadiny1)-4-quinolyloxy group, 6-(3,4-dibenzyl-1-piperadiny1)-5-quinolyloxy group, 7-(2,3,4-tribenzyl-1-piperadiny1)-6-quinolyloxy group, 4-(4-benzyl-1-piperadiny1)-2-quinolyloxy group, 3-(4-(2-phenethyl)-1-piperadiny1)-2-quinolyloxy group, 4-(4-(3-phenylpropyl)-1-piperadiny1)-3-quinolyloxy group, 5-(4-(4-phenylbutyl)-1-piperadiny1)-4-quinolyloxy group, 6-(4-(5-phenylpentyl)-1-piperadiny1)-5-quinolyloxy group,
7-(4-(6-phenylhexyl)-1-piperadiny1)-6-quinolyloxy group, 8-(4-(2-fluorobenzyl)-1-piperadiny1)-7-quinolyloxy group, 2-(4-(3-fluorobenzyl)-1-piperadiny1)-8-quinolyloxy group, 3-(4-(4-fluorobenzyl)-1-piperadiny1)-2-quinolyloxy group, 4-(4-(2-chlorobenzyl)-1-piperadiny1)-3-quinolyloxy group, 5-(4-(3-chlorobenzyl)-1-piperadiny1)-4-quinolyloxy group, 2-(4-(4-chlorobenzyl)-1-piperadiny1)-6-quinolyloxy group, 7-(4-(2,3-dichlorobenzyl)-1-piperadiny1)-6-quinolyloxy group, 8-(4-(2,4-dichlorobenzyl)-1-piperadiny1)-7-quinolyloxy group, 2-(4-(3,4-dichlorobenzyl)-1-piperadiny1)-8-quinolyloxy group, 3-(4-(3,5-dichlorobenzyl)-1-piperadiny1)-2-quinolyloxy group, 4-(4-(3,4,5-trichlorobenzyl)-1-piperadiny1)-3-quinolyloxy group, 5-(4-(2,3,4,5,6-pentafluorobenzyl)-1-piperadiny1)-4-quinolyloxy group, 6-(4-(2-trifluoromethylbenzyl)-1-piperadiny1)-5-quinolyloxy group, 7-(4-(3-trifluoromethylbenzyl)-1-piperadiny1)-6-quinolyloxy group, 2-(4-(4-trifluoromethylbenzyl)-1-piperadiny1)-6-quinolyloxy group, 2-(4-(4-methylbenzyl)-1-piperadiny1)-8-quinolyloxy group, 3-(4-(3,4-dimethylbenzyl)-1-piperadiny1)-2-quinolyloxy group, 4-(4-(2,4,6-trimethylbenzyl)-1-piperadiny1)-3-quinolyloxy group, 5-(4-(2-pentafluoroethylbenzyl)-1-piperadiny1)-4-quinolyloxy group, 6-(4-(3-pentafluoroethylbenzyl)-1-piperadiny1)-5-quinolyloxy group, 7-(4-(4-pentafluoroethylbenzyl)-1-piperadiny1)-6-quinolyloxy group, 2-(4-(4-trifluoromethoxybenzyl)-1-piperadiny1)-8-quinolyloxy group, 5-(4-(3,4-dimethylbenzyl)-1-piperadiny1)-2-quinolyloxy group, 6-(4-(3-pentafluoroethylbenzyl)-1-piperadiny1)-5-quinolyloxy group, 7-(4-(4-pentafluoroethylbenzyl)-1-piperadiny1)-6-quinolyloxy group, 2-(4-(4-trifluoromethoxybenzyl)-1-piperadiny1)-8-quinolyloxy group.
piperadiny1)-6-quinolyloxy group, 2-(4-(3-
trifluoromethoxybenzyl)-1-piperadiny1)-8-quinolyloxy
group, 3-(4-(4-trifluoromethoxybenzyl)-1-piperadiny1)-
2-quinolyloxy group, 4-(4-(4-methoxybenzyl)-1-
piperadiny1)-3-quinolyloxy group, 5-(4-(3,4-
dimethoxybenzyl)-1-piperadiny1)-4-quinolyloxy group, 6-
(4-(2,4,6-trimethoxybenzyl)-1-piperadiny1)-5-
quinolyloxy group, 7-(4-(2-pentafluoroethoxybenzyl)-1-
piperadiny1)-6-quinolyloxy group, 8-(4-(3-
pentafluoroethoxybenzyl)-1-piperadiny1)-2-quinolyloxy
group, 3-(4-(4-pentafluoroethoxybenzyl)-1-piperadiny1)-
2-quinolyloxy group, 4-(4-(2-(4-
trifluoromethoxyphenyl)ethyl)-1-piperadiny1)-3-
quinolyloxy group, 5-(4-(3-(4-
trifluoromethoxyphenyl)propyl)-1-piperadiny1)-4-
quinolyloxy group, 6-(4-(4-(4-
trifluoromethoxyphenyl)butyl)-1-piperadiny1)-5-
quinolyloxy group, 7-(4-(5-(4-
trifluoromethoxyphenyl)pentyl)-1-piperadiny1)-6-
quinolyloxy group, 8-(4-(6-(4-
trifluoromethoxyphenyl)hexyl)-1-piperadiny1)-7-
quinolyloxy group, 2-(4-(2-(4-
trifluoromethylphenyl)ethyl)-1-piperadiny1)-8-
quinolyloxy group, 3-(4-(3-(4-
trifluoromethylphenyl)propyl)-1-piperadiny1)-2-
quinolyloxy group, 4-(4-(4-(4-
trifluoromethylphenyl)butyl)-1-piperadiny1)-2-
quinolyloxy group, 5-(4-(5-(4-
trifluoromethylphenyl)pentyl)-1-piperadiny1)-2-quinolyloxy group, 6-(4-(6-(4-
trifluoromethylphenyl)hexyl)-1-piperadiny1)-2-
quino1yoxy group, 3-(2-piperidyl)-2-quinolyloxy group, 4-(3-piperidyl)-3-quinolyloxy group, 5-(4-piperidyl)-4-
quino1yoxy group, 6-(2,4-diamino-1-piperidyl)-5-
quino1yoxy group, 7-(2,4,6-triamino-1-piperidyl)-6-
quino1yoxy group, 6-(4-aminol-1-piperidyl)-7-
quino1yoxy group, 2-(4-aminol-1-piperidyl)-8-
quino1yoxy group, 3-(4-aminol-1-piperidyl)-2-
quino1yoxy group, 4-(4-methylamino-1-piperidyl)-3-
quino1yoxy group, 5-(4-ethylamino-1-piperidyl)-4-
quino1yoxy group, 6-(4-n-propylamino-1-piperidyl)-5-
quino1yoxy group, 7-(4-di1methylamino-1-piperidyl)-6-
quino1yoxy group, 8-(4-diethylamino-1-piperidyl)-7-
quino1yoxy group, 9-(4-di-n-propylamino-1-piperidyl)-
8-quinolyloxy group, 3-(4-phenylamino-1-piperidyl)-2-
quino1yoxy group, 4-(4-(N-phenyl-N-methylamino)-1-
piperidyl)-3-quinolyloxy group, 5-(4-(2-
fluorophenylamino)-1-piperidyl)-4-quinolyloxy group, 6-
(4-(3-fluorophenylamino)-1-piperidyl)-5-quinolyloxy
group, 7-(4-(4-fluorophenylamino)-1-piperidyl)-6-
quino1yoxy group, 8-(4-(2-chlorophenylamino)-1-
piperidyl)-7-quinolyloxy group, 2-(4-(3-
chlorophenylamino)-1-piperidyl)-8-quinolyloxy group, 3-
(4-(4-chlorophenylamino)-1-piperidyl)-2-quinolyloxy
group, 4-(4-(2,3-dichlorophenylamino)-1-piperidyl)-3-
quino1yoxy group, 5-(4-(2,4,6-trifluorophenylamino)-1-
quinolyloxy group, 6-(4-(6-(4-trifluoromethylphenyl)he
piperidyl)-4-quinolyloxy group, 6-(4-(2,4-dichlorophenylamino)-1-piperidyl)-5-quinolyloxy group, 7-(4-(3,4-dichlorophenylamino)-1-piperidyl)-6-quinolyloxy group, 8-(4-(3,5-dichlorophenylamino)-1-piperidyl)-7-quinolyloxy group, 2-(4-(2,3,4,5,6-pentafluorophenylamino)-1-piperidyl)-8-quinolyloxy group, 3-(4-(2-trifluoromethylphenylamino)-1-piperidyl)-2-quinolyloxy group, 4-(4-(2-methylphenylamino)-1-piperidyl)-3-quinolyloxy group, 5-(4-(2,3-dimethylphenylamino)-1-piperidyl)-4-quinolyloxy group, 6-(4-(2-trifluoromethylphenylamino)-1-piperidyl)-5-quinolyloxy group, 7-(4-(2,4,6-trimethylphenylamino)-1-piperidyl)-6-quinolyloxy group, 8-(4-(4-trifluoromethylphenylamino)-1-piperidyl)-7-quinolyloxy group, 2-(4-(2-pentafluoroethylphenylamino)-1-piperidyl)-8-quinolyloxy group, 3-(4-(3-pentafluoroethylphenylamino)-1-piperidyl)-2-quinolyloxy group, 4-(4-(4-pentafluoroethylphenylamino)-1-piperidyl)-3-quinolyloxy group, 5-(4-(2-trifluoromethoxyphenylamino)-1-piperidyl)-4-quinolyloxy group, 6-(4-(2-methoxyphenylamino)-1-piperidyl)-5-quinolyloxy group, 7-(4-(2,3-dimethoxyphenylamino)-1-piperidyl)-6-quinolyloxy group, 8-(4-(2,4,6-trimethoxyphenylamino)-1-piperidyl)-7-quinolyloxy group, 2-(4-(N-methyl-N-(2,4,6-trimethoxyphenylamino))-1-piperidyl)-8-quinolyloxy group, 3-(4-(N-methyl-N-(3,4-dimethylphenylamino))-1-piperidyl)-2-quinolyloxy group,
4-[(4-(3-trifluoromethoxyphenylamino)-1-piperidyl)-2-quinolyloxy group, 5-[(4-(4-
trifluoromethoxyphenylamino)-1-piperidyl)-2-quinolyloxy group, 6-[(4-(2-pentafluoroethoxyphenylamino)-1-
piperidyl)-2-quinolyloxy group, 7-[(4-(3-
pentafluoroethoxyphenylamino)-1-piperidyl)-2-
quinolyloxy group, 8-[(4-(4-
pentafluoroethoxyphenylamino)-1-piperidyl)-2-
quinolyloxy group, 2-[(4-(2-fluorophenylamino)-1-
piperidyl)-3-quinolyloxy group, 3-[(4-(3-
fluorophenylamino)-1-piperidyl)-2-quinolyloxy group, 4-
(4-(4-fluorophenylamino)-1-piperidyl)-2-quinolyloxy group, 2-[(4-(N-ethyl-N-(4-chlorophenylamino))-1-
piperidyl)-6-quinolyloxy group, 2,4-di(1-piperadiny1)-
6-quinolyloxy group, 3-(1-piperidyl)-4-(1-piperadiny1)-
2-quinolyloxy group, 2,4,6-tri(1-piperadiny1)-3-
quinolyloxy group, 5-chloro-3-quinolyloxy group, 2-[(4-
trifluoromethoxyphenoxy)-6-quinolyloxy group, 2-[(4-(4-
trifluoromethoxybenzylidene)-1-piperidyl)-6-quinolyloxy group, 2-[(4-(4-chlorobenzylidene)-1-piperidyl)-6-
quinolyloxy group, 2-[(4-(4-trifluoromethylbenzylidene)-
1-piperidyl)-6-quinolyloxy group, 2-[(4-benzyl-1-
piperidyl)-4-quinolyloxy group, 2-[(3,4-dibenzyl-1-
piperidyl)-4-quinolyloxy group, 5-[(2,3,4-tribenzy1-1-
piperidyl)-2-quinolyloxy group, 4-[(4-(2-phenethyl)-1-
piperidyl)-2-quinolyloxy group, 4-[(4-(3-phenylpropyl)-
1-piperidyl)-5-quinolyloxy group, 4-[(4-(4-phenylbutyl)-
1-piperidyl)-6-quinolyloxy group, 4-[(4-(5-
phenylpentyl)-1-piperidyl)-7-quinolyloxy group, 2-(4-(6-phenylhexyl)-1-piperidyl)-4-quinolyloxy group, 4-(4-(2-fluorobenzyl)-1-piperidyl)-2-quinolyloxy group, 2-(4-(3-fluorobenzyl)-1-piperidyl)-4-quinolyloxy group, 5-2-(4-(4-fluorobenzyl)-1-piperidyl)-5-quinolyloxy group, 2-(4-(2-chlorobenzyl)-1-piperidyl)-6-quinolyloxy group, 2-(4-(3-chlorobenzyl)-1-piperidyl)-7-quinolyloxy group, 5-2-(4-(4-chlorobenzyl)-1-piperidyl)-4-quinolyloxy group, 6-(4-(2,3-dichlorobenzyl)-1-piperidyl)-4-quinolyloxy group, 7-(4-(2,4-dichlorobenzyl)-1-piperidyl)-8-quinolyloxy group, 2-(4-(3,4-dichlorobenzyl)-1-piperidyl)-8-quinolyloxy group, 4-(4-(3,5-dichlorobenzyl)-1-piperidyl)-2-quinolyloxy group, 4-(4-(3,4,5-trichlorobenzyl)-1-piperidyl)-5-quinolyloxy group, 4-(4-(2,3,4,5,6-pentafluorobenzyl)-1-piperidyl)-2-quinolyloxy group, 4-(4-(2-trifluoromethylbenzyl)-1-piperidyl)-6-quinolyloxy group, 4-(4-(3-trifluoromethylbenzyl)-1-piperidyl)-7-quinolyloxy group, 2-(4-(4-trifluoromethylbenzyl)-1-piperidyl)-8-quinolyloxy group, 5-(4-(4-methylbenzyl)-1-piperidyl)-4-quinolyloxy group, 6-(4-(3,4-dimethylbenzyl)-1-piperidyl)-4-quinolyloxy group, 8-(4-(2,4,6-trimethylbenzyl)-1-piperidyl)-4-quinolyloxy group, 3-(4-(2-pentafluoroethylbenzyl)-1-piperidyl)-2-quinolyloxy group, 8-(4-(3-pentafluoroethylbenzyl)-1-piperidyl)-5-quinolyloxy group, 4-(4-(4-pentafluoroethylbenzyl)-1-piperidyl)-6-quinolyloxy group, 4-(4-(2-trifluoromethoxybenzyl)-1-piperidyl)-7-
quinolylxoxy group, 5-([6-(3-trifluoromethoxybenzyl)-1-piperidyl]-4-quinolylxoxy group, 6-([4-
trifluoromethoxybenzyl]-1-piperidyl)-5-quinolylxoxy group, 7-([4-(4-methoxybenzyl)-1-piperidyl]-5-
quinolylxoxy group, 6-([4-(3,4-dimethoxybenzyl)-1-piperidyl]-4-quinolylxoxy group, 7-([4-(2,4,6-
trimethoxybenzyl)-1-piperidyl]-4-quinolylxoxy group, 5-([4-(2-pentafluoromethoxybenzyl)-1-piperidyl]-4-
quinolylxoxy group, 4-([4-(3-pentafluoromethoxybenzyl)-1-piperidyl]-2-quinolylxoxy group, 6-([4-
pentafluoromethoxybenzyl]-1-piperidyl)-4-quinolylxoxy group, 4-([4-(2-(4-trifluoromethoxyphenyl)ethyl]-1-
piperidyl)-2-quinolylxoxy group, 4-([4-(3-(4-trifluoromethoxyphenyl)propyl)-1-piperidyl]-2-
quinolylxoxy group, 4-([4-(4-(4-trifluoromethoxyphenyl)butyl)-1-piperidyl]-2-quinolylxoxy group, 4-([4-(5-(4-
trifluoromethoxyphenyl)pentyl)-1-piperidyl]-3-quinolylxoxy group, 4-([4-(6-(4-
trifluoromethoxyphenyl)hexyl]-1-piperidyl)-3-quinolylxoxy group, 4-([4-(2-[4-
trifluoromethylphenyl)ethyl]-1-piperidyl]-2-quinolylxoxy group, 5-([4-(3-(4-trifluoromethylphenyl)propyl)-1-
piperidyl]-2-quinolylxoxy group, 6-([4-(4-(4-
trifluoromethylphenyl)butyl]-1-piperidyl)-2-quinolylxoxy group, 7-([4-(5-(4-trifluoromethylphenyl)pentyl)-2-
piperidyl]-2-quinolylxoxy group, 5-([4-(6-(4-
trifluoromethylphenyl)hexyl]-1-piperidyl)-2-quinolylxoxy
group, 2-(4-phe noxy-1-piperidyl)-4-quinol yloxy group, 2-(3,4-diphen oxy-1-piperidyl)-4-quinol yloxy group, 5-
(2,3,4-triphenoxy-1-piperidyl)-2-quinol yloxy group, 4-
(4-(2-fluorophenoxy)-1-piperidyl)-2-quinol yloxy group, 2-(4-(3-fluorophenoxy)-1-piperidyl)-4-quinol yloxy group, 2-(4-(4-fluorophenoxy)-1-piperidyl)-5-
quinol yloxy group, 2-(4-(2-chlorophenoxy)-1-piperidyl)-
6-quinol yloxy group, 2-(4-(3-chlorophenoxy)-1-
piperidyl)-7-quinol yloxy group, 5-(4-(4-chlorophenoxy)-1-
piperidyl)-4-quinol yloxy group, 6-(4-(2,3-
dichlorophenoxy)-1-piperidyl)-4-quinol yloxy group, 7-
(4-(2,4-dichlorophenoxy)-1-piperidyl)-4-quinol yloxy group, 2-(4-(3,4-dichlorophenoxy)-1-piperidyl)-8-
quinol yloxy group, 4-(4-(3,5-dichlorophenoxy)-1-
piperidyl)-2-quinol yloxy group, 4-(4-(3,4,5-
trichlorophenoxy)-1-piperidyl)-5-quinol yloxy group, 4-
(4-(2,3,4,5,6-pentafluorophenoxy)-1-piperidyl)-2-
quinol yloxy group, 4-(4-(2-trifluoromethylphenoxy)-1-
piperidyl)-6-quinol yloxy group, 4-(4-(3-
trifluoromethylphenoxy)-1-piperidyl)-7-quinol yloxy group, 2-(4-(4-trifluoromethylphenoxy)-1-piperidyl)-4-
quinol yloxy group, 5-(4-(4-methylphenoxy)-1-piperidyl)-
4-quinol yloxy group, 6-(4-(3,4-dimethylphenoxy)-1-
piperidyl)-4-quinol yloxy group, 7-(4-(2,4,6-
trimethylphenoxy)-1-piperidyl)-4-quinol yloxy group, 4-
(4-(2-pentafluoroethylphenoxy)-1-piperidyl)-2-
quinol yloxy group, 4-(4-(3-pentafluoroethylphenoxy)-1-
piperidyl)-5-quinol yloxy group, 4-(4-(4-

pentafluoroethylphenoxy)-1-piperidyl)-6-quinolyloxy group, 4-(4-((2-trifluoromethoxyphenoxy)-1-piperidyl)-7-quinolyloxy group, 5-(4-(3-trifluoromethoxyphenoxy)-1-piperidyl)-4-quinolyloxy group, 6-(4-(4-trifluoromethoxyphenoxy)-1-piperidyl)-5-quinolyloxy group, 7-(4-(4-methoxyphenoxy)-1-piperidyl)-5-quinolyloxy group, 6-(4-(3,4-dimethoxyphenoxy)-1-piperidyl)-4-quinolyloxy group, 8-(4-(2,4,6-trimethoxyphenoxy)-1-piperidyl)-4-quinolyloxy group, 5-(4-(2-pentafluoroethoxyphenoxy)-1-piperidyl)-4-quinolyloxy group, 4-(4-(3-pentafluoroethoxyphenoxy)-1-piperidyl)-2-quinolyloxy group, 6-(4-(4-pentafluoroethoxyphenoxy)-1-piperidyl)-4-quinolyloxy group, 2,5,6-trifenoxy-7-quinolyloxy group, 4,5,6-trichloro-2-quinolyloxy group, 2-phenoxy-5-bromo-5-quinolyloxy group, 2-(2,3-dimethylphenoxy)-5-quinolyloxy group, 2-(3,4,5-trimethylphenoxy)-6-quinolyloxy group, 2-(2,3-dimethoxyphenoxy)-7-quinolyloxy group, 2-(3,4,5-trimethoxyphenoxy)-8-quinolyloxy group, 2-(2,3,4,5,6-pentafluorophenoxy)-6-quinolyloxy group, 2-(2-methylphenoxy)-4-quinolyloxy group, 2-(3-methylphenoxy)-3-quinolyloxy group, 3-(4-methoxyphenoxy)-2-quinolyloxy group, 4-(2-methoxyphenoxy)-3-quinolyloxy group, 5-(3-methoxyphenoxy)-4-quinolyloxy group, 6-(4-methoxyphenoxy)-5-quinolyloxy group, 7-(2-fluorophenoxy)-6-quinolyloxy group, 8-(3-fluorophenoxy)-7-quinolyloxy group, 2-(4-
fluorophenoxy)-5-quinolylxoy group, 3-(2-chlorophenoxy)-2-quinolylxoy group, 4-(3-chlorophenoxy)-6-quinolylxoy group, 5-(4-chlorophenoxy)-2-quinolylxoy group, 6-(2-bromophenoxy)-3-quinolylxoy group, 7-(3-bromophenoxy)-4-quinolylxoy group, 8-(4-bromophenoxy)-2-quinolylxoy group, 2-(2,3-dichlorophenoxy)-6-quinolylxoy group, 3-(3,4-dichlorophenoxy)-7-quinolylxoy group, 4-(2,4-dichlorophenoxy)-5-quinolylxoy group, 2-(3,4,5-trichlorophenoxy)-6-quinolylxoy group, 2-(2,4,6-trichlorophenoxy)-5-quinolylxoy group, 2-(3-trifluoromethylphenox)-7-quinolylxoy group, 2-(4-(3-(4-trifluoromethylphenyl)-2-propenyl)-(1-, 2- or 3-)piperadiny)-(3-, 4-, 5-, 6-, 7- or 8-)quinolylxoy group, 2-(4-(4-methoxyphenyl)-(1-, 2- or 3-)piperadiny)-(3-, 4-, 5-, 6-, 7- or 8-)quinolylxoy group, 2-(4-(3,4-dimethylphenyl)-(1-, 2- or 3-)piperadiny)-(3-, 4-, 5-, 6-, 7- or 8-)quinolylxoy group, 2-(4-(4-fluorophenyl)-(1-, 2- or 3-)piperadiny)-(3-, 4-, 5-, 6-, 7- or 8-)quinolylxoy group, 2-(4-(4-trifluoromethylphenyl)-(1-, 2- or 3-)piperadiny)-(3-, 4-, 5-, 6-, 7- or 8-)quinolylxoy group, 2-(4-(4-methylphenyl)-(1-, 2- or 3-)piperadiny)-(3-, 4-, 5-, 6-, 7- or 8-)quinolylxoy group, 2-(4-(3,4-dichlorophenyl)-(1-, 2- or 3-)piperadiny)-(3-, 4-, 5-, 6-, 7- or 8-)quinolylxoy group, 2-(4-(4-trifluoromethoxyphenyl)-(1-, 2- or 3-)piperadiny)-(3-, 4-, 5-, 6-, 7- or 8-)quinolylxoy group
group, 2-(4-(4-chlorophenoxy)phenyl)-(1-, 2- or 3-)-piperadinyloxy group, 2-(4-(3,4-dichlorobenzyloxy)-(1-, 2- or 3-)-piperadinyloxy group, 2-(4-(4-methylbenzyloxy)-(1-, 2- or 3-)-piperadinyloxy group, 2-(4-(4-trifluoromethoxybenzyloxy)-(1-, 2- or 3-)-piperadinyloxy group, 2-(4-(4-methoxyphenyl)-(1-, 2- or 3-)-piperadinyloxy group, 2-(4-(3,4-dichlorophenyl)-(1-, 2- or 3-)-piperadinyloxy group, 2-(4-(4-methylenedioxyphenyl)-(1-, 2- or 3-)-piperadinyloxy group, 2-(4-(chlorobenzyloxy)-(1-, 2- or 3-)-piperadinyloxy group or the like.

A phenyl C1-C6 alkoxy substituted C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) is a group composed of a phenyl C1-C6 alkoxy group and C1-C6 alkyl group which may be substituted by 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group as defined above, examples of which include a benzyloxyethyl group, 2-phenylethoxymethyl group, 3-phenylpropoxymethyl group, 2-phenylpropoxymethyl group, 4-phenylbutoxymethyl group, 5-phenylpentoxymethyl group, 4-phenylpentoxymethyl group, 6-phenylhexyloxymethyl group, 2-fluorobenzylloxymethyl group, 4-fluorobenzylloxymethyl group, 4-chlorobenzylloxymethyl group, 3-chlorobenzylloxymethyl group, 2-chlorobenzylloxymethyl group, 3,5-dichlorobenzylloxymethyl group, 3,4-dichlorobenzylloxymethyl group, 2-(3-
fluorobenzyl)ethyl group, 1-(4-fluorobenzyl)oxyethyl group, 3-(2-(2-fluorophenyl)ethoxy)propyl group, 4-(2-(3-fluorophenyl)ethoxy)propyl group, 5-(2-(4-fluorophenyl)ethoxy)pentyl group, 6-(2-chlorobenzyl)hexyl group, 3-chlorobenzylloxymethyl group, 2-(4-chlorobenzyl)oxyethyl group, 1-(2-fluoro-4-bromobenzyl)oxyethyl group, 3-(4-chloro-3-fluorobenzyl)oxypropyl group, 4-(2,3,4-trichlorobenzyl)oxybutyl group, 5-(3,4,5-trifluorobenzyl)oxypentyl group, 6-(2,3,4,5,6-pentafluorobenzyl)oxyhexyl group, 2,4,6-trichlorobenzylloxymethyl group, 2-(4-isopropylbenzyl)oxyethyl group, 1-(4-n-butylbenzyl)oxyethyl group, 3-(4-methylbenzyl)oxypropyl
group, 4-(2-methylbenzyloxy)butyl group, 5-(3-methylbenzyloxy)pentyl group, 6-(2,4-dimethylbenzyloxy)hexyl group, 2,3-dimethylbenzyloxyethyl group, 4-methylbenzyloxyethyl group, 4-ethylbenzyloxyethyl group, 3,5-dimethylbenzyloxyethyl group, 4-isopropylbenzyloxyethyl group, 3-trifluoromethylbenzyloxyethyl group, 4-trifluoromethylbenzyloxyethyl group, 2-trifluoromethylbenzyloxyethyl group, 2-(2,6-dimethylbenzyloxy)ethyl group, 1-(3,5-dimethylbenzyloxy)ethyl group, 3-(2,5-dimethylbenzyloxy)propyl group, 4-(2,4,6-trimethylbenzyloxy)butyl group, 5-(3,5-difluoromethylbenzyloxy)pentyl group, 6-(4-isopropoxybenzyloxy)hexyl group, 4-n-butoxybenzyloxyethyl group, 4-trifluoromethoxybenzyloxyethyl group, 2-trifluoromethoxybenzyloxyethyl group, 3-trifluoromethoxybenzyloxyethyl group, 3-methoxybenzyloxyethyl group, 2-(4-methoxybenzyloxy)ethyl group, 1-(2-methoxybenzyloxy)ethyl group, 3-(3-methoxybenzyloxy)propyl group, 4-(2,4-dimethoxybenzyloxy)butyl group, 5-(2,3-dimethoxybenzyloxy)pentyl group, 6-(2,6-dimethoxybenzyloxy)hexyl group, 3,5-dimethoxybenzyloxyethyl group, 2-(7,5-
dimethoxybenzyl group, 1-(2,4,6-trimethoxybenzyl group, 3-(3,5-ditrifluoromethoxybenzyl group, 4-(2-isopropoxybenzyl group, 5-(3-chloro-4-methoxybenzyl group)pentyl group, 6-(2-chloro-4-trifluoromethoxybenzyl group)hexyl group, 3-methyl-4-fluorobenzyl oxymethyl group, 2-(4-bromo-3-trifluoromethylbenzyl group)ethyl group, 1-(2-(2-chlorophenyl)ethoxy)methyl group, 3-(2-(3-chlorophenyl)ethoxy)propyl group, 4-(2-(3-chlorophenyl)ethoxy)butyl group, 5-(2-trifluoromethylbenzyl group)pentyl group, 6-(3-trifluoromethylbenzyl group)hexyl group, 4-trifluoromethylbenzyl oxymethyl group, 2-(2-trifluoromethoxybenzyl group)ethyl group, 1-(3-trifluoromethoxybenzyl group)ethyl group, 3-(4-trifluoromethoxybenzyl group)propyl group, 4-(2-(2-trifluoromethylphenyl)ethoxy)butyl group, 5-(2-(3-trifluoromethylphenyl)ethoxy)pentyl group, 6-(2-(4-trifluoromethylphenyl)ethoxy)hexyl group, (2-(2-trifluoromethoxyphenyl)ethoxy)methyl group, 2-(2-(3-trifluoromethoxyphenyl)ethoxy)ethyl group, 1-(2-(4-trifluoromethoxyphenyl)ethoxy)ethyl group, 3-(3-(2-trifluoromethylphenyl)propoxy)propyl group, 4-(3-(3-trifluoromethylphenyl)propoxy)butyl group, 5-(3-(4-trifluoromethylphenyl)propoxy)pentyl group, 6-(3-(2-trifluoromethylphenyl)propoxy)pentyl group, (3-(3-trifluoromethoxyphenyl)propoxy)methyl group, 2-(3-(4-
trifluoromethoxyphenyl)propoxy)ethyl group, 1-(4-(4-
trifluoromethylphenyl)butoxy)ethyl group, 3-(5-(4-
trifluoromethylphenyl)pentyloxy)butyl group, 4-(4-(4-
trifluoromethylphenyl)pentyloxy)butyl group, 5-(4-(4-
trifluoromethoxyphenyl)pentyloxy)pentyloxy)hexyl group, 6-(6-(4-
trifluoromethylphenyl)hexyloxy)hexyl group, 6-(4-
trifluoromethylphenyl)hexyloxy)methyl group, 2-(6-(4-
trifluoromethoxyphenyl)hexyloxy)ethyl group or the
like.

A piperidyl group (wherein, on the piperidine
ring, at least one selected from the group consisting
of a phenoxy group (wherein, on the phenyl ring, at
least one selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted
Cl-C6 alkyl group and a halogen substituted or
unsubstituted Cl-C6 alkoxy group may be substituted), a
phenyl Cl-C6 alkoxy substituted Cl-C6 alkyl group
(wherein, on the phenyl ring, at least one selected
from the group consisting of a halogen atom, a halogen
substituted or unsubstituted Cl-C6 alkyl group and a
halogen substituted or unsubstituted Cl-C6 alkoxy group
may be substituted), a phenoxy Cl-C6 alkyl group
(wherein, on the phenyl ring, at least one selected
from the group consisting of a halogen atom, a halogen
substituted or unsubstituted Cl-C6 alkyl group and a
halogen substituted or unsubstituted Cl-C6 alkoxy group
may be substituted) and a phenyl Cl-C6 alkyl group
(wherein, on the phenyl ring, at least one selected
from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted] may be substituted) includes a piperidyl group [wherein, on the piperidine ring, 1 to 3 substituents selected from the group consisting of a phenoxy group [wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted] a phenyl Cl-C6 alkoxy substituted Cl-C6 alkyl group [wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted], a phenoxy Cl-C6 alkyl group having a straight or branched alkyl group containing 1 to 6 carbon atoms on the alkyl part described later [wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted] and a phenyl Cl-C6 alkyl group [wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted), for example, a 1-piperidyl group, 4-piperidyl group, 2-piperidyl group, 3-piperidyl group, 4-phenoxo-1-piperidyl group, 2,4-diphenoxo-1-piperidyl group, 2,4,6-triphenoxo-1-piperidyl group, 2-[2-fluorophenoxo)-1-piperidyl group, 3-(3-fluorophenoxo)-2-piperidyl group, 4-(4-fluorophenoxo)-3-piperidyl group, 2-(2-chlorophenoxo)-4-piperidyl group, 3-(3-chlorophenoxo)-5-piperidyl group, 4-(4-chlorophenoxo)-2-piperidyl group, 5-(2-bromophenoxo)-2-piperidyl group, 6-(3-bromophenoxo)-3-piperidyl group, 4-(4-bromophenoxo)-1-piperidyl group, 3-(2,3-dichlorophenoxo)-2-piperidyl group, 4-(3,4-dichlorophenoxo)-3-piperidyl group, 3-(2,4-dichlorophenoxo)-4-piperidyl group, 2-(3,4,5-trichlorophenoxo)-3-piperidyl group, 6-(2,4,6-trichlorophenoxo)-2-piperidyl group, 3-(2,3,4,5,6-pentafluorophenoxo)-1-piperidyl group, 4-[2-methylphenoxo)-1-piperidyl group, 5-(3-methylphenoxo)-2-piperidyl group, 6-(4-methylphenoxo)-3-piperidyl group, 3-(2-ethylphenoxo)-4-piperidyl group, 2-(3-ethylphenoxo)-1-piperidyl group, 3-(4-ethylphenoxo)-2-piperidyl group, 4-(4-n-propylphenoxo)-3-piperidyl group, 3-(4-n-butylphenoxo)-4-piperidyl group, 2-(4-n-butylphenoxo)-3-piperidyl group, 4-(2-trifluoromethylphenoxo)-2-piperidyl group, 2-(3-trifluoromethylphenoxo)-1-piperidyl group, 3-(4-
trifluoromethylphenoxy)-1-piperidyl group, 1-(2-
pentafluoroethylphenoxy)-4-piperidyl group, 1-(3-
pentafluoroethylphenoxy)-4-piperidyl group, 4-(2,3-
dimethylphenoxy)-1-piperidyl group, 3-(3,4,5-
trimethylphenoxy)-4-piperidyl group, 1-(4-n-
pentylphenoxy)-4-piperidyl group, 4-(4-n-hexylphenoxy)-
1-piperidyl group, 4-(2-methoxyphenoxy)-1-piperidyl

group, 1-(3-methoxyphenoxy)-4-piperidyl group, 3-(4-
methoxyphenoxy)-4-piperidyl group, 2-(2-ethoxyphenoxy)-
3-piperidyl group, 3-(3-ethoxyphenoxy)-4-piperidyl
group, 4-(4-ethoxyphenoxy)-3-piperidyl group, 3-(4-n-
propoxyphenoxy)-2-piperidyl group, 2-(4-tert-
butoxyphenoxy)-2-piperidyl group, 4-(4-n-
butoxyphenoxy)-2-piperidyl group, 2-(2-
trifluoromethoxyphenoxy)-3-piperidyl group, 3-(3-
trifluoromethoxyphenoxy)-4-piperidyl group, 4-(4-
trifluoromethoxyphenoxy)-3-piperidyl group, 3-(2-
pentafluoroethoxyphenoxy)-2-piperidyl group, 2-(4-
pentafluoroethoxyphenoxy)-1-piperidyl group, 3-(2,3-
dimethoxyphenoxy)-4-piperidyl group, 4-(3,4,5-
trimethoxyphenoxy)-1-piperidyl group, 4-(4-n-
pentyloxyphenoxy)-1-piperidyl group, 4-(4-n-
hexyloxyphenoxy)-1-piperidyl group, 4-benzyl-1-
piperidyl group, 2,4-dibenzyl-1-piperidyl group, 2,4,6-
tribenzyl-1-piperidyl group, 2-(2-fluorobenzyl)-1-
piperidyl group, 3-(2-(3-fluorophenyl)ethyl)-2-
piperidyl group, 4-(1-(4-fluorophenyl)ethyl)-3-
piperidyl group, 2-(3-(2-chlorophenyl)propyl)-4-
piperidyl group, 3-(4-(3-chlorophenyl)butyl)-5-piperidyl group, 4-(5-(4-chlorophenyl)pentyl)-2-piperidyl group, 5-(6-(2-bromophenyl)hexyl)-2-piperidyl group, 6-(3-bromobenzyl)-3-piperidyl group, 4-(4-bromobenzyl)-1-piperidyl group, 3-(2,3-dichlorobenzyl)-2-piperidyl group, 4-(3,4-dichlorobenzyl)-3-piperidyl group, 3-(2,4-dichlorobenzyl)-4-piperidyl group, 2-(3,4,5-trichlorobenzyl)-3-piperidyl group, 6-(2,4,6-trichlorobenzyl)-2-piperidyl group, 3-(2,3,4,5,6-pentafluorobenzyl)-1-piperidyl group, 4-(2-methylbenzyl)-1-piperidyl group, 5-(2-(3-methylphenyl)ethyl)-2-piperidyl group, 6-(3-(4-methylphenyl)propyl)-3-piperidyl group, 1-(4-(2-ethylphenyl)butyl)-4-piperidyl group, 2-(5-(3-ethylphenyl)pentyl)-1-piperidyl group, 3-(6-(4-ethylphenyl)hexyl)-2-piperidyl group, 4-(4-n-propylbenzyl)-3-piperidyl group, 3-(4-tert-butylbenzyl)-4-piperidyl group, 2-(4-n-butylbenzyl)-3-piperidyl group, 1-(2-trifluoromethylbenzyl)-2-piperidyl group, 2-(3-trifluoromethylbenzyl)-1-piperidyl group, 4-(4-trifluoromethylbenzyl)-1-piperidyl group, 1-(2-pentafluoroethylbenzyl)-4-piperidyl group, 1-(3-pentafluoroethylbenzyl)-4-piperidyl group, 4-(2,3-dimethylbenzyl)-1-piperidyl group, 1-(3,4,5-trimethylbenzyl)-4-piperidyl group, 1-(4-n-pentylbenzyl)-4-piperidyl group, 4-(4-n-hexylbenzyl)-1-piperidyl group, 4-(2-methobenzyl)-1-
piperidyl group, 1-(2-(3-methoxyphenyl)ethyl)-4-piperidyl group, 1-(1-(4-methoxyphenyl)ethyl)-4-piperidyl group, 2-(3-(2-ethoxyphenyl)propyl)-3-piperidyl group, 3-(4-(3-ethoxyphenyl)butyl)-4-piperidyl group, 3-(4-(3-ethoxyphenyl)butyl)-4-piperidyl group, 4-(5-(4-ethoxyphenyl)pentyl)-3-piperidyl group, 3-(6-(4-n-propoxyphenyl)hexyl)-2-piperidyl group, 2-(4-tert-butoxybenzyl)-1-piperidyl group, 1-(4-n-butoxybenzyl)-2-piperidyl group, 2-(2-
trifluoromethoxybenzyl)-3-piperidyl group, 3-(3-trifluoromethoxybenzyl)-4-piperidyl group, 4-(4-
trifluoromethoxybenzyl)-1-piperidyl group, 3-(2-
pentafluoroethoxybenzyl)-2-piperidyl group, 2-(4-
pentafluoroethoxybenzyl)-1-piperidyl group, 1-(2,3-
dimethoxybenzyl)-4-piperidyl group, 4-(3,4,5-
trimethoxybenzyl)-1-piperidyl group, 4-(4-n-
pentyloxybenzyl)-1-piperidyl group, 4-(4-n-
hexyloxybenzyl)-1-piperidyl group, 4-benzyl-3-phenoxy-
1-piperidyl group, 4-benzylmethoxymethyl-1-piperidyl group, 2,4-dibenzylmethoxymethyl-1-piperidyl group, 2,4,6-
tribenzylmethoxymethyl-1-piperidyl group, 2-(2-
fluorobenzyloxy)methyl]-1-piperidyl group, 3-(2-(2-(3-
fluorophenyl)ethoxy)ethyl)-2-piperidyl group, 4-(1-(1-
(4-fluorophenyl)ethyl)ethoxy)-3-piperidyl group, 2-(3-
(3-(2-chlorophenyl)propoxy)propyl)-4-piperidyl group, 3-(4-(4-(3-chlorophenyl)butoxy)butyl)-5-piperidyl group, 4-(5-(5-(4-chlorophenyl)pentyloxy)pentyl)-2-
piperidyl group, 5-(6-(6-(2-bromophenyl)hexyloxy)-2-
piperidyl group, 6-(3-bromobenzylloxymethyl)-3-piperidyl group, 4-{4-bromobenzylloxymethyl}-1-piperidyl group, 3-
(2,3-dichlorobenzylloxymethyl)-2-piperidyl group, 4-
(3,4-dichlorobenzylloxymethyl)-3-piperidyl group, 3-
(2,4-dichlorobenzylloxymethyl)-4-piperidyl group, 2-
(3,4,5-trichlorobenzylloxymethyl)-3-piperidyl group, 6-
(2,4,6-trichlorobenzylloxymethyl)-2-piperidyl group, 3-
(2,3,4,5,6-pentafluorobenzylloxymethyl)-1-piperidyl
group, 4-{2-methylbenzylloxymethyl}-1-piperidyl group,
5-(2-(2-(3-methylphenyl)ethoxy)ethyl)-2-piperidyl
group, 6-(3-(3-(4-methylphenyl)propoxy)propyl)-3-
piperidyl group, 1-{4-(4-(2-ethylphenyl)butoxy)butyl}-
4-piperidyl group, 2-(5-(5-(3-
ethylphenyl)pentyl)pentyl)-1-piperidyl group, 3-(6-
(6-(4-ethylphenyl)hexyloxy)hexyl)-2-piperidyl group, 4-
(4-n-propylbenzylloxymethyl)-3-piperidyl group, 3-{4-
tert-butylbenzylloxymethyl)-4-piperidyl group, 2-(4-n-
butylbenzylloxymethyl)-3-piperidyl group, 1-{2-
trifluoromethylbenzylloxymethyl)-2-piperidyl group, 2-
(3-trifluoromethylbenzylloxymethyl)-1-piperidyl group,
4-{3-trifluoromethylbenzylloxymethyl)-1-piperidyl group,
1-(2-pentafluoroethylbenzylloxymethyl)-4-piperidyl
group, 1-{3-pentafluoroethylbenzylloxymethyl)-4-
piperidyl group, 4-(2,3-dimethylbenzylloxymethyl)-1-
piperidyl group, 1-(3,4,5-trimethylbenzylloxymethyl)-4-
piperidyl group, 1-{4-n-pentylbenzylloxymethyl)-4-
piperidyl group, 4-(4-n-hexylbenzylloxymethyl)-1-
piperidyl group, 4-(2-methoxybenzylloxymethyl)-1-
piperidyl group, 1-(2-(2-(3-methoxyphenyl)ethoxy)ethyl)-4-piperidyl group, 1-(1-(1-(4-methoxyphenyl)ethoxy)ethyl)-4-piperidyl group, 2-(3-(3-(2-ethoxyphosphoryl)propoxy)propyl)-3-piperidyl group,

3-(4-(4-(3-ethoxyphenyl)butoxy)butyl)-4-piperidyl group, 4-(5-(5-(4-ethoxyphenyl)pentyloxy)pentylol)-3-piperidyl group, 3-(6-(6-(4-n-propoxyphenyl)hexyloxy)hexyl)-2-piperidyl group, 2-((4-tert-butoxybenzyl)oxy)methyl)-1-piperidyl group, 1-(4-n-butoxybenzyl)oxy)methyl)-2-piperidyl group, 2-((2-trifluoromethoxybenzyl)oxy)methyl)-3-piperidyl group, 3-(3-trifluoromethoxybenzyl)oxy)methyl)-4-piperidyl group, 4-(4-trifluoromethoxybenzyl)oxy)methyl)-1-piperidyl group, 3-(2-pentafluoroethoxybenzyl)oxy)methyl)-2-piperidyl group, 2-(4-pentafluoroethoxybenzyl)oxy)methyl)-1-piperidyl group, 1-(2,3-dimethoxybenzyl)oxy)methyl)-4-piperidyl group, 4-(3,4,5-trimethoxybenzyl)oxy)methyl)-1-piperidyl group, 4-(4-n-pentyloxybenzyl)oxy)methyl)-1-piperidyl group, 4-(4-n-hexyloxybenzyl)oxy)methyl)-1-piperidyl group, 4-benzyl)oxy)methyl)-3-phenoxy-1-piperidyl group, 4-benzyl-3-phenoxy-1-piperidyl group, 4-(4-chlorophenoxy)methyl)-1-piperidyl group or the like.

A pyridyloxy group (wherein, on the pyridine ring, at least one selected from the group consisting of a (d-1) piperidyl group [wherein, on the piperidine ring, at least one selected from the group consisting of a phenoxy group (wherein, on the phenyl ring, at
least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a phenyl C1-C6 alkoxy substituted C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a phenoxy C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) and a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted] and a (d-2)piperidinyl group [wherein, on the piperidine ring, at least one selected from the group consisting of a C1-C6 alkoxy carbonyl group, a furyl C1-C6 alkyl group [wherein, on the furan ring, at least one phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group
may be substituted) may be substituted, a pyridyl C1-C6 alkyl group (wherein, on the pyridine ring, at least one selected from the group consisting of a furyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a benzothiophenyl C1-C6 alkyl group (wherein, on the benzothiophene ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a benzofuryl C1-C6 alkyl group (wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a benzofuryl C2-C6 alkenyl group (wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group
may be substituted], a thiazolyl C1-C6 alkyl group
(wherein, on the thiazole ring, at least one phenyl
group (wherein, on the phenyl ring, at least one
selected from the group consisting of a halogen atom, a
halogen substituted or unsubstituted C1-C6 alkyl group
and a halogen substituted or unsubstituted C1-C6 alkoxy
group may be substituted), a
phenoxy C1-C6 alkyl group (wherein, on the phenyl ring,
at least one selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted
C1-C6 alkyl group and a halogen substituted or
unsubstituted C1-C6 alkoxy group may be substituted), an
indolyl C1-C6 alkyl group (wherein, on the indole
ring, at least one selected from the group consisting
of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted) and a phenyl C1-C6 alkyl group (wherein,
on the phenyl ring, at least one selected from the
group consisting of a benzofuryl group, a halogen atom,
a halogen substituted or unsubstituted C1-C6 alkyl
group and a halogen substituted or unsubstituted C1-C6
alkoxy group may be substituted), may be substituted)
includes a pyridyloxy group
(wherein, on the pyridine ring, 1 to 3 substituents
selected from the group consisting of a pyridyl group
(wherein, on the piperidine ring, 1 to 5, preferably 1
to 3 substituents selected from the group consisting of
a phenoxy group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a phenyl C1-C6 alkoxy substituted C1-C6 alkyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a phenoxy C1-C6 alkyl group having a straight or branched alkyl group containing 1 to 6 carbon atoms on the alkyl part as described later (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) and a phenyl C1-C6 alkyl group as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) and a (d-2)piperadiny group (wherein, on the piperadine ring, 1 to 3 substituents selected from the group consisting of a C1-C6
alkoxycarbonyl group as described above, a furyl C1-C6 alkyl group having a straight or branched alkyl group containing 1 to 6 carbon atoms on the alkyl part as described later (wherein, on the furan ring, 1 to 3 phenyl groups (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted), a pyridyl C1-C6 alkyl group having a straight or branched alkyl group containing 1 to 6 carbon atoms on the alkyl part as described later (wherein, on the pyridine ring, 1 to 3 substituents selected from the group consisting of a furyl group and a phenyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted), a benzothienyl C1-C6 alkyl group having a straight or branched alkyl group containing 1 to 6 carbon atoms on the alkyl part as described later (wherein, on the benzothiophene ring, 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a phenyl C2-C6 alkenyl group having a
straight or branched alkanyl group containing 2 to 6 carbon atoms and having 1 to 3 double bonds, and including both trans and cis forms as described later (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a benzofuryl C1-C6 alkyl group having a straight or branched alkyl group containing 1 to 6 carbon atoms on the alkyl part as described later (wherein, on the benzofuran ring, 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a benzofuryl C2-C6 alkenyl group having a straight or branched alkenyl group containing 2 to 6 carbon atoms on the alkenyl part and having 1 to 3 double bonds, and including both trans and cis forms as described later (wherein, on the benzofuran ring, 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a thiazolyl C1-C6 alkyl group having a straight or branched alkyl group containing 1 to 6 carbon atoms on the alkyl part as described later (wherein, on the thiazole ring, 1 or 2 phenyl groups (wherein, on the
phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), a phenoxy Cl-C6 alkyl group having a straight or branched alkyl group containing 1 to 6 carbon atoms on the alkyl part as described later (wherein, on the indole ring, 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), an indolyl Cl-C6 alkyl group having a straight or branched alkyl group containing 1 to 6 carbon atoms on the alkyl part as described later (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) and a phenyl Cl to C6 alkyl group alkyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a benzofuranyl group, a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) may be substituted, for example, a 2-pyridyloxy group, 3-pyridyloxy group, 4-pyridyloxy group, 3-(1-piperidyl)-
2-pyridyloxy group, 2-({4-piperidyl}-3-pyridyloxy group, 4-({2-piperidyl}-3-pyridyloxy group, 5-({3-piperidyl}-2-pyridyloxy group, 2,4-di(1-piperidyl)-3-pyridyloxy group, 2-{1-piperidyl}-4-({2-(2-fluorophenoxy)-1-piperidyl}-3-pyridyloxy group, 2,4,6-tri(1-piperidyl)-3-pyridyloxy group, 2-({4-phenoxy-1-piperidyl}-3-pyridyloxy group, 2-({2,4-diphenoxy-1-piperidyl}-3-pyridyloxy group, 3-({2,4,6-triphenoxy-1-piperidyl}-4-pyridyloxy group, 4-({2-(2-fluorophenoxy)-1-piperidyl}-3-pyridyloxy group, 5-({3-(3-fluorophenoxy)-2-piperidyl}-3-pyridyloxy group, 6-({4-(4-fluorophenoxy)-3-piperidyl}-4-pyridyloxy group, 2-({2-(2-chlorophenoxy)-4-piperidyl}-3-pyridyloxy group, 3-({3-(3-chlorophenoxy)-5-piperidyl}-4-pyridyloxy group, 4-({4-(4-chlorophenoxy)-5-piperidyl}-4-pyridyloxy group, 5-({5-(2-bromophenoxy)-2-piperidyl}-3-pyridyloxy group, 2-({6-(3-bromophenoxy)-3-piperidyl}-4-pyridyloxy group, 2-({4-(4-bromophenoxy)-1-piperidyl}-2-pyridyloxy group, 3-({3-(2,3-dichlorophenoxy)-2-piperidyl}-4-pyridyloxy group, 3-({4-(3,4-dichlorophenoxy)-2-piperidyl}-4-pyridyloxy group, 4-({3-(2,4-dichlorophenoxy)-4-piperidyl}-2-pyridyloxy group, 5-({2-(3,4,5-trichlorophenoxy)-3-piperidyl}-2-pyridyloxy group, 6-({6-(2,4,5-trichlorophenoxy)-2-piperidyl}-3-pyridyloxy group, 2-({3-(2,3,4,5,6-pentafluorophenoxy)-1-piperidyl}-3-pyridyloxy group, 4-({4-(2-methylphenoxy)-1-piperidyl}-2-pyridyloxy group, 3-({5-{3-methylphenoxy)-2-piperidyl}-2-pyridyloxy group, 5-({6-
(4-methylphenoxy)-3-piperidy1)-3-pyridyloxy group, 2-
(1-(2-ethylphenoxy)-4-piperidy1)-4-pyridyloxy group, 2-
(2-(3-ethylphenoxy)-1-piperidy1)-3-pyridyloxy group, 3-
(3-(4-ethylphenoxy)-2-piperidy1)-4-pyridyloxy group, 4-
(4-(4-n-propylphenoxy)-3-piperidy1)-2-pyridyloxy group,
5-(5-(4-tert-butylphenoxy)-4-piperidy1)-3-pyridyloxy
group, 6-(2-(4-n-butylphenoxy)-3-piperidy1)-2-
pyridyloxy group, 2-(1-(2-trifluoromethylphenoxy)-2-
piperidy1)-4-pyridyloxy group, 3-(2-(3-
trifluoromethylphenoxy)-1-piperidy1)-4-pyridyloxy
group, 4-(3-(4-trifluoromethylphenoxy)-1-piperidy1)-2-
pyridyloxy group, 5-(1-(2-pentafluoroethylphenoxy)-4-
piperidy1)-3-pyridyloxy group, 6-(1-(3-
pentafluoroethylphenoxy)-4-piperidy1)-2-pyridyloxy
group, 2-(4-(2,3-dimethylphenoxy)-1-piperidy1)-3-
pyridyloxy group, 3-(3-(3,4,5-trimethylphenoxy)-4-
piperidy1)-2-pyridyloxy group, 4-(1-(4-n-
penty1phenoxy)-4-piperidy1)-3-pyridyloxy group, 5-{4-
(4-n-hexylphenoxy)-1-piperidy1)-2-pyridyloxy group, 6-
(4-(2-methoxyphenoxy)-1-piperidy1)-2-pyridyloxy group,
2-(1-(3-methoxyphenoxy)-4-piperidy1)-4-pyridyloxy
group, 3-(1-(4-methoxyphenoxy)-4-piperidy1)-2-
pyridyloxy group, 4-(2-(2-ethoxyphenoxy)-3-piperidy1)-
2-pyridyloxy group, 5-(3-(3-ethoxyphenoxy)-4-
piperidy1)-3-pyridyloxy group, 2-(4-(4-ethoxyphenoxy)-
5-piperidy1)-4-pyridyloxy group, 2-(3-(4-n-
propoxyphenoxy)-2-piperidy1)-4-pyridyloxy group, 3-(2-
(4-tert-butoxyphenoxy)-1-piperidy1)-4-pyridyloxy group,
4-(1-{4-n-butoxyphenoxy})-2-piperidyl]-2-pyridyloxy group, 5-{2-(2-trifluoromethoxyphenoxy)-3-piperidyl]-2-pyridyloxy group, 6-{3-(3-trifluoromethoxyphenoxy)-4-piperidyl]-2-pyridyloxy group, 6-{4-{4-trifluoromethoxyphenoxy}-3-piperidyl]-2-pyridyloxy group, 2-{3-(2-pentafluoroethoxyphenoxy)-2-piperidyl]-3-pyridyloxy group, 3-{4-(4-pentafluoroethoxyphenoxy)-1-piperidyl]-2-pyridyloxy group, 4-{1-(2,3-dimethoxyphenoxy)-4-piperidyl]-2-pyridyloxy group, 5-{4-(3,4,5-trimethoxyphenoxy)-1-piperidyl]-3-pyridyloxy group, 6-{4-{4-n-phenyloxyphenoxy}-1-piperidyl]-3-pyridyloxy group, 5-{4-(4-n-hexyloxyphenoxy)-1-piperidyl]-3-pyridyloxy group, 2-(4-{4-(trifluoromethylbenzyloxymethyl)-1-piperidyl]-5-pyridyloxy group, 2-{4-trifluoromethoxybenzyl-1-piperidyl]-5-pyridyloxy group, 2-{4-{4-chlorobenzyl}-1-piperazinyl]-5-pyridyloxy group, 2-{4-{4-trifluoromethylbenzyl-1-piperidyl]-5-pyridyloxy group, 2-{4-{4-chlorobenzylloxymethyl}-1-piperazinyl]-5-pyridyloxy group, 4-{4-fluorobenzyl-1-piperadiny]-6-pyridyloxy group, 4-phenoxy-3-{4-{4-trifluoromethoxybenzylloxymethyl]-1-piperidyl]-2-pyridyloxy group, 2-{4-tert-butoxycarbonyl-(1, 2- or 3-piperadiny]-{(3, 4-, 5- or 6-)pyridyloxy group, 2-{4-{(2-, 3-, 4-, 5-, 6- or 7-)benzofuryl]benzyl-(1, 2- or 3-piperadiny]-{(3, 4-, 5- or 6-)pyridyloxy group, 2-{4-{3-{(2- or 3-)furyl)]pyridylmethyl}-(1, 2- or 3-piperadiny]-{(3, 4-, 5- or 6-)pyridyloxy group,
2-[(1-(2-(4-trifluoromethoxyphenyl)pyridylmethyl]-1-, 2- or 3-)piperadiny]-{(3-, 4-, 5- or 6-)pyridyloxy group, 2-[(4-(2-(3-chloro-4-fluorophenyl)pyridylmethyl]-(2-, 2- or 3-)piperadiny]-(3-, 4-, 5- or 6-)pyridyloxy group, 2-[(4-(5-trifluoromethyl-2, 3-, 4-, 6- or 7-)benzofurylmethyl]-{(1-, 2- or 3-)piperadiny]-(3-, 4-, 5- or 6-)pyridyloxy group, 2-[(4-(6-trifluoromethyl-2, 3-, 4-, 5- or 7-)benzofurylmethyl]-{(1-, 2- or 3-)piperadiny]-(3-, 4-, 5- or 6-)pyridyloxy group, 2-[(4-(5-chloro-2, 3-, 4-, 6- or 7-)benzo[b]thiophenylmethyl]-{(1-, 2- or 3-)piperadiny]-(3-, 4-, 5- or 6-)pyridyloxy group, 2-[(4-(6-chloro-2, 3-, 4-, 5- or 7-)benzofurylmethyl]-{(1-, 2- or 3-)piperadiny]-(3-, 4-, 5- or 6-)pyridyloxy group, 2-[(4-(5-trifluoromethoxy-2, 3-, 4-, 6- or 7-)benzofurylmethyl]-{(1-, 2- or 3-)piperadiny]-(3-, 4-, 5- or 6-)pyridyloxy group, 2-[(4-(3-(4-trifluoromethylenphenyl)-2-propenyl]-{(1-, 2- or 3-)piperadiny]pyridyloxy group, 2-[(4-(3-(3,4-dichlorophenyl)-2-propenyl]-{(1-, 2- or 3-)piperadiny]pyridyloxy group, 2-[(4-(3-(4-chlorophenyl)-2-propenyl]-{(1-, 2- or 3-)piperadiny]pyridyloxy group, 2-[(4-(3-(6-trifluoromethyl-2, 3-, 4-, 5- or 7-)benzofuryl]-2-propenyl]-{(1-, 2- or 3-)piperadiny]pyridyloxy group, 2-[(4-(3-(5-chloro-2, 3-, 4-, 5- or 7-)benzofuryl]-2-propenyl]-{(1-, 2- or 3-)piperadiny]pyridyloxy group, 2-[(4-(5-chloro-2, 3-, 4-, 6- or 7-)benzofurylmethyl]-{(1-, 2- or 3-)piperadiny]-(3-, 4-, 5- or 6-)pyridyloxy group, 2-[(4-(2-(4-trifluoromethylenphenyl)-4-propenyl]-{(4- or 5-)
thiazolylmethyl]-(1-, 2- or 3-)piperadiny1)pyridylxoxy group, 2-(4-(2-(4-trifluoromethoxyphenoxy)ethyl)-]--(1-, 2- or 3-)piperadiny1)pyridylxoxy group, 2-(4-(3-(4-trifluoromethoxyphenyl)-2-propenyl)-(1-, 2- or 3-)piperadiny1)pyridylxoxy group, 2-(4-(5-trifluoromethoxy-(1-, 2-, 3-, 4-, 6- or 7-)indolylmethyl)-(1-, 2- or 3-)piperadiny1)pyridylxoxy group, 2-(4-(4-chlorophenoxymethyl)-(1-, 2- or 3-)piperidiny1)-(1-, 2- or 3-)pyridylxoxy group, 2-(4-(2-(4-chlorophenyl)-(3-, 4- or 5-)furylmethyl)-(1-, 2- or 3-)piperadiny1)pyridylxoxy group, 2-(4-(2-(2-chloro-5-trifluoromethylphenyl)-(3-, 4- or 5-)furylmethyl)-(1-, 2- or 3-)piperadiny1)pyridylxoxy group or the like.

A 1,2,3,4-tetrahydroquinolinyloxy group (wherein, on the 1,2,3,4-tetrahydroquinoline ring, at least one selected from the group consisting of an oxo group, a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) and a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted) includes a 1,2,3,4-tetrahydroquinolinyloxy group (wherein, on the 1,2,3,4-
tetrahydroquinoline ring, 1 to 3 substituents selected from the group consisting of an oxo group, a phenyl group as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) and a phenyl Cl-C6 alkyl group as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), for example, a 1,2,3,4-tetrahydro-(1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-)quinolylolxy group, 1-(4-trifluoromethylbenzyl)-2-oxo-1,2,3,4-tetrahydro-6-quinolylolxy group, 1-(4-trifluoromethoxybenzyl)-2-oxo-1,2,3,4-tetrahydro-6-quinolylolxy group, 1-(4-chlorobenzyl)-2-oxo-1,2,3,4-
tetrahydro-6-quinolylolxy group, 1-(4-
trifluoromethylbenzyl)-1,2,3,4-tetrahydro-6-quinolylolxy group, 1-(4-trifluoromethoxybenzyl)-1,2,3,4-tetrahydro-
6-quinolylolxy group, 1-(4-chlorobenzyl)-1,2,3,4-
tetrahydro-6-quinolylolxy group, 1-(4-chlorophenyl)-
1,2,3,4-tetrahydro-6-quinolylolxy group, 1-(4-
trifluoromethoxyphenyl)-1,2,3,4-tetrahydro-6-
quinolylolxy group, 1-(4-trifluoromethylphenyl)-1,2,3,4-
tetrahydro-6-quinolylolxy group, 1-(3,4-dichlorobenzyl)
1,2,3,4-tetrahydro-6-quinolyloxy group, 1-(3,4-
5 trifluoromethoxyphenyl)-1,2,3,4-tetrahydro-5-
quinolyloxy group, 1-(4-trifluoromethylphenyl)-1,2,3,4-
tetrahydro-5-quinolyloxy group, 1-(4-chorobenzyl)-
1,2,3,4-tetrahydro-5-quinolyloxy group, 1-(4-
5 trifluoromethoxybenzyl)-1,2,3,4-tetrahydro-5-
quinolyloxy group, 1-(4-trifluoromethylbenzyl)-1,2,3,4-
tetrahydro-5-quinolyloxy group, 1-13,4,5-
tri(trifluoromethyl)benzyl)-1,2,3,4-tetrahydro-6-
quinolyloxy group, 1-benzyl-4-phenyl-1,2,3,4-
tetrahydro-5-quinolyloxy group, 1-phenyl-4,6-dibenzyl-
1,2,3,4-tetrahydro-5-quinolyloxy group, 4-phenyl-2-oxo-
1,2,3,4-tetrahydro-1-quinolyloxy group or the like.

A 1,2,3,4-tetrahydronaphthyloxy group

(wherein, on the 1,2,3,4-tetrahydronaphthalene ring, at
least one oxo group may be substituted) includes a

1,2,3,4-tetrahydronaphthyloxy group (wherein, on the
1,2,3,4-tetrahydronaphthalene ring, 1 to 3 oxo groups
may be substituted)., for example, a (1-, 2-, 5- or
6-)1,2,3,4-tetrahydronaphthyloxy group, 4-oxo-7-
1,2,3,4-tetrahydronaphthyloxy group, 1,4-dioxo-6-
1,2,3,4-tetrahydronaphthyloxy group, 1,2,4-trioxo-5-
1,2,3,4-tetrahydronaphthyloxy group or the like.

A 2H-chromenioxyl group (wherein, on the 2H-
chromene ring, at least one oxo group may be
substituted) includes a 2H-chromenioxyl group (wherein, on the 2H-chromene ring, at least one oxo group may be substituted), for example, a 2H-chromenioxyl group, 2-oxo-2H-chromenioxyl group or the like.

A naphthyloxy group (wherein, on the naphthalene ring, at least one piperidyl group [wherein, on the piperidyl ring, at least one phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted] may be substituted) includes a naphthyloxy group (wherein, on the naphthalene ring, 1 to 3 piperidyl groups as described above [wherein, on the piperidine ring, 1 to 3 phenoxy groups (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted], for example, a (1- or 2-)naphthyloxy group, 6-(4-(4-trifluoromethoxyphenoxy)-1-piperidyl)-2-naphthyloxy group, 5-(1-piperidyl)-2-naphthyloxy group, 2-(4-piperidyl)-3-naphthyloxy group, 4-(2-piperidyl)-1-naphthyloxy group, 5-(3-piperidyl)-2-naphthyloxy group, 5,6-di(1-piperidyl)-1-naphthyloxy group, 7-(1-piperidyl)-6-(2-[2-fluorophenoxy]-1-piperidyl]-1-
naphthyloxy group, 5,6,7-tri(1-piperidyl)-2-naphthyloxy group, 6-(4-phenoxy-1-piperidyl)-3-naphthyloxy group, 2-(2,4-diphenoxy-1-piperidyl)-4-naphthyloxy group, 3-(2,4,6-triphenoxy-1-piperidyl)-5-naphthyloxy group, 4-(2-(2-fluorophenoxy)-1-piperidyl)-6-naphthyloxy group, 4-(3-(3-fluorophenoxy)-2-piperidyl)-2-naphthyloxy group, 3-(4-(4-fluorophenoxy)-3-piperidyl)-1-naphthyloxy group, 5-(2-(2-chlorophenoxy)-4-piperidyl)-2-naphthyloxy group, 6-(5-(3-chlorophenoxy)-5-piperidyl)-1-naphthyloxy group, 4-(4-(4-chlorophenoxy)-2-piperidyl)-2-naphthyloxy group, 5-(5-(2-bromophenoxy)-2-piperidyl)-3-naphthyloxy group, 6-(6-(3-bromophenoxy)-3-piperidyl)-4-naphthyloxy group, 6-(4-(4-bromophenoxy)-1-piperidyl)-2-naphthyloxy group, 3-(3-(2,3-dichlorophenoxy)-2-piperidyl)-4-naphthyloxy group, 6-(4-(3,4-dichlorophenoxy)-3-piperidyl)-1-naphthyloxy group, 4-(3-(2,4-dichlorophenoxy)-4-piperidyl)-2-naphthyloxy group, 5-(2-(3,4,5-trichlorophenoxy)-3-piperidyl)-2-naphthyloxy group, 6-(6-(2,4,6-trichlorophenoxy)-2-piperidyl)-3-naphthyloxy group, 2-(3-(2,3,4,5,6-pentafluorophenoxy)-1-piperidyl)-3-naphthyloxy group, 4-(4-(2-methylphenoxy)-1-piperidyl)-2-naphthyloxy group, 3-(5-(3-methylphenoxy)-2-piperidyl)-2-naphthyloxy group, 5-(6-(4-methylphenoxy)-3-piperidyl)-3-naphthyloxy group, 6-(1-(2-ethylphenoxy)-4-piperidyl)-4-naphthyloxy group, 2-(2-(3-ethylphenoxy)-1-piperidyl)-3-naphthyloxy group, 3-(3-(4-ethylphenoxy)-2-piperidyl)-4-naphthyloxy group,
4-(4-(4-n-propylphenoxy)-3-piperidyl)-2-naphthyloxy group, 5-(5-(4-text-butylphenoxy)-4-piperidyl)-1-naphthyloxy group, 6-(2-(4-n-butylphenoxy)-3-piperidyl)-2-naphthyloxy group, 2-(1-(2-trifluoromethylphenoxy)-2-piperidyl]-4-naphthyloxy group, 3-(2-(3-trifluoromethylphenoxy)-1-piperidyl]-4-naphthyloxy group, 4-(3-(4-trifluoromethylphenoxy)-1-piperidyl]-2-naphthyloxy group, 5-(1-(2-pentafluoromethylphenoxy)-4-piperidyl]-3-naphthyloxy group, 6-(1-(3-pentafluoromethylphenoxy)-4-piperidyl]-2-naphthyloxy group, 2-(4-(2,3-dimethylphenoxy)-1-piperidyl]-1-naphthyloxy group, 3-((1,3,4,5-trimethylphenoxy)-4-piperidyl]-2-naphthyloxy group, 4-(1-(4-n-pentylphenoxy)-4-piperidyl]-1-naphthyloxy group, 5-(4-(4-n-hexylphenoxy)-1-piperidyl]-2-naphthyloxy group, 6-(4-(2-methoxyphenoxy)-1-piperidyl]-2-naphthyloxy group, 2-(1-(3-methoxyphenoxy)-4-piperidyl]-4-naphthyloxy group, 3-(1-(4-methoxyphenoxy)-6-piperidyl]-2-naphthyloxy group, 4-(2-(2-ethoxyphenoxy)-3-piperidyl]-2-naphthyloxy group, 5-(3-(3-ethoxyphenoxy)-4-piperidyl]-1-naphthyloxy group, 6-(4-(4-ethoxyphenoxy)-5-piperidyl]-4-naphthyloxy group, 2-(3-(4-n-propoxyphenoxy)-2-piperidyl]-4-naphthyloxy group, 3-(2-(4-text-butoxyphenoxy)-1-piperidyl]-4-naphthyloxy group, 4-(1-(4-n-butoxyphenoxy)-2-piperidyl]-2-naphthyloxy group, 5-(2-(2-trifluoromethoxyphenoxy)-3-piperidyl]-2-naphthyloxy group, 6-(3-(3-trifluoromethoxyphenoxy)-4-
piperidyl]-2-naphthoxy group, 6-{4-(4-
trifluoromethoxyphenoxy)-3-piperidyl]-2-naphthoxy
group, 2-{3-(2-pentafluoroethoxyphenoxy)-2-piperidyl]-
3-naphthoxy group, 3-{4-(4-pentafluoroethoxyphenoxy)-
1-piperidyl]-2-naphthoxy group, 4-{1-(2,3-
dimethoxyphenoxy)-4-piperidyl]-2-naphthoxy group, 5-
(4-(3,4,5-trimethoxyphenoxy)-1-piperidyl]-1-naphthoxy
group, 6-{4-(4-n-pentoxyphenoxy)-1-piperidyl]-3-
naphthoxy group, 5-{4-(4-n-hexyloxyphenoxy)-1-
piperidyl]-1-naphthoxy group or the like.

A 1,2,3,4-tetrahydroisoquinolyl group
(wherein, on the 1,2,3,4-tetrahydroisoquinoline ring,
at least one selected from the group consisting of a
Cl-C6 alkoxy carbonyl group, a phenyl Cl-C6 alkyl group
[wherein, on the phenyl ring, at least one selected
from the group consisting of a halogen atom, a halogen
substituted or unsubstituted Cl-C6 alkyl group and a
halogen substituted or unsubstituted Cl-C6 alkoxy group
may be substituted] and a phenyl group [wherein, on the
phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted Cl-C6 alkyl group and a halogen
substituted or unsubstituted Cl-C6 alkoxy group may be
substituted] may be substituted includes a 1,2,3,4-
tetrahydroisoquinolyl group (wherein, on the
1,2,3,4-tetrahydroisoquinoline ring, 1 to 3
substituents selected from the group consisting of a
Cl-C6 alkoxy carbonyl group, a phenyl Cl-C6 alkyl group
(wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) and a phenyl group as described above [wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted], for example, a 1,2,3,4-tetrahydroisoquinolyl (1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-)quinolyloxy group, 2-tert-butoxycarbonyl-1,2,3,4-tetrahydro-6-isoquinolyloxy group, 2-[(4-chlorobenzyl)-1,2,3,4-tetrahydro-6-isoquinolyloxy group, 2-[(4-trifluoromethoxybenzyl]-1,2,3,4-tetrahydro-6-isoquinolyloxy group, 2-[(4-trifluoromethylbenzyl)-1,2,3,4-tetrahydro-6-isoquinolyloxy group, 2-ethoxycarbonyl-4-benzyl-1,2,3,4-tetrahydro-7-isoquinolyloxy group, 1,4,6-tribenzyl-1,2,3,4-tetrahydro-8-isoquinolyloxy group, 1-(3,4-di(trifluoromethoxy)benzyl)-1,2,3,4-tetrahydro-6-isoquinolyloxy group, 1-(3,4,5-tri(trifluoromethyl)benzyl]-1,2,3,4-tetrahydro-6-isoquinolyloxy group, 2-[(4-trifluoromethoxyphenyl)-1-, 3-, 4-, 5-, 6-, 7- or 8-)isoquinolyloxy group or the like.

A phenyl group [wherein, on the phenyl ring,
at least one piperidyl group (wherein, on the piperidine ring, at least one phenoxy group (wherein, on the phenyl group, at least one selected from the group consisting of a halogen atom, a halogen 5 substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted) is substituted] includes, a phenyl group [wherein, on the phenyl ring, 1 to 3 piperidyl groups as described above (wherein, on the piperidine ring, 1 to 3 phenoxy groups (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted)] may be substituted), for example, a 4-(1-piperidyl)phenyl group, 3-(2-piperidyl)phenyl group, 4-(4-(4-trifluoromethoxyphenoxy)-1-piperidyl)phenyl group, 4-(4-(4-trifluoromethylphenoxy)-1-piperidyl)phenyl group, 20 4-(4-(4-chlorophenoxy)-1-piperidyl)phenyl group, 4-(4-(3,4-di(trifluoromethoxy)phenoxy-1-piperidyl))phenyl group, 4-(4-(3,4,5-tri(trifluoromethyl)phenoxy-1-piperidyl))phenyl group, 4-(4-(2,4-dichlorophenoxy)-1-piperidyl)phenyl group, 4-(4-(2,4,6-trifluorophenoxy)-1-piperidyl)phenyl group, 2-(2,4,5-triphenox1-piperidyl)phenyl group, 3-(1,2-diphenoxy-4-piperidyl)phenyl group, 2,4-di(4-piperidyl)phenyl group, 2,4,6-tri(3-piperidyl)phenyl group or the like.
A phenyl C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of at least one piperidyl group (wherein, on the piperidine ring, a phenoxy group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] is substituted) and a group-NR²R³ (R²⁴ represents a halogen atom or C1-C6 alkyl group. R²⁵ represents a phenyl C2-C6 alkenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted]) are substituted] includes a phenyl C1-C6 alkyl group as described above [wherein, on the phenyl ring, 1 to 3 substituents selected from the group consisting of 1 to 3 piperidyl groups as described above (wherein, on the piperidine ring, 1 to 3 phenoxy groups [wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] are substituted) and a group-NR²R³ (R²⁴ represents a halogen atom or C1-C6 alkyl group. R²⁵ represents a phenyl C2-C6 alkenyl group as described.
later (a group composed of 1 or 2 phenyl groups unsubstituted or substituted by 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkoxy group) are substituted and an alkenyl group containing 2 to 6 carbon atoms and having 1 to 3 double bonds.), for example, a 4-((1-piperidyl)benzyl group, 2,4-di((4-piperidyl)benzyl group, 2,4,6-tri((2-piperidyl)benzyl group, 4-(4-(4-trifluoromethoxyphenoxy)-1-piperidyl)benzyl group, 4-(N-methyl-N-(4-trifluoromethoxycinnamyl)amino)benzyl group, 4-(N-(4-trifluoromethoxycinnamyl)amino)benzyl group, 4-(4-(4-trifluoromethylphenoxy)-1-piperidyl)benzyl group, 4-(4-(4-chlorophenoxy)-1-piperidyl)benzyl group, 4-(4-(3,4-di(trifluoromethoxy)phenoxy)-1-piperidyl)benzyl group, 4-(4-(2,4,6-tri(trifluoromethyl)phenoxy)-1-piperidyl)benzyl group, 4-(4-(2,4-dichlorophenoxy)-1-piperidyl)benzyl group, 4-(4-(2,4,6-trifluorophenoxy)-1-piperidyl)benzyl group, 3-(2,4-diphenoxy-3-piperidyl)benzyl group, 2-(1,2,3-triphenoxy-4-piperidyl)benzyl group, 4-(N-methyl-N-(4-trifluoromethoxycinnamyl)amino)-3-(4-(4-trifluoromethoxyphenoxy)-1-piperidyl)benzyl group or the like.

A piperidyl C1-C6 alkyl group (wherein, on the piperidine ring, at least one phenyl group
(wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C₆ alkyl group and a halogen substituted or unsubstituted Cl-C₆ alkoxy group may be substituted) is substituted) includes a piperidyl Cl-C₆ alkyl group (wherein, on the piperidine ring, 1 to 3 phenyl groups as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C₆ alkyl group and a halogen substituted or unsubstituted Cl-C₆ alkoxy group may be substituted) are substituted), for example, a (4-phenyl-1-piperidyl)methyl group, 2-(3-phenyl-2-piperidyl)ethyl group, 3-(2-phenyl-3-piperidyl)propyl group, 4-(1-phenyl-4-piperidyl)butyl group, 5-(4-phenyl-1-piperidyl)pentyl group, 6-(1-phenyl-2-piperidyl)hexyl group, 1-(4-trifluoromethoxyphenyl)-4-piperidylmethyl group, 1-(4-trifluoromethylphenyl)-4-piperidylmethyl group, 1-(3-methoxyphenyl)-4-piperidylmethyl group, 1-(2-methylphenyl)-4-piperidylmethyl group, 1-(4-chlorophenyl)-4-piperidylmethyl group, 1-(3,4-di(trifluoromethoxy)phenyl)-4-piperidylmethyl group, 1-(2,4,6-tri(trifluoromethyl)phenyl)-4-piperidylmethyl group, 1-(3,4-dimethylphenyl)-4-piperidylmethyl group, 1-(2,4,6-trimethoxyphenyl)-4-piperidylmethyl group, 1-(3,4-dichlorophenyl)-4-piperidylmethyl group, 1-(2,4,6-tribromophenyl)-4-piperidylmethyl group, (1,2,6-
triphenyl-4-piperidyl)methyl group, (2,4-diphenyl-1-piperidyl)methyl group or the like.

A piperadinylic C1-C6 alkyl group (wherein, on the piperadine ring, at least one phenyl group
5 [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] may be substituted) includes a
10 piperadinylic C1-C6 alkyl group (wherein, on the piperadine ring, 1 to 3 phenyl groups as described above [wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], for example, a 1-
piperadinylmethyl group, 1-(2-piperadiny1)ethyl group,
20 2-(1-piperadiny1)ethyl group, 3-(1-piperadiny1)propyl group, 2-(1-piperadiny1)propyl group, 4-(2-
piperadiny1)butyl group, 5-(2-piperadiny1)pentyl group,
4-(1-piperadiny1)pentyl group, 6-(1-piperadiny1)hexyl group, 2-methyl-3-(1-piperadiny1)propyl group, 1,1-
dimethyl-2-(1-piperadiny1)ethyl group, (4-phenyl-1-piperadiny1)methyl group, (2,4-diphenyl-1-
piperadiny1)methyl group, (2,4,5-triphenyl-1-piperadiny1)methyl group, (4-(4-
trifluoromethoxyphenyl)-1-piperadiny1)methyl group, (4-
(4-trifluoromethylphenyl)-1-piperadiny1)methyl group,
(4-(4-chlorophenyl)-1-piperadiny1)methyl group, (4-
(2,4-dichlorophenyl)-1-piperadiny1)methyl group, (4-
(2,4,6-trifluorophenyl)-1-piperadiny1)methyl group,
5 (2,4-di(trifluoromethyl)phenyl-1-piperadiny1)methyl
group, (2,4,6-tri(trifluoromethoxy)phenyl-1-
piperadiny1)methyl group or the like.

A piperidyl Cl-C6 alkyl group (wherein, on
the piperidine ring, at least one phenoxy group
10 [wherein, on the phenyl ring, at least one selected
from the group consisting of a halogen atom, a halogen
substituted or unsubstituted Cl-C6 alkyl group and a
halogen substituted or unsubstituted Cl-C6 alkoxy group
may be substituted] may be substituted) includes a
piperidyl Cl-C6 alkyl group (wherein, on the piperidine
ring, 1 to 3 phenoxy groups as described above
[wherein, on the phenyl ring, 1 to 5, preferably 1 to 3
substituents selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted
Cl-C6 alkyl group and a halogen substituted or unsubstituted
20 Cl-C6 alkoxy group and a halogen substituted or
unsubstituted Cl-C6 alkoxy group may be substituted; may be substituted), for example, a 1-piperidylmethyl
group, 2-(2-piperidyl)ethyl group, 3-(3-
piperidyl)propyl group, 4-(4-piperidyl)butyl group, 5-
25 (1-piperidyl)pentyl group, 6-(2-piperidyl)hexyl group,
1-(4-trifluoromethoxyphenoxy)-4-piperidylmethyl group,
1-(4-trifluoromethylphenoxy)-4-piperidylmethyl group,
2-methyl-3-(piperidine-1-yl)propyl group, 1,1-dimethyl-
2-(piperidine-1-yl)ethyl group, 1-(4-chlorophenoxy)-4-piperidylmethy group, 1-(3,4-di(trifluoromethoxy)phenoxy)-4-piperidylmethy group, 1-(2,4,6-tri(trifluoromethoxy)phenoxy)-4-piperidylmethy group, 1-(3,4-dichlorophenoxy)-4-piperidylmethy group, 1-(2,4,6-tribromophenoxy)-4-piperidylmethy group, (1,2,6-triphenoxy-4-piperidyl)methyl group, (2,4-diphenoxy-1-piperidyl)methyl group or the like.

A thiazolyl group [wherein, on the thiazole ring, at least one selected from the group consisting of a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), a piperadiny1 Cl-C6 alkyl group (wherein, on the piperidine ring, at least one phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted; may be substituted) and a piperidyl Cl-C6 alkyl group (wherein, on the piperidine ring, at least one phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or
unsubstituted Cl-C6 alkoxy group may be substituted] may be substituted] includes a thiazolyl group [wherein, on the thiazole ring, 1 or 2 substituents selected from the group consisting of a phenyl group as described above [wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted], a piperadiny1 Cl-C6 alkyl group as described above [wherein, on the piperidine ring, 1 to 3 phenyl groups [wherein, on the phenyl group, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted] may be substituted] and a piperidinyl Cl-C6 alkyl group as described above [wherein, on the piperidine ring, 1 to 3 phenoxo groups [wherein, on the phenyl group, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted] may be substituted], for example, a (2-, 4- or 5-)thiazolyl group, 2-([4-trifluoromethoxyphenyl]-5-thiazolyl group, 2-([4-(4-trifluoromethoxyphenyl)-1-piperadiny1]methyl-5-thiazolyl group, 2-([4-(4-trifluoromethoxyphenoxy]-1-
piperidyl)methyl-5-thiazolyl group, 2-(2,4-
di(trifluoromethoxy)phenyl)-5-thiazolyl group, 2-(4-
(2,4-di(trifluoromethoxy)phenyl)-1-piperadiny1)methyl-
5-thiazolyl group, 2-(4-(2,4-
di(trifluoromethoxy)phenoxy)-1-piperadiny1)methyl-5-
thiazolyl group, 2-(4-(4-
(4-trifluoromethylphenyl)-1-piperidinyl)methyl-5-thiazolyl group, 2-(4-(4-
trifluoromethylphenyl)-1-piperidinyl)methyl-5-thiazolyl
group, 2-(2,4,6-
tri(trifluoromethyl)phenyl)-5-thiazolyl group, 2-(4-
(2,4,6-
tri(trifluoromethyl)phenyl)-1-piperadiny1)methyl-5-
thiazolyl group, 2-(2-
(2,4,6-
tri(trifluoromethyl)phenoxy)-1-piperidinyl)methyl-5-
thiazolyl group, 2-(4-
(2,4,6-
tri(trifluoromethyl)phenoxy)-1-piperidinyl)methyl-5-
thiazolyl group, 2-(4-
(2,4,6-
dichlorophenyl)-5-thiazolyl group, 2-(4-
(2,4-dichlorophenyl)-1-piperadiny1)methyl-5-thiazolyl
group, 2-(2-
(2,4-dichlorophenyl)-1-piperadiny1)methyl-5-thiazolyl
group, 2-(4-
(2,4-dichlorophenox)-1-piperidinyl)methyl-5-thiazolyl
group, 2-(2,4,6-
trifluorophenyl)-5-thiazolyl group, 2-(4-
(2,4,6-
trifluorophenyl)-1-piperadiny1)methyl-5-thiazolyl
group, 2-(4-
(2,4,6-trifluorophenoxy)-1-
piperidinyl)methyl-5-thiazolyl group, 2-(2,4-diphenox-
piperidyl)methyl-5-thiazolyl group, 5-(2,4,5-
tri phenoxy-1-piperidyl)methyl-2-thiazolyl group, 5-
(2,4-diphenyl-1-piperadiny l)methyl-2-thiazolyl group,
2-(2,4,5-triphenyl-1-piperadiny l)methyl-4-thiazolyl
5 group, 4-(1-piperidyl)-2-{1-piperadiny l}-5-thiazolyl
group or the like.

A benzooxazolyloxy group (wherein, on the
benzooxazole ring, at least one selected from the group
consisting of a piperezaryl group (wherein, on the
piperadine ring, 1 to 3 groups selected from the group
consisting of a phenyl C1-C6 alkyl group (wherein, on the
phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted) and a phenyl C2-C6 alkenyl group having a
straight or branched alkenyl group containing 2 to 6
carbon atoms on the alkenyl part and having 1 to 3
double bonds and including both trans and cis forms as
described later (wherein, on the phenyl ring, 1 to 5,
preferably 1 to 3 substituents selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted) may be substituted!, a piperidyl group
(wherein, on the piperidine ring, 1 to 3 substituents
selected from the group consisting of a phenyl C1-C6
alkyl group as described above (wherein, on the phenyl
ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted] and an amino group [wherein, on the amino group, 1 or 2 substituents selected from the group consisting of a Cl-C6 alkyl group as described above and a phenyl group as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted] may be substituted) and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) includes a benzooxazolylalcohol group (wherein, on the benzooxazole ring, 1 to 3 substituents selected from the group consisting of a piperadiny1 group as described above [wherein, on the piperadine ring, at least one selected from the group consisting of a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or
unsubstituted C1-C6 alkoxy group may be substituted) and a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted], a piperidyl group (wherein, on the piperidine ring, at least one selected from the group consisting of a phenyl C1-C6 alkyl group wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] and an amino group [wherein, on the amino group, at least one selected from the group consisting of a C1-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted] and a phenyl group as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], for example, a 2-(4-{4-
trifluoromethoxybenzyl]-1-piperadiny1]-6-
benzooxazolyloxy group, 2-phenyl-5-benzooxazolyloxy
group, 2-(4-chlorophenyl)-5-benzooxazolyloxy group, 2-
(4-(4-trifluoromethylbenzyl]-1-piperadiny1]-6-
benzooxazolyloxy group, 2-(4-(4-chlorobenzyl]-1-
piperadiny1]-6-benzooxazolyloxy group, 2-(4-(2,4,6-
tri(trifluoromethoxy)benzyl]-1-piperadiny1]-6-
benzooxazolyloxy group, 2-{4-(2,4-
di(trifluoromethyl)benzyl]-1-piperadiny1]-6-
benzooxazolyloxy group, 2-{4-(2,4-dichlorobenzyl]-1-
piperadiny1]-6-benzooxazolyloxy group, 2-{4-(2,4,6-
trifluorobenzyl]-1-piperadiny1]-6-benzooxazolyloxy
group, 2-(4-benzyl-1-piperadiny1]-4-benzooxazolyloxy
group, 2-{4-(2,4-dibenzyl-1-piperadiny1]-7-
benzooxazolyloxy group, 2-{2,4,6-tribenzyl-1-
piperadiny1]-6-benzooxazolyloxy group, 2-(4-
trifluoromethoxyphenyl]-5-benzooxazolyloxy group, 2-{4-
trifluoromethylphenyl]-5-benzooxazolyloxy group, 2-
(2,4-dibromophenyl]-5-benzooxazolyloxy group, 2-{2,4,6-
trichlorophenyl]-5-benzooxazolyloxy group, 2-{2,4,6-
tri(trifluoromethoxy)phenyl]-5-benzooxazolyloxy group,
2-{2,4-di(trifluoromethyl)phenyl]-5-benzooxazolyloxy
group, 4-phenyl-5-(1-pipersdinyl]-2-benzooxazolyloxy
group, 2,4,5-triphenyl-7-benzooxazolyloxy group, 2-{4-
(4-trifluoromethoxybenzyl]-1-, 2- or 3-)piperidiny1]-2-
4-, 5-, 6- or 7-)benzooxazolyloxy group, 2-{4-(3-(4-
trifluoromethylphenyl]-2-propenyl]-1-, 2- or
3-)piperadiny1]-2-, 4-, 5-, 6- or 7-)benzooxazolyloxy
group, 4-(N-methyl-N-(4-chlorophenyl)amino)-(1-, 2- or 3-)piperidyl)-(2-, 4-, 5-, 6- or 7-)benzo oxazolyl oxy group or the like.

A benzoimidazolyl oxy group (wherein, on the benzoimiazole ring, at least one selected from the group consisting of a C1-C6 alkyl group, a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a piperidyl group (wherein, on the piperidine ring, at least one phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a piperadiny1 group (wherein, on the piperidine ring, at least one phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) and a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) and a phenyl C1-C6 alkyl group
may be substituted] may be substituted) includes a benzoimidazolyloxy group (wherein, on the benzoimidazole ring, 1 to 3 substituents selected from the group consisting of a C1-C6 alkyl group, a phenyl group [wherein, on the phenyl ring, 1 to 3, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], a piperidyl group as described above [wherein, on the piperidine ring, 1 to 3 phenoxy groups (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], a piperadinylox group as described above [wherein, on the piperadine ring, 1 to 3 phenyl C1-C6 alkyl groups (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] may be substituted] and a phenyl C1-C6 alkyl group as described above [wherein, on the phenyl ring, 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be substituted), for example, a (1-, 2-, 4-, 5-, 6- or 7-) benzoimidazolylloxy group, 2-phenyl-5-benzoimidazolylloxy group, 1-methyl-5-
benzoimidazolylloxy group, 1-methyl-2-phenyl-5-
benzoimidazolylloxy group, 2-(4-chlorophenyl)-5-
benzoimidazolylloxy group, 1-methyl-2-(4-chlorophenyl)-
5-benzoimidazolylloxy group, 1,2-diphenyl-5-
benzoimidazolylloxy group, 1,4-dimethyl-5-
benzoimidazolylloxy group, 1-methyl-2,6-diphenyl-5-
benzoimidazolylloxy group, 2-(4-trifluoromethylphenyl)-
5-benzoimidazolylloxy group, 1-methyl-2-(4-
trifluoromethoxyphenyl)-5-benzoimidazolylloxy group,
1,2,7-triphenyl-5-benzoimidazolylloxy group, 1,2,4-
trimethyl-5-benzoimidazolylloxy group, 1-ethyl-2,5-
diphenyl-5-benzoimidazolylloxy group, 2-(2,4-
di(trifluoromethyl)phenyl)-5-benzoimidazolylloxy group,
1-methyl-2-(2,4,6-tri(trifluoromethoxy)phenyl)-5-
benzoimidazolylloxy group, 2-(2,4-dichlorophenyl)-5-
benzoimidazolylloxy group, 2-(2,4,6-trifluorophenyl)-5-
benzoimidazolylloxy group, 2-(3-bromophenyl)-5-
benzoimidazolylloxy group, 2-(2-iodophenyl)-5-
benzoimidazolylloxy group, 2-(4-trifluoromethoxyphenoxy-
(1-, 2- or 3-)piperidyl-(1-, 4-, 5-, 6- or
7-)imidazolylloxy group, 1-benzyl-2-(4-
trifluoromethoxybenzyl-(1-, 2- or 3-)piperadiny1)-
(4-, 5-, 6- or -7)imidazolylloxy group, 1-(4-
trifluoromethoxybenzyl)-(2-, 4-, 5-, 6- or
7-)imidazolylloxy group or the like.

A 1,2,3,4-tetrahydroisoquinolyl group
(wherein, on the 1,2,3,4-tetrahydroisoquinoline ring, at least one selected from the group consisting of a

5 (m-1) amino group (wherein, on the amino group, at least one selected from the group consisting of a C1-C6 alkyl group, a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or

10 unsubstituted C1-C6 alkyl group and a halogen

substituted or unsubstituted C1-C6 alkoxy group may be substituted) and a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen

15 substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be selected] and a (m-2) phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen

20 atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted; includes a 1,2,3,4-tetrahydroisoquinolyl group (wherein, on the 1,2,3,4-tetrahydroisoquinoline ring, 1 to 3 substituents selected from the group consisting of an amino group as described later
(wherein, on the amino group, 1 or 2 substituents selected from the group consisting of a C1-C6 alkyl
group, a phenyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) and a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) and a phenoxy group as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), for example, a (1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-)1,2,3,4-tetrahydroisoquinolyl group, 7-(N-methyl-N-(4-trifluoromethoxyphenyl)amino)-1,2,3,4-tetrahydro-2-tetrahydroisoquinolyl group, 7-(N-methyl-N-(4-trifluoromethoxybenzyl)amino)-1,2,3,4-tetrahydro-2-tetrahydroisoquinolyl group, 6-(4-trifluoromethoxyphenoxy)-1,2,3,4-tetrahydro-2-tetrahydroisoquinolyl group, 7-(N-methyl-N-(4-trifluoromethylphenyl)amino)-1,2,3,4-tetrahydro-2-tetrahydroisoquinolyl group, 7-(N-methyl-N-(4-trifluoromethylbenzyl)amino)-1,2,3,4-tetrahydro-2-tetrahydroisoquinolyl group, 7-(N-methyl-N-(4-trifluoromethylbenzyl)amino)-1,2,3,4-tetrahydro-2-
isoquinolyl group, 6-\{(4-trifluoromethylphenoxy)-1,2,3,4-tetrahydro-2-isoquinolyl group, 7-(N-methyl-N-(4-chlorophenyl)amino)-1,2,3,4-tetrahydro-2-isoquinolyl group, 7-(N-(4-chlorophenyl)amino)-1,2,3,4-tetrahydro-
5 2-isoquinolyl group, 7-(N-methyl-N-(4-chlorobenzyl)amino)-1,2,3,4-tetrahydro-2-isoquinolyl group, 7-(N-(4-chlorobenzyl)amino)-1,2,3,4-tetrahydro-2-isoquinolyl group, 6-(4-chlorophenoxy)-1,2,3,4-
tetrahydro-2-isoquinolyl group, 7-(N-methyl-N-(2,4-
10 di(trifluoromethoxy)phenyl)amino)-1,2,3,4-tetrahydro-2-isoquinolyl group, 7-(N-methyl-N-(2,4,6-
tri(trifluoromethoxy)benzyl)amino)-1,2,3,4-tetrahydro-
2-isoquinolyl group, 6-(2,4-
di(trifluoromethoxy)phenoxy)-1,2,3,4-tetrahydro-2-
15 isoquinolyl group, 7-(N-methyl-N-(2,4,6-
tri(trifluoromethyl)phenyl)amino)-1,2,3,4-tetrahydro-2-
isoquinolyl group, 7-(N-methyl-N-(2,4-
di(trifluoromethyl)benzyl)amino)-1,2,3,4-tetrahydro-2-
isoquinolyl group, 6-(2,4,6-tri(trifluoromethyl)-
20 phenoxy)-1,2,3,4-tetrahydro-2-isoquinolyl group, 7-(N-
methyl-N-(2,4-dibromophenyl)amino)-1,2,3,4-tetrahydro-
2-isoquinolyl group, 7-(N-methyl-N-(2,3-
diodobenzyl)amino)-1,2,3,4-tetrahydro-2-isoquinolyl-
group, 6-(2,4,6-trifluorophenoxy)-1,2,3,4-tetrahydro-2-
25 isoquinolyl group, 7-amino-6-phenoxy-1,2,3,4-
tetrahydro-2-isoquinolyl group, 4,5,6-triphenoxy-
1,2,3,4-tetrahydro-7-isoquinolyl group or the like.

A C1-C6 alkoxy group substituted by 2 phenyl
groups [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] includes a C1-C6 alkoxy group substituted by 2 phenyl groups (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), for example, a 1,1-diphenylmethoxy group, 1,2-diphenylethoxy group, 3,3-diphenylpropoxy group, 3,4-diphenylbutoxy group, 3,5-diphenylpentyl oxy group, 4,6-diphenylhexyloxy group, 1,1-di(4-trifluoromethoxyphenyl) methoxy group, 1-(2-fluorophenyl)-1-(3-fluorophenyl)methoxy group, 1-(4-fluorophenyl)-1-(2-chlorophenyl)methoxy group, 1-(3-chlorophenyl)-1-(4-chlorophenyl)methoxy group, 1-(2-bromophenyl)-1-(3-bromophenyl)methoxy group, 1-(4-bromophenyl)-2-(2-iodoanenyl)ethoxy group, 3-(3-iodophenyl)-3-(4-iodophenyl)propoxy group, 1-(2,3-difluorophenyl)-1-(3,4-difluorophenyl)methoxy group, 4-(3,5-difluorophenyl)-4-(2,4-difluorophenyl)butoxy group, 5-(2,6-difluorophenyl)-5-(2,3-dichlorophenyl)pentyloxy group, 6-(3,4-dichlorophenyl)-6-(3,5-dichlorophenyl)hexyloxy group, 1-(2,4-dichlorophenyl)-1-(2,6-dichlorophenyl)methoxy group, 1-(3,4,5-trifluorophenyl)-1-(3,4,5-trichlorophenyl)methoxy group,
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1-((2,3,4,5,6-pentafluorophenyl)-1-(2,4,6-trimethylphenyl)methoxy group, 1-(4-n-butylphenyl)-1-(2,4-dimethylphenyl)methoxy group, 1-(3,5-ditrifluoromethylphenyl)-1-(4-n-butoxyphenyl)methoxy group, 1-(2,4-dimethoxyphenyl)-1-(2,3-dimethoxyphenyl)methoxy group, 1-(2,4,6-trimethoxyphenyl)-1-(3,5-ditrifluoromethoxyphenyl)methoxy group, 1-(3-chloro-4-methoxyphenyl)1=(2-chloro-4-trifluoromethoxyphenyl)methoxy group, 1-(3-methyl-4-fluorophenyl)-1-(2-bromo-3-trifluoromethylphenyl)methoxy group, 1-(2-methylphenyl)-1-(3-methylphenyl)methoxy group, 1-(2-pentafluoroethylphenyl)-1-(3-pentafluoroethylphenyl)methoxy group, 1-(2-isopropylphenyl)-1-(2-tert-butylphenyl)methoxy group, 1-(2-sec-butylphenyl)1-(2-n-heptafluoropropylphenyl)methoxy group, 1-(4-pentylphenyl)-1-(4-hexylphenyl)methoxy group, 1-(2-methoxyphenyl)-1-(2,6-dimethoxyphenyl)methoxy group, 1-(2-pentafluoroethoxyphenyl)-1-(isopropoxyphenyl)methoxy group, 1-(2-tert-butoxyphenyl)-1-(2-sec-butoxyphenyl)methoxy group, 1-(2-n-heptafluoropropoxyphenyl)-1-(4-n-pentoxyphenyl)methoxy group, 1,1-dimethylphenyl)methoxy or the like.

A piperidyl group (wherein, on the piperidine ring, at least one selected from the group consisting of (n-1) a phenyl group (wherein, on the phenyl ring, at least one group-NR"R" (R" represents a hydrogen atom or Cl-6 alkyl group. R") represents a phenyl group
[wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], (n-2) a group-W1NR2R29 [W1 represents a C1-C6 alkylens group, R28 represents a hydrogen atom or C1-C6 alkyl group and R29 represents a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted)]}, (n-3) a C1-C6 alkoxy group substituted by 2 phenyl groups [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] and (n-4) a phenyl C1-C6 alkyl group [wherein, on the phenyl group ring, at least one phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) is substituted] may be substituted) includes a piperidyl group (wherein, on the piperidine ring, 1 to 3 substituents selected from the group consisting of (n-1) a phenyl group (wherein, on the phenyl ring, 1 to 3
groups—NRNR²⁶R²⁷ (R²⁶ represents a hydrogen atom or Cl-C₆ alkyl group. R²⁷ represents a phenyl group as described above [wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C₆ alkyl group and a halogen substituted or unsubstituted Cl-C₆ alkoxy group may be substituted]) are substituted). (n-2) a group—W₁NR²⁸R²⁹ (W₁ represents Cl-C₆ alkylene group, R²⁸ represents a hydrogen atom or a Cl-C₆ alkyl group as described above and R²⁹ represents a phenyl group as described above [wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C₆ alkyl group and a halogen substituted or unsubstituted Cl-C₆ alkoxy group may be substituted]). (n-3) a Cl-C₆ alkoxy group substituted by 2 phenyl groups as described above [wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C₆ alkyl group and a halogen substituted or unsubstituted Cl-C₆ alkoxy group may be substituted] and (n-4) a phenyl Cl-C₆ alkyl group as described later [wherein, on the phenyl group ring, 1 to 3 phenyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C₆ alkyl group and a
halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted] may be substituted), for example, a (1-, 2-, 3- or 4-)piperidyl group, 4-(N-methyl-N- (4-trifluoromethoxyphenyl)amino]phenyl-1-piperidyl group, 4-(N-(4-trifluoromethoxyphenyl)-aminomethyl]-1-piperidyl group, 4-(N-methyl-N-(4-trifluoromethoxyphenyl)aminomethyl]-1-piperidyl group, 4-(N-ethyl-N-(4-trifluoromethoxyphenyl)aminomethyl]-1-piperidyl group, 4-(1,1-di(4-trifluoromethoxyphenyl)-methoxy]-1-piperidyl group, 4-(N-methyl-N-(4-trifluoromethylphenyl)amino]phenyl-1-piperidyl group, 4-(N-(4-trifluoromethylphenyl)aminomethyl]-1-piperidyl group, 4-(N-methyl-N-(2,4-di(trifluoromethyl)phenyl)-aminomethyl]-1-piperidyl group, 4-(N-ethyl-N-(2,4,6-trifluoromethoxy)phenyl)aminomethyl]-1-piperidyl group, 4-(1,1-di(4-trifluoromethylphenyl)methoxy]-1-piperidyl group, 4-(N-methyl-N-(4-chlorophenyl)amino]-phenyl-1-piperidyl group, 4-(N-(2,4-dibromophenyl)-aminomethyl]-1-piperidyl group, 4-(N-methyl-N-(2,4,6-trifluorophenyl)aminomethyl]-1-piperidyl group, 4-(N-ethyl-N-(4-chlorophenyl)aminomethyl]-1-piperidyl group, 4-(1,1-di(4-chlorophenyl)methoxy]-1-piperidyl group, 4-(N-methyl-N-(2,4-dibromophenyl)amino]phenyl-1-piperidyl group, 4-(1,1-di(2,4-dibromophenyl)methoxy]-1-piperidyl group, 4-(N-methyl-N-(2,4,6-trifluorophenyl)-amino]phenyl-1-piperidyl group, 4-(1,1-di(2,4,6-trifluorophenyl)methoxy]-1-piperidyl group, 4-(N-methyl-N-(2,4-di(trifluoromethyl)phenyl)amino]phenyl-1-
piperidyl group, 4-{N-methyl-N-(2,4,6-tri(trifluoromethoxy)phenyl)amino)phenyl-1-piperidyl group, 4-{1-(2,4-di(trifluoromethyl)phenyl)-1-[2,4,6-tri(trifluoromethoxy)phenyl]methoxy}-1-piperidyl group, 4-{N-(4-trifluoromethoxyphenyl)aminomethyl}-3-{N-(4-trifluoromethylphenyl)aminomethyl]-1-piperidyl group, 3,4,6-tri(1,1-diphenylethoxy)-1-piperidyl group, 4-[(4-phenylbenzyl)-{1-, 2- or 3-}piperidinyl group or the like.

A C1-C6 alkyl group substituted by 2 phenyl groups [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] includes a C1-C6 alkyl group substituted by 2 phenyl groups [wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], for example, a 1,1-diphenylethyl group, 1,2-diphenylethyl group, 3,3-diphenylpropyl group, 3,4-diphenylethyl group, 3,5-diphenylpentyl group, 4,6-diphenylhexyl group, 1,1-di(4-trifluoromethoxyphenyl)methyl group, 1,2-di(4-chlorophenyl)methyl group, 1-(2-fluorophenyl)-1-(3-fluorophenyl)methyl group, 1-(4-fluorophenyl)-1-(2-chlorophenyl)methyl group, 1-(3-chlorophenyl)-1-(4-
chlorophenyl)methyl group, 1-(2-bromophenyl)-1-(3-bromophenyl)methyl group, 1-(4-bromophenyl)-2-(2-iodophenyl)ethyl group, 3-(3-iodophenyl)-3-(4-iodophenyl)propyl group, 1-(2,3-difluorophenyl)-1-(3,4-difluorophenyl)methyl group, 4-(3,5-difluorophenyl)-4-(2,4-difluorophenyl)butyl group, 5-(2,6-difluorophenyl)-5-(2,3-dichlorophenyl)pentyl group, 6-(3,4-dichlorophenyl)-6-(3,5-dichlorophenyl)hexyl group, 1-(2,4-dichlorophenyl)-1-(2,6-dichlorophenyl)methyl group, 1-(3,4,5-trifluorophenyl)-1-(3,4,5-trichlorophenyl)methyl group, 1-(2,3,4,5,6-pentafluorophenyl)-1-(2,4,6-trimethylphenyl)methyl group, 1-(4-n-butylyphenyl)-1-(2,4-dimethylphenyl)methyl group, 1-(3,5-ditrifluoromethylphenyl)-1-(4-n-butoxyphenyl)methyl group, 1-(2,4-dimethoxyphenyl)-1-(2,3-dimethoxyphenyl)methyl group, 1-(2,4,6-trimethoxyphenyl)-1-(3,5-ditrifluoromethoxyphenyl)methyl group, 1-(3-chloro-4-methoxyphenyl)-1-(2-chloro-4-trifluoromethoxyphenyl)methyl group, 1-(3-methyl-4-fluorophenyl)-1-(4-bromo-3-trifluoromethylphenyl)methyl group, 1-(2-methylphenyl)-1-(3-methylphenyl)methyl group, 1-(2-pentafluoroethylphenyl)-1-(3-pentafluoroethylphenyl)methyl group, 1-(2-isopropylphenyl)-1-(2-tert-butylyphenyl)methyl group, 1-(2-sec-butylyphenyl)-1-(2-n-heptafluoropropylphenyl)methyl group, 1-(4-n-pentlyphenyl)-1-(4-n-hexylphenyl)methyl group, 1-(2-methoxyphenyl)-1-(2,6-dimethoxyphenyl)methyl group, 1-(2-pentafluoro-
ethoxyphenyl)-1-(isopropoxyphenyl)methyl group, 1-(2-tert-butoxyphenyl)-1-(2-sec-butoxyphenyl)methyl group, 1-(2-n-heptafluoropropoxyphenyl)-1-(4-n-pentoxyp phenyl)methyl group, 1,1-di(4-n-hexyloxyp phenyl)methyl group or the like.

A phenyl C2-C6 alkenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen 10 substituted or unsubstituted C1-C6 alkoxy group may be substituted] is a group composed of 1 or 2 phenyl groups substituted by 1 to 5, preferably 1 to 3 - substituents selected from the group consisting of a halogen atom, a halogen C1-C6 alkyl and a halogen 15 substituted or unsubstituted C1-C6 alkoxy group and an alkenyl group containing 2 to 6 carbon atoms and 1 to 3 double bonds. The phenyl C2-C6 alkenyl group includes both trans and cis forms. Such a phenyl C2-C6 alkenyl group includes a 3-(2-fluorophenyl)-2-propenyl group, 3,3-di(2-fluorophenyl)-2-propenyl group, 3-(3-fluorophenyl)-2-propenyl group, 3-(4-fluorophenyl)-2-propenyl group, 3-(2,3-difluorophenyl)-2-propenyl group, 3-(2,3,4,5,6-pentafluorophenyl)-2-propenyl group, 3-(2,4-difluorophenyl)-2-propenyl group, 3-(3,4- 25 difluorophenyl)-2-propenyl group, 3-(3,5- difluorophenyl)-2-propenyl group, 3-(2-chlorophenyl)-2-propenyl group, 3-(3-chlorophenyl)-2-propenyl group, 3-(4-chlorophenyl)-2-propenyl group, 3-(2,3-
dichlorophenyl)-2-propenyl group, 3-(2,4-
dichlorophenyl)-2-propenyl group, 3-(3,4-
dichlorophenyl)-2-propenyl group, 3-(3,5-
dichlorophenyl)-2-propenyl group, 3-(2-bromophenyl)-2-
propepnyl group, 3-(3-bromophenyl)-2-propenyl group, 3-
(4-bromophenyl)-2-propenyl group, 3-(2-methylphenyl)-2-
propenyl group, 3-(3-methylphenyl)-2-propenyl group, 3-
(4-methylphenyl)-2-propenyl group, 3-(2-
trifluoromethylphenyl)-2-propenyl group, 3-(2-fluoro-4-
bromophenyl)-2-propenyl group, 3-(4-chloro-3-
fluorophenyl)-2-propenyl group, 3-(2,3,4-
trichlorophenyl)-2-propenyl group, 3-(2,4,6-
trichlorophenyl)-2-propenyl group, 3-(4-
isopropylphenyl)-2-propenyl group, 3-(4-n-butylphenyl)-
2-propenyl group, 3-(2,4-dimethylphenyl)-2-propenyl
group, 3-(2,3-dimethylphenyl)-2-propenyl group, 3-(2,6-
dimethylphenyl)-2-propenyl group, 3-(3,5-
dimethylphenyl)-2-propenyl group, 3-(2,5-
dimethylphenyl)-2-propenyl group, 3-(2,4,6-
trimethylphenyl)-2-propenyl group, 3-(3,5-
ditrifluoromethylphenyl)-2-propenyl group, 3-(4-n-
butoxyphenyl)-2-propenyl group, 3-(2,4-
dimethoxyphenyl)-2-propenyl group, 3-(2,3-
dimethoxyphenyl)-2-propenyl group, 3-(2,6-
dimethoxyphenyl)-2-propenyl group, 3-(3,5-
dimethoxyphenyl)-2-propenyl group, 3-(2,5-
dimethoxyphenyl)-2-propenyl group, 3-(3,5-
ditrifluoromethoxyphenyl)-2-propenyl group, 3-(3-
chloro-4-methoxyphenyl-2-propenyl group, 3-(2-chloro-4-
thifluoromethoxyphenyl-2-propenyl group, 3-(3-methyl-4-
fluorophenyl)-2-propenyl group, 3-(4-bromo-3-
trifluoromethylphenyl)-2-propenyl group, 3-(3-
trifluoromethylphenyl)-2-propenyl group, 3-(4-
trifluoromethylphenyl)-2-propenyl group, 3-(2-
trifluoromethoxyphenyl)-2-propenyl group, 3-(3-
trifluoromethoxyphenyl)-2-propenyl group, 3-(4-
methoxyphenyl)-2-propenyl group, 3-(3-methoxyphenyl)-2-
propenyl group, 3-(4-methoxyphenyl)-2-propenyl group,
3-(3,4-dimethoxyphenyl)-2-propenyl group, 3-(3,5-
dimethoxyphenyl)-2-propenyl group, 4-(4-chlorophenyl)-
2-butenyl group, 4-(4-chlorophenyl)-3-butenyl group, 5-
(4-chlorophenyl)-2-pentenyl group, 5-(4-chlorophenyl)-
4-pentenyl group, 5-(4-chlorophenyl)-3-pentenyl group,
6-(4-chlorophenyl)-5-hexenyl group, 6-(4-chlorophenyl)-
4-hexenyl group, 6-(4-chlorophenyl)-3-hexenyl group, 6-
(4-chlorophenyl)-3-hexenyl group or the like.

An imidazolyl group (wherein, on the
imidazole ring, at least one phenyl group (wherein, on
the phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted Cl-C6 alkyl group and a halogen
substituted or unsubstituted Cl-C6 alkoxy group may be
substituted) may be substituted) includes an imidazolyl
group (wherein, on the imidazole ring, 1 to 3 phenyl
groups (wherein, on the phenyl ring, 1 to 5, preferably
1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted), for example, a (1-, 2-, 4 or 5-1imidazolyl group, 1-phenyl-2-imidazolyl group, 2-(2-fluorophenyl)-1-imidazolyl group, 4-(3-fluorophenyl)2-imidazolyl group, 5-(4-fluorophenyl)3-imidazolyl group, 1-(2-chlorophenyl)-3-imidazolyl group, 2-(3-chlorophenyl)-5-imidazolyl group, 1-(4-chlorophenyl)2-imidazolyl group, 4-(2-bromophenyl)5-imidazolyl group, 5-(3-bromophenyl)2-imidazolyl group, 1-(4-bromophenyl)3-imidazolyl group, 2-(2-iodophenyl)-5-imidazolyl group, 4-(3-iodophenyl)5-imidazolyl group, 5-(4-iodophenyl)1-imidazolyl group, 1-(2,3-difluorophenyl)2-imidazolyl group, 1-(3,4-difluorophenyl)2-imidazolyl group, 1-(3,5-difluorophenyl)2-imidazolyl group, 1-(2,4-difluorophenyl)4-imidazolyl group, 1-(2,6-difluorophenyl)5-imidazolyl group, 1-(2,3-dichlorophenyl)2-imidazolyl group, 1-(3,4-dichlorophenyl)4-imidazolyl group, 1-(3,5-dichlorophenyl)5-imidazolyl group, 1-(2,4-dichlorophenyl)2-imidazolyl group, 1-(2,6-dichlorophenyl)4-imidazolyl group, 1-(3,4,5-trifluorophenyl)5-imidazolyl group, 1-(3,4,5-trichlorophenyl)2-imidazolyl group, 1-(2,4,6-trifluorophenyl)4-imidazolyl group, 1-(2,4,6-
trichlorophenyl)-5-imidazolyl group, 1-(2-fluro-4-bromophenyl)-2-imidazolyl group, 1-(4-chloro-3-fluorophenyl)-4-imidazolyl group, 1-(2,3,4-trichlorophenyl)-5-imidazolyl group, 1-(2,3,4,5,6-pentafluorophenyl)-2-imidazolyl group, 1-(2,4,6-trimethylphenyl)-2-imidazolyl group, 2-(4-n-butylphenyl)-4-imidazolyl group, 4-(2,4-dimethylphenyl)-1-imidazolyl group, 5-(2,3-dimethylphenyl)-2-imidazolyl group, 1-(2,6-dimethylphenyl)-4-imidazolyl group, 2-(3,5-dimethylphenyl)-5-imidazolyl group, 4-(2,5-dimethylphenyl)-1-imidazolyl group, 5-(3,5-difluorotrimethylphenyl)-2-imidazolylgroup, 1-(4-n-butoxyphenyl)-2-imidazolyl group, 1-(2,4-dimethoxyphenyl)-2-imidazolyl group, 1-(2,3-dimethoxyphenyl)-2-imidazolyl group, 1-(2,6-dimethoxyphenyl)-2-imidazolyl group, 2-(3,5-dimethoxyphenyl)-4-imidazolyl group, 4-(2,5-dimethoxyphenyl)-1-imidazolyl group, 5-(2,4,6-triethoxyphenyl)-2-imidazolyl group, 1-(3,5-dinitrifluoromethoxyphenyl)-2-imidazolyl group, 1-(3-chloro-4-methoxyphenyl)-2-imidazolyl group, 1-(2-chloro-4-trifluoromethoxyphenyl)-2-imidazolyl group, 1-(4-bromo-3-trifluoromethylphenyl)-2-imidazolyl group, 1-(2-methylphenyl)-2-imidazolyl group, 2-(3-methylphenyl)-4-imidazolyl group, 4-(4-methylphenyl)-3-imidazolyl group, 5-(2-methyl-3-chlorophenyl)-1-imidazolyl group, 1-(3-methyl-4-chlorophenyl)-2-
imidazolyl group, 2-(2-chloro-4-methylphenyl)-4-imidazolyl group, 4-(2-methyl-3-fluorophenyl)-5-imidazolyl group, 5-(2-trifluoromethylphenyl)-1-imidazolyl group, 1-(3-trifluoromethylphenyl)-2-imidazolyl group, 2-(4-trifluoromethylphenyl)-4-imidazolyl group, 4-(2-pentafluoroethylphenyl)-5-imidazolyl group, 5-(3-pentafluoroethylphenyl)-1-imidazolyl group, 1-(4-pentafluoroethylphenyl)-2-imidazolyl group, 2-(2-isopropylphenyl)-4-imidazolyl group, 4-(3-isopropylphenyl)-5-imidazolyl group, 5-(4-isopropylphenyl)-1-imidazolyl group, 1-(2-tert-butylphenyl)-2-imidazolyl group, 2-(3-tert-butylphenyl)-4-imidazolyl group, 4-(4-tert-butylphenyl)-5-imidazolyl group, 5-(2-sec-butylphenyl)-1-imidazolyl group, 1-(3-sec-butylphenyl)-2-imidazolyl group, 2-(4-sec-butylphenyl)-4-imidazolyl group, 4-(2-n-heptafluoropropylphenyl)-5-imidazolyl group, 5-(3-n-heptafluoropropylphenyl)-1-imidazolyl group, 1-(4-n-heptafluoropropylphenyl)-2-imidazolyl group, 2-(4-pentylphenyl)-4-imidazolyl group, 4-(4-hexylphenyl)-5-imidazolyl group, 1-(2-methoxyphenyl)-2-imidazolyl group, 5-(3-methoxyphenyl)-1-imidazolyl group, 1-(4-methoxyphenyl)-2-imidazolyl group, 2-(3-chloro-2-methoxyphenyl)-4-imidazolyl group, 4-(2-fluoro-3-methoxyphenyl)-5-imidazolyl group, 5-(2-fluoro-4-methoxyphenyl)-1-imidazolyl group, 1-(2,6-dimethoxyphenyl)-2-imidazolyl group, 1-(2,3,4-trifluorophenyl)-2-imidazolyl group, 1-(2-
trifluoromethoxyphenyl)-2-imidazolyl group, 2-(3-
trifluoromethoxyphenyl)-4-imidazolyl group, 1-(4-
trifluoromethoxyphenyl)-2-imidazolyl group, 1-(3-
fluoro-2-trifluoromethoxyphenyl)-2-imidazolyl group, 1-
(2-fluoro-3-trifluoromethoxyphenyl)-2-imidazolyl group,
1-(3-fluoro-4-trifluoromethoxyphenyl)-2-imidazolyl
group, 1-(3-chloro-2-trifluoromethoxyphenyl)-2-
imidazolyl group, 1-(2-chloro-3-
trifluoromethoxyphenyl)-2-imidazolyl group, 1-(3-
chloro-4-trifluoromethoxyphenyl)-2-imidazolyl group, 1-
(2-pentafluoroethoxyphenyl)-2-imidazolyl group, 1-(3-
pentafluoroethoxyphenyl)-2-imidazolyl group, 1-(4-
pentafluoroethoxyphenyl)-2-imidazolyl group, 1-(3-
chloro-2-pentafluoroethoxyphenyl)-2-imidazolyl group,
1-(2-chloro-3-pentafluoroethoxyphenyl)-2-imidazolyl
group, 1-(3-chloro-4-pentafluoroethoxyphenyl)-2-
imidazolyl group, 1-(2-isopropoxyphenyl)-2-imidazolyl
group, 1-(3-isopropoxyphenyl)-2-imidazolyl group, 1-(4-
isopropoxyphenyl)-2-imidazolyl group, 1-(2-tert-
butoxyphenyl)-2-imidazolyl group, 1-(3-tert-
butoxyphenyl)-2-imidazolyl group, 1-(4-tert-
butoxyphenyl)-2-imidazolyl group, 1-(2-sec-
butoxyphenyl)-2-imidazolyl group, 1-(3-sec-
butoxyphenyl)-2-imidazolyl group, 1-(4-sec-
butoxyphenyl)-2-imidazolyl group, 1-(2-n-
heptafluoropropoxyphenyl)-2-imidazolyl group, 1-(3-n-
heptafluoropropoxyphenyl)-2-imidazolyl group, 1-(4-n-
heptafluoropropoxyphenyl)-2-imidazolyl group, 1-(4-n-
pentoxyphenyl)-2-imidazolyl group, 1-(4-n-hexyloxyphenyl)-2-imidazolyl group, 1,4-diphenyl-2-imidazolyl group, 1,4,5-triphenyl-2-imidazolyl group or the like.

A piperadiny1 group (wherein, on the piperadine ring, at least one selected from the group consisting of a Cl-C6 alkyl group substituted by 2 phenyl groups (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), a thiazolyl group (wherein, on the thiazole ring, at least one phenyl group may be substituted), a phenoxy Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted), a phenyl C2-C6 alkenyl group (wherein, on
the phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted) and a imidazolyl group (wherein, on the
imidazole ring, at least one phenyl group (wherein, on
the phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted) may be substituted) is substituted)
includes a piperadiny1 group (wherein, on the
piperadine ring, 1 to 3 substituents selected from the
group consisting of a C1-C6 alkyl group substituted by
2 phenyl groups as described above (wherein, on the
phenyl ring, 1 to 5, preferably 1 to 3 substitutes
selected from the group consisting of a halogen atom, a
halogen substituted or unsubstituted C1-C6 alkyl group
and a halogen substituted or unsubstituted C1-C6 alkoxy
group may be substituted), a phenyl C1-C6 alkyl group
(wherein, on the phenyl ring, 1 to 3 phenoxy groups
(wherein, on the phenyl ring, 1 to 5, preferably 1 to 3
substitutes selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted
C1-C6 alkyl group and a halogen substituted or
unsubstituted C1-C6 alkoxy group may be substituted) are substituted, a thiazcyl group as described later (wherein, on the thiazole ring, 1 or 2 phenyl groups may be substituted), a phenoxy C1-C6 alkyl group as described later (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a phenyl group as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substitutes selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a phenyl C2-C6 alkenyl group [a group composed of a 1 or 2 phenyl groups substituted by 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group and an alkenyl group containing 2 to 6 carbon atoms and having 1 to 3 double bonds] and an imidazolyi group [wherein, on the imidazole ring, 1 to 3 phenyl groups (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy
group may be substituted, may be substituted, are substituted, for example, 4-(1,1-di(4-chlorophenyl)methyl)-1-piperadiny1 group, 4-(1,1-di(4-trifluoromethoxyphenyl)methyl)-1-piperadiny1 group, 4-(4-chlorocinnamyl)-1-piperadiny1 group, 4-(4-trifluoromethoxyxycinnamyl)-1-piperadiny1 group, 4-(1-[(4-chlorophenyl)-2-imidazolyl]-1-piperadiny1 group, 4-(1,1-di(2,4-dibromophenyl)methyl]-1-piperadiny1 group, 4-(1,1-di[4-trifluoromethylphenyl)methyl]-1-piperadiny1 group, 4-(2,4-dichlorocinnamyl)-1-piperadiny1 group, 4-(4-trifluoromethylcinnamyl]-1-piperadiny1 group, 4-(1,1-di(2,4-di(trifluoromethoxy)phenyl)-2-imidazolyl)-1-piperadiny1 group, 4-(1,1-di(2,4,6-trifluorophenyl)methyl]-1-piperadiny1 group, 4-(1,1-di(2,4-di(trifluoromethoxy)phenyl)methyl]-1-piperadiny1 group, 4-(2,4,6-tri(trifluoromethoxy)cinnamyl]-1-piperadiny1 group, 4-(2,4,6-di(trifluoromethoxy)-cinnamyl]-1-piperadiny1 group, 4-(1-(4-trifluoromethylphenyl)-2-imidazolyl]-1-piperadiny1 group, 4-(2,4,6-trifluorocinnamyl)-1-piperadiny1 group, 4-(1-(2,4-dibromophenyl)-2-imidazolyl]-1-piperadiny1 group, 4-(1,1-di(4-chlorophenyl)methyl]-3-(4-chlorocinnamyl]-1-l-piperadiny1 group, 4-(4-trifluoromethoxyxycinnamyl]-2-(1-(4-chlorophenyl)-2-imidazolyl]-6-(1-imidazolyl]-1-piperadiny1 group, 4-(4-(4-trifluoromethoxyphenoxy)benzyl]-1-, 2- or
3-)piperadiny1 group, 4-{4-phenyl-(2- or 5-)thiazolyl}-(1-, 2- or 3-)piperadiny1 group, 4-{2-(4-
trifluoromethoxyphenoxy)ethyl}-(1-, 2- or 3-)piperadiny1 group, 4-{2-(4-phenylphenoxy)ethyl}-(1-, 2- or 3-)piperadiny1 group, 4-{2-(4-
chlorophenoxy)ethyl}-(1-, 2- or 3-)piperadiny1 group, 4-{2-(3,4-dichlorophenoxy)ethyl}-(1-, 2- or 3-)piperadiny1 group, 4-{2-(4-
trifluoromethoxyphenoxy)ethyl}-(1-, 2- or 3-)piperadiny1 or the like.

An anilino C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) includes a group composed of an anilino group which may be substituted by a C1-C6 alkyl group on the N position of the anilino group and is unsubstituted or substituted by 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen substituted or unsubstituted C1-C6 alkyl group as defined above, a halogen substituted or unsubstituted C1-C6 alkoxy group and a halogen, and a C1-C6 alkyl group, examples of which include an anilinomethyl group, N-methyl-N-anilinomethyl group, N-ethyl-N-anilinomethyl group, N-n-propyl-N-anilinomethyl group, N-n-butyl-N-anilinomethyl group, N-n-pentyl-N-
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anilinomethyl group, N-n-hexyl-N-anilinomethyl group,
2-anilinoethyl group, 3-anilinopropyl group, 4-
anilinobutyl group, 5-anilinopentyl group, 6-
anilinohexyl group, 4-fluoroanilinomethyl group, 2-
5 fluoro-4-bromoanilinomethyl group, 4-chloro-3-
fluoroanilinomethyl group, 2,3,4-trichloroanilinomethyl
group, 3,4,5-trichloroanilinomethyl group, 2,4,6-
trichloroanilinomethyl group, N-methyl-N-2,4,6-
trichloroanilinomethyl group, 4-isopropylanilinomethyl
group, 4-n-butylanilinomethyl group, 4-
methylanilinomethyl group, 2-methylanilinomethyl group,
3-methylanilinomethyl group, 2,4-dimethylanilinomethyl
group, 2,3-dimethylanilinomethyl group, 2,6-
dimethylanilinomethyl group, 3,5-dimethylanilinomethyl
group, 2,5-dimethylanilinomethyl group, N-methyl-N-2,5-
dimethoxyanilinomethyl group, 2,4,6-
trimethylanilinomethyl group, 3,5-
ditrifluoromethylanilinomethyl group, 2,3,4,5,6-
pentafluorooanilinomethyl group, 4-
isopropoxyanilinomethyl group, 4-n-butoxyanilinomethyl
group, 4-methoxyanilinomethyl group, 2-
methoxyanilinomethyl group, 3-methoxyanilinomethyl
group, N-methyl-N-3-methoxyanilinomethyl group, 2,4-
dimethoxyanilinomethyl group, 2,3-
dimethoxyanilinomethyl group, 2,6-
dimethoxyanilinomethyl group, 3,5-
dimethoxyanilinomethyl group, 2,5-
dimethoxyanilinomethyl group, 2,4,6-
trimethoxyanilinomethyl group, 3,5-
ditrifluoromethoxyanilinomethyl group, 2-
isopropoxyanilinomethyl group, 3-chloro-4-
methoxyanilinomethyl group, 2-chloro-4-
3 trifluoromethoxyanilinomethyl group, 3-methyl-4-
fluoroanilinomethyl group, 4-bromo-3-
trifluoromethylanilinomethyl group, 2-(4-
fluoroanilino)ethyl group, 3-(4-fluoroanilino)propyl
group, 4-(4-fluoroanilino)butyl group, 5-(4-
fluoroanilino)pentyl group, 6-(4-fluoroanilino)hexyl
group, 4-chloroanilinomethyl group, 2-(4-
chloroanilino)ethyl group, 3-(4-chloroanilino)propyl
group, 4-(4-chloroanilino)butyl group, 5-(4-
chloroanilino)pentyl group, 6-(4-chloroanilino)hexyl
group, 4-methylanilinomethyl group, 2-(4-
methylanilino)ethyl group, 3-(4-methylanilino)propyl
group, 4-(4-methylanilino)butyl group, 5-(4-
methylanilino)pentyl group, 6-(4-methylanilino)hexyl
group, 4-trifluoromethylanilinomethyl group, 2-(4-
trifluoromethylanilino)ethyl group, 3-(4-
trifluoromethylanilino)propyl group, 4-(4-
trifluoromethylanilino)butyl group, N-methyl-N-(4-(4-
trifluoromethylanilino)butyl group, 5-(4-
trifluoromethylanilino)pentyl group, 6-(4-
trifluoromethylanilino)hexyl group, 4-
trifluoromethoxyanilinomethyl group, N-methyl-N-
4 trifluoromethoxyanilinomethyl group, 2-(4-
trifluoromethoxyanilino)ethyl group, 3-(4-
trifluoromethoxyanilino)propyl group, 4-(4-trifluoromethoxyanilino)butyl group, 5-(4-trifluoromethoxyanilino)pentyl group, 6-(4-trifluoromethoxyanilino)hexyl group, 4-methoxyanilinomethyl group, 2-(4-methoxyanilino)ethyl group, 3-(4-methoxyanilino)propyl group, 4-(4-methoxyanilino)butyl group, 5-(4-methoxyanilino)pentyl group, 6-(4-methoxyanilino)hexyl group or the like.

A thiazolyl C1-C6 alkoxy group (wherein, on the thiazole ring, at least one selected from the group consisting of a (p-1)phenoxy C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], a (p-2)anilino C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], a (p-3)phenyl C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], a (p-4)piperaciny1 group C1-C6 alkyl group [wherein, on the piperidine ring, at least one phenyl group (wherein, on the phenyl ring, at least
one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted] and a (p-S)piperidyl C1-C6 alkyl group [wherein, on the piperidine ring, at least one phenoxy group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] may be substituted] includes a thiazolyl C1-C6 alkoxy group [wherein, on the thiazole ring, 1 to 3 substituents selected from the group consisting of a phenoxy C1-C6 alkyl group as described later [wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], an anilino C1-C6 alkyl group as described above [wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], a phenyl C1-C6 alkyl group as described above [wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting
of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted), a piperadiny1 C1-C6 alkyl group as
described above [wherein, on the piperadine ring, 1 to
3 phenyl groups (wherein, on the phenyl ring, 1 to 5,
preferably 1 to 3 substituents selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted) may be substituted] and a piperidyl C1-C6
alkyl group as described above [wherein, on the
piperidine ring, 1 to 3 phenoxy groups (wherein, on the
phenyl ring, 1 to 5, preferably 1 to 3 substituents
selected from the group consisting of a halogen atom, a
halogen substituted or unsubstituted C1-C6 alkyl group
and a halogen substituted or unsubstituted C1-C6 alkoxy
group may be substituted) may be substituted], for example, a (2-thiazolyl)methoxy group,
2-(4-thiazolyl)ethoxy group, 3-(5-thiazolyl)propoxy
group, 4-(2-thiazolyl)butoxy group, 5-(4-
thiazolyl)pentyloxy group, 6-(5-thiazolyl)hexyloxy
group, 4-(4-(4-(4-chlorophenoxy)-1-piperidylmethyl)-2-
thiazolyl)methoxy group, 4-(4-(4-
trifluoromethylphenoxy)-1-piperidylmethyl)-2-
thiazolyl)methoxy group, 2-methyl-3-(2-
thiazolyl)propoxy group, 1,1-dimethyl-2-(2-
thiazolyl)ethoxy group, 4-(4-(4-
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trifluoromethoxyphenoxyl)-1-piperidylmethyl)-2-thiazolyl)methoxy group, (4-(4-(2,4-di(trifluoromethoxy)phenoxy)-1-piperidylmethyl)-2-thiazolyl)methoxy group, (4-(4-(2,4,6-trifluorophenoxy)-1-piperidylmethyl)-2-thiazolyl)methoxy group, (4-(4-(2,4,6-dibromophenoxy)-1-piperidylmethyl)-2-thiazolyl)methoxy group, (4-(4-(2,4-dibromophenoxy)-1-piperidylmethyl)-2-thiazolyl)methoxy group, (4-(4-(2,4,6-trifluoromethoxyphenoxy)-1-piperidylmethyl)-2-thiazolyl)methoxy group, (4-(4-(2,4-chlorophenyl)-1-piperazinylmethyl)-2-thiazolyl)methoxy group, (4-(4-(2,4-di(trifluoromethyl)phenoxy)-1-piperazinylmethyl)-2-thiazolyl)methoxy group, (4-(4-(2,4,6-trifluorophenyl)-1-piperazinylmethyl)-2-thiazolyl)methoxy group, (4-(4-(2,4,6-trifluoromethyl)phenoxymethyl)-2-thiazolyl) group, (4-(4-(2,4,6-trifluoromethoxyphenoxymethyl)-2-thiazolyl) group, (4-(4-(2,4-chlorophenoxymethyl)-2-thiazolyl)methoxy group, (4-(2,4-di(trifluoromethoxy)phenoxy)methyl)-2-thiazolyl)methoxy group, (4-(2,4,6-trifluoromethyl)phenoxy)methyl)-2-thiazolyl)methoxy group, (4-(2,4,6-trifluoromethyl)phenoxy)methyl)-2-thiazolyl)methoxy group, (4-(2,4,6-trifluoromethyl)phenoxy)methyl)-2-thiazolyl)methoxy group.
trifluorophenoxy)methyl)-2-thiazolyl)methoxy group, (4-
(4-trifluoromethyl)anilinomethyl)-2-thiazolyl)methoxy group, (4-(4-trifluoromethoxyanilinomethyl)-2-
thiazolyl)methoxy group, (4-(4-chloroanilinomethyl)-2-
thiazolyl)methoxy group, (4-(2,4-
di(trifluoromethoxy)anilinomethyl)-2-thiazolyl)methoxy group, (4-(2,4,6-tri(trifluoromethyl)anilinomethyl)-2-
thiazolyl)methoxy group, (4-(2,4-dibromoanilinomethyl]-
2-thiazolyl)methoxy group, (4-(2,4,6-
trifluoroanilinomethyl)-2-thiazolyl)methoxy group, (4-
(3-(4-trifluoromethoxyphenyl)propyl)-2-thiazolyl)methoxy group, (4-(3-(4-
trifluoromethylphenyl)propyl)-2-thiazolyl)methoxy group,
(4-(3-(4-chlorophenyl)propyl)-2-thiazolyl)methoxy group,
(4-(2,4-diiodobenzyl)-2-thiazolyl)methoxy group, (4-
(2,4,6-tribromobenzyl)-2-thiazolyl)methoxy group, (4-
(2,4-di(trifluoromethoxy)benzyl)-2-thiazolyl)methoxy group,
(4-(2,4,6-tri(trifluoromethyl)benzyl)-2-
thiazolyl)methoxy group, (4,5-dibenzyl-2-
thiazolyl)methoxy group, (2-phenoxyethyl-4-benzyl-5-
thiazolyl)methoxy group, (2,5-dianilinomethyl-4-
thiazolyl)methoxy group or the like.

An 8-azabicyclo[3.2.1]octyl group (wherein, on the 8-azabicyclo[3.2.1]octane ring, at least one
phenoxy group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen
atom, a halogen substituted or unsubstituted C1-C6
alkyl group and a halogen substituted or unsubstituted
C1-C6 alkoxy group may be substituted) may be substituted) includes a 8-azabicyclo[3.2.1]octyl group (wherein, on the 8-azabicyclo[3.2.1]octane ring, 1 to 3 phenoxy groups as described above [wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] may be substituted); for example, a 8-azabicyclo[3.2.1]octyl group, 3-(4-
trifluoromethoxyphenoxy)-8-azabicyclo[3.2.1]octyl group, 3-(4-trifluoromethylphenoxy)-8-azabicyclo[3.2.1]octyl group, 3-(4-chlorophenoxy)-8-azabicyclo[3.2.1]octyl group, 3-(2,4-dichlorophenoxy)-8-azabicyclo[3.2.1]octyl group, 3-(2,4,6-trichlorophenoxy)-8-
azabicyclo[3.2.1]octyl group, 3-(2-bromophenoxy)-8-
azabicyclo[3.2.1]octyl group, 3-(3-fluorophenoxy)-8-
azabicyclo[3.2.1]octyl group, 3-(2,4-
di(trifluoromethoxy)phenoxy)-8-azabicyclo[3.2.1]octyl group, 3-(2,4,6-tri(trifluoromethoxy)phenoxy)-8-
azabicyclo[3.2.1]octyl group, 3-(2,4-
di(trifluoromethyl)phenoxy)-8-azabicyclo[3.2.1]octyl group, 3-(2,4,6-tri(trifluoromethyl)phenoxy)-8-
azabicyclo[3.2.1]octyl group, 3,6-diphenoxy-8-
azabicyclo[3.2.1]octyl group, 3,7,6-triphenoxy-8-
azabicyclo[3.2.1]octyl group, 3-(4-methoxyphenoxy)-8-
azabicyclo[3.2.1]octyl group, 3-(4-methylphenoxy)-8-
azabicyclo[3.2.1]octyl group, 3-(2,4-dimethoxyphenoxy)-
8-azabicyclo[3.2.1]octyl group, 3-(2,4,5-trimethoxyphenoxy)-8-azabicyclo[3.2.1]octyl group, 3-(2,4-dimethylphenoxy)-8-azabicyclo[3.2.1]octyl group, 3-(2,4,6-trimethylphenoxy)-8-azabicyclo[3.2.1]octyl group or the like.

An amino substituted C1-C6 alkyl group which may have a C1-C6 alkyl group as a substituent includes an amino-C1-C6 alkyl group which may have 1 or 2 C1-C6 alkyl groups as a substituent, for example, an aminomethyl group, 2-aminoethyl group, 1-aminooethyl group, 3-aminopropyl group, 4-aminobutyl group, 5-aminopentyl group, 6-aminohexyl group, 2-methyl-3-aminopropyl group, 1,1-dimethyl-2-aminoethyl group, ethylaminomethyl group, 1-(propylamino)ethyl group, 2-(methylamino)ethyl group, 3-(isopropylamino)propyl group, 4-(n-butylamino)butyl group, 5-(n-pentylamino)pentyl group, 6-(n-hexylamino)hexyl group, dimethylaminomethyl group, (N-ethyl-N-propylamino)methyl group, 2-(N-methyl-N-hexylamino)ethyl group or the like.

A C1-C6 alkylene group includes a methylene group, ethylene group, trimethylene group, 2-methyltrimethylene group, 2,2-dimethyltrimethylene group, 1-methyltrimethylene group, methylmethylene group, ethylmethylene group, tetramethylene group, pentamethylene group, hexamethylene group or the like.

A phenyl C1-C6 alkoxy carbonyl group (wherein, on the phenyl ring, at least one selected from the
group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) includes a group composed of aphenyl C1-C6 alkoxy group which may be substituted by 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group as defined above and a carbonyl group, examples of which include a benzyloxy carbonyl group, 2-phenylethoxy carbonyl group, 3-phenylpropoxy carbonyl group, 2-phenylpropoxy carbonyl group, 4-phenylbutoxy carbonyl group, 5-phenylpent oxy carbonyl group, 4-phenylpent oxy carbonyl group, 6-phenylhexyloxy carbonyl group, 2-fluorobenzyl loxy carbonyl group, 3-fluorobenzylloxy carbonyl group, 4-fluorobenzylloxy carbonyl group, 2-(2-fluorophenyl)ethoxy carbonyl group, 2-(3-fluorophenyl)ethoxy carbonyl group, 2-(4-fluorophenyl)ethoxy carbonyl group, 2-chlorobenzylloxy carbonyl group, 3-chlorobenzylloxy carbonyl group, 4-chlorobenzylloxy carbonyl group, 2-fluoro-4-bromobenzylloxy carbonyl group, 4-chloro-3-fluorobenzylloxy carbonyl group, 2,3,4-trichlorobenzylloxy carbonyl group, 3,4,5-trifluorobenzylloxy carbonyl group, 2,3,4,5,6-
pentfluorobenzylloxycarbonyl group, 2,4,6-
trichlorobenzylloxycarbonyl group, 4-
isopropylbenzylloxycarbonyl group, 4-n-
butylbenzylloxycarbonyl group, 4-methylbenzylloxycarbonyl
group, 2-methylbenzylloxycarbonyl group, 3-
methylbenzylloxycarbonyl group, 2,4-
dimethylbenzylloxycarbonyl group, 2,3-
dimethylbenzylloxycarbonyl group, 2,6-
dimethylbenzylloxycarbonyl group, 3,5-
dimethylbenzylloxycarbonyl group, 2,5-
dimethylbenzylloxycarbonyl group, 2,4,6-
dimethylbenzylloxycarbonyl group, 3,5-
ditrifluoromethylbenzylloxycarbonyl group, 4-
isopropoxybenzylloxycarbonyl group, 4-n-
butoxybenzylloxycarbonyl group, 4-
methoxybenzylloxycarbonyl group, 2-
methoxybenzylloxycarbonyl group, 3-
methoxybenzylloxycarbonyl group, 2,4-
dimethoxybenzylloxycarbonyl group, 2,3-
dimethoxybenzylloxycarbonyl group, 2,6-
dimethoxybenzylloxycarbonyl group, 2,5-
dimethoxybenzylloxycarbonyl group, 2,4,6-
dimethoxybenzylloxycarbonyl group, 3,5-
ditrifluoromethoxybenzylloxycarbonyl group, 2-
isopropoxybenzylloxycarbonyl group, 3-chloro-4-
methoxybenzylloxycarbonyl group, 2-chloro-4-
ditrifluoromethoxybenzylloxycarbonyl group, 3-methyl-4-
fluorobenzlyloxy carbonyl group, 4-bromo-3-
trifluoromethylbenzlyloxy carbonyl group, 2-(2-
chlorophenyl) ethoxy carbonyl group, 2-(3-
chlorophenyl) ethoxy carbonyl group, 2-(4-
chlorophenyl) ethoxy carbonyl group, 2-
trifluoromethylbenzlyloxy carbonyl group, 3-
trifluoromethylbenzlyloxy carbonyl group, 4-
trifluoromethylbenzlyloxy carbonyl group, 2-
trifluoromethoxy benzlyloxy carbonyl group, 3-
10 trifluoromethoxy benzlyloxy carbonyl group, 4-
trifluoromethoxy benzlyloxy carbonyl group, 2-(2-
trifluoromethyl phenyl) ethoxy carbonyl group, 2-(3-
trifluoromethyl phenyl) ethoxy carbonyl group, 2-(4-
trifluoromethyl phenyl) ethoxy carbonyl group, 2-(2-
15 trifluoromethoxy phenyl) ethoxy carbonyl group, 2-(3-
trifluoromethoxy phenyl) ethoxy carbonyl group, 2-(4-
trifluoromethoxy phenyl) ethoxy carbonyl group, 3-(2-
trifluoromethyl phenyl) propoxy carbonyl group, 3-(3-
trifluoromethyl phenyl) propoxy carbonyl group, 3-(4-
20 trifluoromethyl phenyl) propoxy carbonyl group, 3-(2-
trifluoromethyl phenyl) propoxy carbonyl group, 3-(3-
trifluoromethoxy phenyl) propoxy carbonyl group, 3-(4-
trifluoromethoxy phenyl) propoxy carbonyl group, 4-(3-
25 trifluoromethyl phenyl) butoxy carbonyl group, 5-(4-
trifluoromethyl phenyl) pentoxy carbonyl group, 4-(4-
trifluoromethyl phenyl) pentoxy carbonyl group, 4-(4-
trifluoromethoxy phenyl) pentoxy carbonyl group, 6-(3-
trifluoromethyl phenyl) hexycxyl carbonyl group, 6-(4-
trifluoromethylphenyl)hexyloxy carbonyl group, 6-(4-trifluoromethoxyphenyl)hexyloxy carbonyl group or the like.

A phenyl C2-C6 alkenyl carbonyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted] includes a group composed of a phenyl group substituted by 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group and an alkenyl carbonyl group containing 2 to 6 carbon atoms and having 1 to 3 double bonds. The phenyl C2-C6 alkenyl carbonyl group includes both trans and cis forms. Such a phenyl C2-C6 alkenyl carbonyl group includes a 2-phenylvinyl carbonyl group, 3-phenyl-2-propenyl carbonyl group (common name: cinnamoyl), 4-phenyl-2-but enyl carbonyl group, 4-phenyl-3-butenyl carbonyl group, 4-phenyl-1,3-butadienyl carbonyl group, 5-phenyl-1,3,5-hexatrienyl carbonyl group, 3-(2-fluorophenyl)-2-propenyl carbonyl group, 3-(3-fluorophenyl)-2-propenyl carbonyl group, 3-(4-fluorophenyl)-2-propenyl carbonyl group, 3-(2,3-difluorophenyl)-2-propenyl carbonyl group, 3-(2,3,4,5,6-pentafluorophenyl)-2-propenyl carbonyl group, 3-(2,4-
dифлуорофенил)-2-пропенилкарбонил групп, 3-(3,4-дифлуорофенил)-2-пропенилкарбонил групп, 3-(3,5-дифлуорофенил)-2-пропенилкарбонил групп, 3-(2-хлорофенил)-2-пропенилкарбонил групп, 3-(3-
хлорофенил)-2-пропенилкарбонил групп, 3-(4-
хлорофенил)-2-пропенилкарбонил групп, 3-(12,3-
dихлорофенил)-2-пропенилкарбонил групп, 3-(2,4-
dихлорофенил)-2-пропенилкарбонил групп, 3-(3,4-
dихлорофенил)-2-пропенилкарбонил групп, 3-(3,5-
dихлорофенил)-2-пропенилкарбонил групп, 3-(2-
bромофенил)-2-пропенилкарбонил групп, 3-(3-
bромофенил)-2-пропенилкарбонил групп, 3-(4-
bромофенил)-2-пропенилкарбонил групп, 3-(2-
метилфенил)-2-пропенилкарбонил групп, 3-(3-
метилфенил)-2-пропенилкарбонил групп, 3-(4-
метилфенил)-2-пропенилкарбонил групп, 3-(4-
трифлуорометилфенил)-2-пропенилкарбонил групп, 3-(2-
флуро-4-бромофенил)-2-пропенилкарбонил групп, 3-(4-
хлоро-3-флуорофенил)-2-пропенилкарбонил групп, 3-
(2,3,4-трихлорофенил)-2-пропенилкарбонил групп, 3-
(2,4,6-трихлорофенил)-2-пропенилкарбонил групп, 3-(4-
isопропилфенил)-2-пропенилкарбонил групп, 3-(4-
н-бутилфенил)-2-пропенилкарбонил групп, 3-(2,4-
dиметилфенил)-2-пропенилкарбонил групп, 3-(2,3-
dиметилфенил)-2-пропенилкарбонил групп, 3-(2,6-
dиметилфенил)-2-пропенилкарбонил групп, 3-(3,5-
dиметилфенил)-2-пропенилкарбонил групп, 3-(2,5-
dиметилфенил)-2-пропенилкарбонил групп, 3-(2,4,6-
trimethylphenyl)-2-propenylcarbonyl group, 3-(3,5-
ditrifluoromethylphenyl)-2-propenylcarbonyl group, 3-
(4-n-butoxyphenyl)-2-propenylcarbonyl group, 3-(2,4-
dimethoxyphenyl)-2-propenylcarbonyl group, 3-(2,3-
dimethoxyphenyl)-2-propenylcarbonyl group, 3-(2,6-
dimethoxyphenyl)-2-propenylcarbonyl group, 3-(3,5-
dimethoxyphenyl)-2-propenylcarbonyl group, 3-(2,5-
dimethoxyphenyl)-2-propenylcarbonyl group, 3-(3,5-
ditrifluoromethoxyphenyl)-2-propenylcarbonyl group, 3-
(3-chloro-4-methoxyphenyl)-2-propenylcarbonyl group, 3-
(2-chloro-4-trifluoromethoxyphenyl)-2-propenylcarbonyl
group, 3-(3-methyl-4-fluorophenyl)-2-propenylcarbonyl
group, 3-(4-bromo-3-trifluoromethylphenyl)-2-
propenylcarbonyl group, 3-(3-trifluoromethylphenyl)-2-
propenylcarbonyl group, 3-(4-trifluoromethylphenyl)-2-
propenylcarbonyl group, 3-(2-trifluoromethoxyphenyl)-2-
propenylcarbonyl group, 3-(3-trifluoromethoxyphenyl)-2-
propenylcarbonyl group, 3-(4-trifluoromethoxyphenyl)-2-
propenylcarbonyl group, 3-(2-methoxyphenyl)-2-
propenylcarbonyl group, 3-(3-methoxyphenyl)-2-
propenylcarbonyl group, 3-(4-methoxyphenyl)-2-
propenylcarbonyl group, 3-(3,4-dimethoxyphenyl)-2-
propenylcarbonyl group, 3-(3,5-dimethoxyphenyl)-2-
propenylcarbonyl group, 4-(4-chlorophenyl)-2-
butenylcarbonyl group, 4-(4-chlorophenyl)-3-
butenylcarbonyl group, 5-(4-chlorophenyl)-2-
pentenylcarbonyl group, 5-(4-chlorophenyl)-4-
pentenylcarbonyl group, 5-(4-chlorophenyl)-3-
pentenylcarbonyl group, 6-(4-chlorophenyl)-5-
hexenylcarbonyl group, 6-(4-chlorophenyl)-4-
hexenylcarbonyl group, 6-(4-chlorophenyl)-3-
hexenylcarbonyl group, 6-(4-chlorophenyl)-3-
hexenylcarbonyl group or the like.

A C1-C4 alkylenedioxy group includes a
methylenedioxy group, ethylenedioxy group,
trimethylenedioxy group, tetramethylenedioxy group or
the like.

An amino substituted sulfonyl group which may
have a C1-C6 alkyl group as a substituent includes an
aminosulfonyl group which may have 1 to 2 C1-C6 alkyl
groups as substituent, for example an aminosulfonyl
group, methylaminosulfonyl group, ethylaminosulfonyl
group, propylaminosulfonyl group,
isopropylaminosulfonyl group, butylaminosulfonyl group,
tert-butyldiaminosulfonyl group, pentylaminosulfonyl
group, hexylaminosulfonyl group, dimethylaminosulfonyl
group, diethylaminosulfonyl group,
dipropylaminosulfonyl group, dibutylaminosulfonyl group,
dipentylaminosulfonyl group, dihexylaminosulfonyl group,
N-methyl-N-ethylaminosulfonyl group, N-ethyl-N-
propylaminosulfonyl group, N-methyl-N-
butylaminosulfonyl group, N-methyl-N-hexylaminosulfonyl
group or the like.

A phenyl C1-C6 alkoxy group includes a
benzyloxy group, 2-phenylethoxy group, 1-phenylethoxy
group, 3-phenylpropanoxy group, 2-phenylpropoxy group, 4-
phenylbutoxy group, 5-phenylpentoxyc group, 4-phenylpentoxy group, 6-phenylhexyloxy group, 2-methyl-3-phenylpropxy group, 1,1-dimethyl-2-phenylethoxy group or the like.

A pyrroloidinyl group [wherein, on the pyrrolidine ring, at least one oxo group may be substituted] includes a pyrroloidinyl group [wherein, on the pyrrolidine ring, 1 or 2 oxo groups may be substituted], for example, a pyrroloidinyl group, 2-oxopyrroloidinyl group, 2,5-dioxopyrroloidinyl group or the like.

A pyrroloidinyl Cl-C6 alkoxy group includes a (1-pyrroloidinyl)methoxy group, 2-(1-pyrroloidinyl)-ethoxy group, 1-(2-pyrroloidinyl)-ethoxy group, 3-(1-pyrroloidinyl)propoxy group, 2-(3-pyrroloidinyl)propxy group, 4-(1-pyrroloidinyl)butoxy group, 5-(2-pyrroloidinyl)pentoxgy group, 4-(3-pyrroloidinyl)pentoxgy group, 6-(1-pyrroloidinyl)hexyloxy group, 2-methyl-3-(1-pyrroloidinyl)propxy group, 1,1-dimethyl-2-(1-pyrroloidinyl)-ethoxy group or the like.

A benzofuronyl Cl-C6 alkyl group [wherein, on the benzofuran ring, at least one halogen atom may be substituted as a substituent] includes a benzofuryl substituted Cl-C6 alkyl group which may be substituted by 1 to 3 halogen atoms on the benzofuran ring, for example, a 2-benzofurylmethyl group, 1-(2-benzofuryl)ethyl group, 2-(4-benzofuryl)ethyl group, 3-(5-benzofuryl)propyl group, 4-(6-benzofuryl)butyl group,
5-(7-benzofurylpentyl group, 6-(2-benzofuryl)hexyl group, 4-fluoro-2-benzofurylmethyl group, 5-fluoro-2-benzofurylmethyl group, 6-fluoro-2-benzofurylmethyl group, 7-fluoro-2-benzofurylmethyl group, 4-chloro-2-benzofurylmethyl group, 5-chloro-2-benzofurylmethyl group, 6-chloro-2-benzofurylmethyl group, 7-chloro-2-benzofurylmethyl group, 4-bromo-2-benzofurylmethyl group, 5-bromo-2-benzofurylmethyl group, 6-bromo-2-benzofurylmethyl group, 7-bromo-2-benzofurylmethyl group, 4-iodo-2-benzofurylmethyl group, 5-iodo-2-benzofurylmethyl group, 6-iodo-2-benzofurylmethyl group, 7-iodo-2-benzofurylmethyl group, 4-fluoro-3-benzofurylmethyl group, 5-fluoro-3-benzofurylmethyl group, 6-fluoro-3-benzofurylmethyl group, 7-fluoro-3-benzofurylmethyl group, 4-chloro-3-benzofurylmethyl group, 5-chloro-3-benzofurylmethyl group, 6-chloro-3-benzofurylmethyl group, 7-chloro-3-benzofurylmethyl group, 4-bromo-3-benzofurylmethyl group, 5-bromo-3-benzofurylmethyl group, 6-bromo-3-benzofurylmethyl group, 7-bromo-3-benzofurylmethyl group, 4-iodo-3-benzofurylmethyl group, 5-iodo-3-benzofurylmethyl group, 6-iodo-3-benzofurylmethyl group, 7-iodo-3-benzofurylmethyl group, 2-(4-fluoro-2-benzofuryl)ethyl group, 2-(5-fluoro-2-benzofuryl)ethyl group, 2-(6-fluoro-2-benzofuryl)ethyl group, 2-(7-fluoro-2-benzofuryl)ethyl group, 2-(4-chloro-2-benzofuryl)ethyl group, 2-(5-chloro-2-benzofuryl)ethyl group, 2-(6-chloro-2-benzofuryl)ethyl group, 2-(7-chloro-2-
benzofuryl)ethyl group, 2-(4-fluoro-3-benzofuryl)methyl group, 2-(5-fluoro-3-benzofuryl)methyl group, 2-(6-
fluoro-3-benzofuryl)ethyl group, 2-(7-fluoro-3-
benzofuryl)ethyl group, 2-(4-chloro-3-benzofuryl)ethyl group, 2-(5-chloro-3-benzofuryl)ethyl group, 2-(6-
chloro-3-benzofuryl)ethyl group, 2-(7-chloro-3-
benzofuryl)ethyl group, 2-(4-fluoro-2-benzofuryl)ethyl group, 2-(5-fluoro-2-benzofuryl)hexyl group, 6-(6-
fluoro-2-benzofuryl)hexyl group, 6-(7-fluoro-2-
benzofuryl)hexyl group, 6-(4-chloro-2-benzofuryl)hexyl group, 6-(5-chloro-2-benzofuryl)hexyl group, 6-(6-
chloro-2-benzofuryl)hexyl group, 6-(7-chloro-2-
benzofuryl)hexyl group, 6-(4-fluoro-3-benzofuryl)methyl group, 6-(5-fluoro-3-benzofuryl)hexyl group, 6-(6-
fluoro-3-benzofuryl)hexyl group, 6-(7-fluoro-3-
benzofuryl)hexyl group, 6-(4-chloro-3-benzofuryl)hexyl group, 6-(5-chloro-3-benzofuryl)hexyl group, 6-(6-
chloro-3-benzofuryl)hexyl group, 6-(7-chloro-3-
benzofuryl)hexyl group, (2,4-dibromo-3-
benzofuryl)methyl group, (4,5,6-trichloro-3-
benzofuryl)methyl or the like.

A phenoxy C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) is a group composed of a phenoxy group unsubstituted or substituted by 1 to 5, preferably 1 to
3 substituents selected from a halogen substituted or unsubstituted C1-C6 alkyl group, a halogen substituted or unsubstituted C1-C6 alkoxy group and a halogen as defined above and a C1-C6 alkyl group, examples of which include a phenoxyethyl group, 2-phenoxyethyl group, 3-phenoxypropyl group, 4-phenoxybutyl group, 5-phenoxypentyl group, 6-phenoxyhexyl group, 4-fluoro-6-methylphenoxyethyl group, 2-fluoro-4-bromophenoxyethyl group, 2-fluoro-4-bromophenoxyethyl group, 4-chloro-3-fluorophenoxyethyl group, 2-chlorophenoxyethyl group, 3-chlorophenoxyethyl group, 4-chlorophenoxyethyl group, 3,4-dichlorophenoxyethyl group, 2,3,4-trichlorophenoxyethyl group, 3,4,5-trichlorophenoxyethyl group, 2,4,6-trichlorophenoxyethyl group, 2-(2-chlorophenoxy)ethyl group, 2-(3-chlorophenoxy)ethyl group, 2-(4-chlorophenoxy)ethyl group, 2-(3,4-dichlorophenoxy)ethyl group, 2-(4-fluorophenoxy)ethyl group, 4-isopropylphenoxyethyl group, 4-n-butylyphenoxyethyl group, 4-methylphenoxyethyl group, 2-methylphenoxyethyl group, 3-methylphenoxyethyl group, 4-n-propylphenoxyethyl group, 4-isopropylphenoxyethyl group, 2,4-dimethylphenoxyethyl group, 2,3-dimethylphenoxyethyl group, 2,6-dimethylphenoxyethyl group, 3,5-dimethylphenoxyethyl group, 2,5-dimethylphenoxyethyl group, 2,4,6-trimethylphenoxyethyl group, 2,4,6-trimethylphenoxyethyl group, 4-hexylphenoxyethyl group.
group, 2-(3-methylphenoxy)ethyl group, 2-(3,4-
dimethylphenoxy)ethyl group, 3,5-
difluoromethylphenoxyethyl group, 2,3,4,5,6-
pentafluorophenoxyethyl group, 4-
isopropoxyphenoxyethyl group, 4-n-butoxyphenoxyethyl group, 4-methoxyphenoxyethyl group, 2-
methoxyphenoxyethyl group, 3-methoxyphenoxyethyl group, 2-(3-methoxyphenoxy)ethyl group, 2-(4-
methoxyphenoxy)ethyl group, 2-(3,4-
dimethoxyphenoxy)ethyl group, 2,4-
dimethoxyphenoxyethyl group, 2,3-
dimethoxyphenoxyethyl group, 3,4-
dimethoxyphenoxyethyl group, 2,6-
dimethoxyphenoxyethyl group, 3,5-
dimethoxyphenoxyethyl group, 2,5-
dimethoxyphenoxyethyl group, 2,4,6-
trimethoxyphenoxyethyl group, 3,4,5-
trimethoxyphenoxyethyl group, 3,5-
difluoromethoxyphenoxyethyl group, 2-
isopropoxyphenoxyethyl group, 3-chloro-4-
methoxyphenoxyethyl group, 2-chloro-4-
methoxyphenoxyethyl group, 2-chloro-4-
trifluoromethoxyphenoxyethyl group, 3-methyl-4-
fluorophenoxyethyl group, 4-bromo-3-
trifluoromethylphenoxyethyl group, 2-(4-
fluorophenoxy)ethyl group, 3-(4-fluorophenoxy)propyl group, 4-(4-fluorophenoxy)butyl group, 5-(4-
fluorophenoxy)pentyl group, 6-(4-fluorophenoxy)hexyl
group, 4-chlorophenoxy)methyl group, 3-(4-chlorophenoxy)propyl group, 4-(4-chlorophenoxy)butyl group, 5-(4-chlorophenoxy)pentyl group, 6-(4-chlorophenoxy)hexyl group, 4-methylphenoxymethyl group, 2-(4-methylphenoxo)ethyl group, 2-(2-isopropylphenoxy)ethyl group, 2-(4-isopropylphenoxy)ethyl group, 2-(4-hexylphenoxy)ethyl group, 2-(2-fluoro-5-methylphenoxy)ethyl group, 2-(2-chloro-4-methoxyphenoxy)ethyl group, 2-(3-fluoro-4-chlorophenoxy)ethyl group, 2-(3,4,5-trimethylphenoxy)ethyl group, 3-(4-methylphenoxo)propyl group, 4-(4-methylphenoxy)butyl group, 5-(4-methylphenoxy)pentyl group, 6-(4-methylphenoxy)hexyl group, 4-trifluoromethylphenoxy)methyl group, 2-
2-(4-trifluoromethylphenoxy)methyl group, 3-
2-(4-trifluoromethylphenoxy)methyl group, 2-(4-trifluoromethylphenoxy)ethyl group, 2-(2-trifluoromethylphenoxy)ethyl group, 2-(3-trifluoromethylphenoxy)ethyl group, 3-(4-
2-(4-trifluoromethylphenoxy)propyl group, 4-(4-trifluoromethylphenoxy)butyl group, 5-(4-trifluoromethylphenoxy)pentyl group, 6-(4-trifluoromethylphenoxy)hexyl group, 4-
trifluoromethoxy)phenoxymethyl group, 2-(4-
2-(4-trifluoromethoxy)phenoxo)ethyl group, 2-(3-trifluoromethoxy)phenoxo)ethyl group, 2-(2-trifluoromethoxy)phenoxo)ethyl group, 3-(4-trifluoromethoxy)phenoxo)propyl group, 4-(4-
trifluoromethoxyphenoxy)butyl group, 5-(4-trifluoromethoxyphenoxy)pentyl group, 6-(4-trifluoromethoxyphenoxy)hexyl group, 4-methoxyphenoxymethyl group, 2-isopropoxyphenoxyethyl group, 5-(4-methoxyphenoxy)ethyl group, 3-(4-methoxyphenoxy)propyl group, 4-(4-methoxyphenoxy)butyl group, 5-(4-methoxyphenoxy)pentyl group, 6-(4-methoxyphenoxy)hexyl group or the like.

A thiazolyl C1-C6 alkyl group (wherein, on the thiazole ring, at least one phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] may be substitute) includes a thiazolyl C1-C6 alkyl group (wherein, on the thiazole ring, 1 or 2 phenyl groups [wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] may be substitute), for example, a 2-thiazolylmethyl group, 4-thiazolylmethyl group, 5-thiazolylmethyl group, 5-phenyl-4-thiazolylmethyl group, 4-phenyl-5-thiazolylmethyl group, 2-phenyl-4-thiazolylmethyl group, 2-phenyl-5-thiazolylmethyl group, 2,5-diphenyl-4-thiazolylmethyl group, 2,4-diphenyl-5-thiazolylmethyl group, 5-(2-fluorophenyl)-4-
thiazolylmethyl group, 4-(2-fluorophenyl)-5-
thiazolylmethyl group, 2-(2-chlorophenyl)-4-
thiazolylmethyl group, 2-(2-bromophenyl)-5-
thiazolylmethyl group, 2-(2,3,4,5,6-pentafluorophenyl)-5-
thiazolylmethyl group, 2-(2-bromophenyl)-5-
thiazolylmethyl group, 5-(3-iodophenyl)-4-
thiazolylmethyl group, 4-(3-fluorophenyl)-5-
thiazolylmethyl group, 2-(2,3-difluorophenyl)-4-
thiazolylmethyl group, 2-(3-bromophenyl)-5-
10 thiazolylmethyl group, 2-(3,4,5-trifluorophenyl)-4-
thiazolylmethyl group, 2-(3-fluorophenyl)-5-
thiazolylmethyl group, 5-(2,4,6-trichlorophenyl)-4-
thiazolylmethyl group, 4-(2,3,4,5,6-pentafluorophenyl)-
5-thiazolylmethyl group, 2-(4-fluorophenyl)-4-
15 thiazolylmethyl group, 4-(2-fluorophenyl)-5-
thiazolylmethyl group, 2-(4-fluorophenyl)-5-
thiazolylmethyl group, 5-(2-chlorophenyl)-4-
10 thiazolylmethyl group, 4-(2-chlorophenyl)-5-
thiazolylmethyl group, 2-(2-chlorophenyl)-5-
20 thiazolylmethyl group, 5-(3-methylphenyl)-4-
thiazolylmethyl group, 4-(3-ethylphenyl)-5-
thiazolylmethyl group, 2-(3-propylphenyl)-4-
thiazolylmethyl group, 2-(2-n-butylphenyl)-5-
thiazolylmethyl group, 2-(3-n-pentylphenyl)-4-
25 thiazolylmethyl group, 2-(3-n-hexylphenyl)-5-
thiazolylmethyl group, 5-(3,4-dimethylphenyl)-4-
thiazolylmethyl group, 4-(2,4,6-trimethylphenyl)-5-
thiazolylmethyl group, 2-(4-methoxyphenyl)-4-
thiazolylmethyl group, 2-(4-ethoxyphenyl)-5-
thiazolylmethyl group, 2-(4-propoxyphenyl)-4-
thiazolylmethyl group, 2-(4-n-butoxyphenyl)-5-
thiazolylmethyl group, 2-(2-thiazolyl)ethyl group, 2-
(4-thiazolyl)ethyl group, 2-(5-thiazolyl)ethyl group,
2-(5-(2-n-pentyloxyphenyl)-4-thiazolyl)ethyl group, 2-
(2-(2-n-hexyloxyphenyl)-5-thiazolyl)ethyl group, 2-(2-
(2,5-dimethoxyphenyl)-4-thiazolyl)ethyl group, 2-(2-
(2,4,6-trimethoxyphenyl)-5-thiazolyl)ethyl group, 2-(2-
trifluoromethylphenyl)-4-thiazolylmethyl group, 2,4-
di(trifluoromethyl)phenyl-5-thiazolylmethyl group, 2-
trifluoromethoxyphenyl-4-thiazolylmethyl group, 2,3-
di(trifluoromethoxy)phenyl-5-thiazolylmethyl group, 2-
(2-methyl-5-trifluoromethoxyphenyl-4-thiazolyl)ethyl

A C1-C6 alkoxy carbonyl group is a group
composed of a C1-C6 alkoxy group as defined above and a
carbonyl group, examples of which include a
methoxycarbonyl group, ethoxycarbonyl group,
propoxycarbonyl group, isopropoxycarbonyl group, n-
butoxycarbonyl group, isobutoxycarbonyl group, tert-
butoxycarbonyl group, sec-butoxycarbonyl group, n-
pentoxycarbonyl group, neopentoxycarbonyl group, n-
hexyloxycarbonyl group, isohexyloxycarbonyl group, 3-
methylpentoxycarbonyl group or the like.

A benzoyl group (wherein, on the phenyl ring,
at least one selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted
Cl-C6 alkyl group and a halogen substituted or
unsubstituted Cl-C6 alkoxy group may be substituted)
includes a benzoyl group (wherein, on the phenyl ring,
1 to 5, preferably 1 to 3 substituents selected from
the group consisting of a halogen atom, a halogen
substituted or unsubstituted Cl-C6 alkyl group and a
halogen substituted or unsubstituted Cl-C6 alkoxy group
may be substituted), for example, a benzoyl group, 2-
fluorobenzoyl group, 3-fluorobenzoyl group, 4-
fluorobenzoyl group, 2,3-difluorobenzoyl group, 3,4-
difluorobenzoyl group, 2-chlorobenzoyl group, 3-
chlorobenzoyl group, 4-chlorobenzoyl group, 2,3-
dichlorobenzoyl group, 3,4-dichlorobenzoyl group,
2,4,6-trichlorobenzoyl group, 4-iodobenzoyl group,
2,3,4,5,6-pentafluorobenzoyl group, 2-bromobenzoyl
group, 3-bromobenzoyl group, 4-bromobenzoyl group, 2,3-
dibromobenzoyl group, 3,4-dibromobenzoyl group, 2-
methylbenzoyl group, 3-methylbenzoyl group, 4-

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methylbenzoyl group, 2,3-dimethylbenzoyl group, 3,4-dimethylbenzoyl group, 3,4,5-trimethylbenzoyl group, 2-trifluoromethylbenzoyl group, 3-trifluoromethylbenzoyl group, 4-trifluoromethylbenzoyl group, 2,3-ditrifluoromethylbenzoyl group, 3,4-ditrifluoromethylbenzoyl group, 2-methoxybenzoyl group, 3-methoxybenzoyl group, 4-methoxybenzoyl group, 3,4-dimethoxybenzoyl group, 2,4,6-trimethoxybenzoyl group, 2-trifluoromethoxybenzoyl group, 3-

trifluoromethoxybenzoyl group, 4-

trifluoromethoxybenzoyl group, 2-methoxy-3-fluorobenzoyl group, 3-methyl-4-chlorobenzoyl group, 3-trifluoromethoxy-4-methylbenzoyl group, 2-methoxy-4-trifluoromethylbenzoyl group or the like.

A phenylcarbamoyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) is a group composed of an aniline which may be substituted on the phenyl ring by 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group, an N-C1-C6 alkylaniline or an N-phenyl C1-C6 alkylaniline and a carbonyl group, examples of which include a phenylcarbamoyl group, 2-fluorophenylcarbamoyl group,
3-fluorophenylcarbamoyl group, 4-fluorophenylcarbamoyl group, 2-chlorophenylcarbamoyl group, 3-
chlorophenylcarbamoyl group, 4-chlorophenylcarbamoyl group, 2-bromophenylcarbamoyl group, 3-
bromophenylcarbamoyl group, 4-bromophenylcarbamoyl group, 2-iodophenylcarbamoyl group, 3-
iodophenylcarbamoyl group, 4-iodophenylcarbamoyl group, 2,3-difluorophenylcarbamoyl group, 3,4-
difluorophenylcarbamoyl group, 3,5-
difluorophenylcarbamoyl group, 2,4-
difluorophenylcarbamoyl group, 2,6-
difluorophenylcarbamoyl group, 2,3-
dichlorophenylcarbamoyl group, 3,4-
dichlorophenylcarbamoyl group, 3,5-
dichlorophenylcarbamoyl group, 2,4-
dichlorophenylcarbamoyl group, 2,6-
dichlorophenylcarbamoyl group, 3,4,5-
trifluorophenylcarbamoyl group, 2,3,4,5,6-
pentafluorophenylcarbamoyl group, 3,4,5-
trichlorophenylcarbamoyl group, 2,4,6-
trifluorophenylcarbamoyl group, 2,4,6-
trichlorophenylcarbamoyl group, 2-methylphenylcarbamoyl group, 3-methylphenylcarbamoyl group, 4-
methylphenylcarbamoyl group, 2-methyl-3-
chlorophenylcarbamoyl group, 3-methyl-4-
chlorophenylcarbamoyl group, 2-chloro-4-
methylphenylcarbamoyl group, 2-methyl-3-
fluorophenylcarbamoyl group, 2-
trifluoromethylphenylcarbamoyl group, 3-
trifluoromethylphenylcarbamoyl group, N-methyl-N-
phenylcarbamoyl group, N-(2-fluorophenyl)-N-
methylcarbamoyl group, N-(3-fluorophenyl)-N-
methylcarbamoyl group, N-(4-fluorophenyl)-N-
methylcarbamoyl group, N-(2-chlorophenyl)-N-
methylcarbamoyl group, N-(3-chlorophenyl)-N-
methylcarbamoyl group, N-(4-chlorophenyl)-N-
methylcarbamoyl group, N-(4-bromophenyl)-N-
methylcarbamoyl group, N-(2-iodophenyl)-N-
methylcarbamoyl group, N-(3-iodophenyl)-N-
methylcarbamoyl group, N-(4-iodophenyl)-N-
methylcarbamoyl group, N-(2,3-difluorophenyl)-N-
methylcarbamoyl group, N-(3,4-difluorophenyl)-N-
methylcarbamoyl group, N-(3,5-difluorophenyl)-N-
methylcarbamoyl group, N-(2,4-difluorophenyl)-N-
methylcarbamoyl group, N-(2,6-difluorophenyl)-N-
methylcarbamoyl group, N-(2,3-dichlorophenyl)-N-
methylcarbamoyl group, N-(3,4-dichlorophenyl)-N-
methylcarbamoyl group, N-(3,5-dichlorophenyl)-N-
methylcarbamoyl group, N-(2,4-dichlorophenyl)-N-
methylcarbamoyl group, N-(2,6-dichlorophenyl)-N-
methylcarbamoyl group, N-(3,4,5-trifluorophenyl)-N-
methylcarbamoyl group, N-(3,4,5-trichlorophenyl)-N-
methylcarbamoyl group, N-(2,4,6-trifluorophenyl)-N-
methylcarbamoyl group, N-(2,4,6-trichlorophenyl)-N-
methylcarbamoyl group, N-(2-methylphenyl)-N-
methylcarbamoyl group, N-(3-methylphenyl)-N-
methylcarbamoyl group, N-(4-methylphenyl)-N-
methylcarbamoyl group, N-(2-methyl-3-chlorophenyl)-N-
methylcarbamoyl group, N-(3-methyl-4-chlorophenyl)-N-
methylcarbamoyl group, N-(2-chloro-4-methylphenyl)-N-
methylcarbamoyl group, N-(2-methyl-3-fluorophenyl)-N-
methylcarbamoyl group, N-(2-trifluoromethylphenyl)-N-
methylcarbamoyl group, N-(4-trifluoromethylphenyl)-N-
methylcarbamoyl group, N-benzyl-N-phenylcarbamoyl group,
N-benzyl-N-(2-fluorophenyl)carbamoyl group, N-benzyl-N-(3-fluorophenyl)carbamoyl group, N-benzyl-N-(4-
fluorophenyl)carbamoyl group, N-benzyl-N-(2-
chlorophenyl)carbamoyl group, N-benzyl-N-(3-
chlorophenyl)carbamoyl group, N-benzyl-N-(4-
chlorophenyl)carbamoyl group, N-benzyl-N-(2-
bromophenyl)carbamoyl group, N-benzyl-N-(3-
bromophenyl)carbamoyl group, N-benzyl-N-(4-
bromophenyl)carbamoyl group, N-benzyl-N-(2-
iodophenyl)carbamoyl group, N-benzyl-N-(3-
iodophenyl)carbamoyl group, N-benzyl-N-(4-
iodophenyl)carbamoyl group, N-benzyl-N-(2,3-
difluorophenyl)carbamoyl group, N-benzyl-N-(3,4-
difluorophenyl)carbamoyl group, N-benzyl-N-(3,5-
difluorophenyl)carbamoyl group, N-benzyl-N-(2,4-
difluorophenyl)carbamoyl group, N-benzyl-N-(2,6-
difluorophenyl)carbamoyl group, N-benzyl-N-(2,3-
dichlorophenyl)carbamoyl group, N-benzyl-N-(3,4-
dichlorophenyl)carbamoyl group, N-benzyl-N-(3,5-
dichlorophenyl)carbamoyl group, N-benzyl-N-(2,4-
dichlorophenyl)carbamoyl group.
dichlorophenyl)carbamoyl group, N-benzyl-N-(2,6-
dichlorophenyl)carbamoyl group, N-benzyl-N-(3,4,5-
trifluorophenyl)carbamoyl group, N-benzyl-N-(3,4,5-
trichlorophenyl)carbamoyl group, N-benzyl-N-(2,4,6-
trifluorophenyl)carbamoyl group, N-benzyl-N-(2,4,6-
trichlorophenyl)carbamoyl group, N-benzyl-N-(2-
methylphenyl)carbamoyl group, N-benzyl-N-(3-
methylphenyl)carbamoyl group, N-benzyl-N-(4-
methylphenyl)carbamoyl group, N-benzyl-N-(2-methyl-3-
chlorophenyl)carbamoyl group, N-benzyl-N-(3-methyl-4-
chlorophenyl)carbamoyl group, N-benzyl-N-(2-chloro-4-
methylphenyl)carbamoyl group, N-benzyl-N-(2-methyl-3-
fluorophenyl)carbamoyl group, N-benzyl-N-(2-
trifluoromethylphenyl)carbamoyl group, N-benzyl-N-(3-
trifluoromethylphenyl)carbamoyl group, N-benzyl-N-(4-
trifluoromethylphenyl)carbamoyl group, 2-
pentafluoroethylphenylcarbamoyl group, 3-
pentafluoroethylphenylcarbamoyl group, 4-
pentafluoroethylphenylcarbamoyl group, 2-
isopropylphenylcarbamoyl group, 3-
isopropylphenylcarbamoyl group, 4-
isopropylphenylcarbamoyl group, 2-tert-
butylphenylcarbamoyl group, 3-tert-butylphenylcarbamoyl 
group, 4-tert-butylphenylcarbamoyl group, 2-sec-
butyphenylcarbamoyl group, 3-sec-butyphenylcarbamoyl 
group, 4-sec-butyphenylcarbamoyl group, 2-n-
heptafluoropropylphenylcarbamoyl group, 3-n-
heptafluoropropylphenylcarbamoyl group, 4-n-

heptafluoropropylphenylcarbamoyl group, 4-
pentylphenylcarbamoyl group, 4-hexylphenylcarbamoyl
group, 2,4-dimethylphenylcarbamoyl group, 2,4,6-
trimethylphenylcarbamoyl group, 3,4-
dimethoxyphenylcarbamoyl group, 3,4,5-
trimethoxyphenylcarbamoyl group, 2-
methoxyphenylcarbamoyl group, 3-methoxyphenylcarbamoyl
group, 4-methoxyphenylcarbamoyl group, 2-methoxy-3-
chlorophenylcarbamoyl group, 2-fluoro-3-
methoxyphenylcarbamoyl group, 2-fluoro-4-
methoxyphenylcarbamoyl group, 2,6-
dimethoxyphenylcarbamoyl group, 2,3,4-
trifluorophenylcarbamoyl group, 3,4,5-
trifluorophenylcarbamoyl group, 2-
trifluoronemethoxyphenylcarbamoyl group, 3-
trifluoronemethoxyphenylcarbamoyl group, 4-
trifluoronemethoxyphenylcarbamoyl group, 2-
pentafluoroethoxyphenylcarbamoyl group, 3-
pentafluoroethoxyphenylcarbamoyl group, 4-
pentafluoroethoxyphenylcarbamoyl group, 2-
isopropoxyphenylcarbamoyl group, 3-
isopropoxyphenylcarbamoyl group, 4-
isopropoxyphenylcarbamoyl group, 2-tert-
butoxyphenylcarbamoyl group, 3-tert-butoxyphenylcarbamoyl
group, 4-tert-butoxyphenylcarbamoyl group, 2-sec-
butoxyphenylcarbamoyl group, 3-sec-butoxyphenylcarbamoyl
group, 4-sec-butoxyphenylcarbamoyl group, 2-n-
heptafluoropropyxyphenylcarbamoyl group, 3-n-
heptafluoropropoxyphenylcarbamoyl group, 4-n-
heptafluoropropoxyphenylcarbamoyl group, 4-n-
pentyloxyphenylcarbamoyl group, 4-n-
hexyloxyphenylcarbamoyl group or the like.

A benzothiazolyl group (wherein, on the
benzothiazole ring, 1 to 3 C1-C6 alkyl groups may be
substituted) includes a benzothiazolyl group (wherein,
on the benzothiazole ring, at least one C1-C6 alkyl
group may be substituted), for example, a (2-, 4-, 5-,
6- or 7-) benzothiazolyl group, 2-methyl-5-
benzothiazolyl group, 4-ethyl-6-benzothiazolyl group,
5-propyl-7-benzothiazolyl group, 6-tert-butyl-2-
benzothiazolyl group, 7-pentyl-4-benzothiazolyl group,
2-hexyl-5-benzothiazolyl group, 2,4-dimethyl-5-
benzothiazolyl group, 2,4,6-trimethyl-7-benzothiazolyl
group or the like.

A 2,3-dihydro-1H-indenyl group (wherein, on
the 2,3-dihydro-1H-indene ring, at least one oxo group
may be substituted) includes a 2,3-dihydro-1H-indenyl

group (wherein, on the 2,3-dihydro-1H-indene ring, 1 or
2 oxo groups may be substituted), for example, a 2,3-
dihydro-1H-indenyl group, 1-oxo-2,3-dihydro-1H-indenyl
group, 1,3-dioxo-2,3-dihydro-1H-indenyl group or the
like.

A phenyl C2-C6 alkenyl group (wherein, on the
phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be substituted) is a group composed of 1 or 2 phenyl groups unsubstituted or substituted by 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group and an alkenyl group containing 2 to 6 carbon atoms and having 1 to 3 double bonds. The phenyl C2-C6 alkenyl group includes both trans and cis forms. Such a phenyl C2-C6 alkenyl group includes a 2-phenylvinyl group, 3-phenyl-2-propenyl group (common name: cinnamyl group), 3,3-diphenyl-2-propenyl group, 3-phenyl-2-methyl-2-propenyl group, 4-phenyl-2-butene group, 4,4-diphenyl-2-butene group, 4-phenyl-3-butene group, 4-phenyl-1,3-butadienyl group, 5-phenyl-1,3,5-hexatrienyl group, 5,5-diphenyl-3-pentenyl group, 5,6-diphenyl-2-hexenyl group, 6-phenyl-1,3-hexadienyl group, 3-(2-fluorophenyl)-2-propenyl group, 3-(3-fluorophenyl)-2-propenyl group, 3-(4-fluorophenyl)-2-propenyl group, 3-(2,3-difluorophenyl)-2-propenyl group, 3-(2,3,4,5,6-pentafluorophenyl)-2-propenyl group, 3-(2,4-difluorophenyl)-2-propenyl group, 3-(3,4-difluorophenyl)-2-propenyl group, 3-(3,5-difluorophenyl)-2-propenyl group, 3-(2-chlorophenyl)-2-propenyl group, 3-(3-chlorophenyl)-2-propenyl group, 3-(4-chlorophenyl)-2-propenyl group, 3-(2,3-dichlorophenyl)-2-propenyl group, 3-(2,4-
dichlorophenyl)-2-propenyl group, 3-(3,4-
dichlorophenyl)-2-propenyl group, 3-(3,5-
dichlorophenyl)-2-propenyl group, 3-(2,6-
dichlorophenyl)-2-propenyl group, 3-(3,6-
dichlorophenyl)-2-propenyl group, 3-(3,5,6-
trichlorophenyl)-2-propenyl group, 3-(2,4,5-
trichlorophenyl)-2-propenyl group, 3-(2-bromophenyl)-2-
propenyl group, 3-(3-bromophenyl)-2-propenyl group, 3-
(4-bromophenyl)-2-propenyl group, 3-(2-methylphenyl)-2-
propenyl group, 3-(3-methylphenyl)-2-propenyl group, 3-
(4-methylphenyl)-2-propenyl group, 3-(2-
trifluoromethylphenyl)-2-propenyl group, 3-(2-fluoro-4-
bromophenyl)-2-propenyl group, 3-(4-chloro-3-
fluorophenyl)-2-propenyl group, 3-(2,3,4-
trichlorophenyl)-2-propenyl group, 3-(2,4,6-
trichlorophenyl)-2-propenyl group, 3-(4-ethylphenyl)-2-
propenyl group, 3-(4-n-hexylphenyl)-2-propenyl group,
3-(4-isopropylphenyl)-2-propenyl group, 3-(4-n-
butylphenyl)-2-propenyl group, 3-(2,4-dimethylphenyl)-
2-propenyl group, 3-(2,3-dimethylphenyl)-2-propenyl
group, 3-(2,6-dimethylphenyl)-2-propenyl group, 3-(3,5-
dimethylphenyl)-2-propenyl group, 3-(2,5-
dimethylphenyl)-2-propenyl group, 3-(2,4,6-
trimethylphenyl)-2-propenyl group, 3-(3,5-
ditrifluoromethylphenyl)-2-propenyl group, 3-(4-n-
butoxyphenyl)-2-propenyl group, 3-(2,4-
dimethoxyphenyl)-2-propenyl group, 3-(2,3-
dimethoxyphenyl)-2-propenyl group, 3-(2,6-
dimethoxyphenyl)-2-propenyl group, 3-(3,5-
dimethoxyphenyl)-2-propenyl group, 3-(2,5-
dimethoxyphenyl)-2-propenyl group, 3-(3,5-
ditrifluoromethoxyphenyl)-2-propenyl group, 3-(3-
chloro-4-methoxyphenyl)-2-propenyl group, 3-(2-chloro-
4-trifluoromethoxyphenyl)-2-propenyl group, 3-(3-
methyl-4-fluorophenyl)-2-propenyl group, 3-(2-methyl-4-
fluorophenyl)-2-propenyl group, 3-(2-trifluoromethyl-4-
fluorophenyl)-2-propenyl group, 3-(3-trifluoromethyl-2-
fluorophenyl)-2-propenyl group, 3-(4-bromo-3-
trifluoromethylphenyl)-2-propenyl group, 3-(4-chloro-3-
trifluoromethylphenyl)-2-propenyl group, 3-(3-
trifluoromethylphenyl)-2-propenyl group, 3-(2-
trifluoromethylphenyl)-2-propenyl group, 3-(4-
trifluoromethylphenyl)-2-propenyl group, 3-(2-
trifluoromethoxyphenyl)-2-propenyl group, 3-(3-
trifluoromethoxyphenyl)-2-propenyl group, 3-(4-
trifluoromethoxyphenyl)-2-propenyl group, 3-(2-
methoxyphenyl)-2-propenyl group, 3-(3-methoxyphenyl)-2-
propenyl group, 3-(4-methoxyphenyl)-2-propenyl group,
3-(4-n-hexyloxyphenyl)-2-propenyl group, 3-(3,4-
dimethoxyphenyl)-2-propenyl group, 3-(3,5-
dimethoxyphenyl)-2-propenyl group, 4-(4-chlorophenyl)-
2-buteryl group, 4-(4-chlorophenyl)-3-buteryl group, 5-
(4-chlorophenyl)-2-pentenyl group, 5-(4-chlorophenyl)-
4-pentenyl group, 5-(4-chlorophenyl)-3-pentenyl group,
6-(4-chlorophenyl)-5-hexenyl group, 6-(4-chlorophenyl)-
4-hexenyl group, 6-(4-chlorophenyl)-3-hexenyl group, 6-
(4-chlorophenyl)-3-hexenyl group or the like.

A phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a Cl-C4 alkylendioxy group, a cyano group, a nitro group, an amino group which may have a Cl-C6 alkyl group as a substituent, an amino substituted sulfonyl group which may have a Cl-C6 alkyl group as a substituent, a Cl-C6 alkoxy carbonyl group, a Cl-C6 alkylthio group, a phenoxy group, a phenyl Cl-C6 alkoxy group, a pyrrolidinyl group (wherein, on the pyrrolidine ring, at least one oxo group may be substituted), an imidazolyl group, an isooxazolyl group, an oxazolyl group, a phenyl Cl-C6 alkyl group, a phenyl group, an amino Cl-C6 alkyl group which may have a Cl-C6 alkyl group as a substituent, a pyrrolidinyl Cl-C6 alkoxy group, a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) includes, in addition to a phenyl group as described above (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), a phenyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a Cl-C4 alkylendioxy group as described above, a cyano group, a nitro group, an amino group which may have 1
or 2 Cl-C6 alkyl groups as a substituent as described later, an amino substituted sulfonyl group which may have 1 or 2 Cl-C6 alkyl groups as a substituent as described above, a Cl-C6 alkoxy carbonyl group as described later, a Cl-C6 alkylthio group as described later, a phenoxy group, a phenyl Cl-C6 alkoxy group as described above, a pyrrolidinyl group as described above (wherein, or the pyrrolidine ring, at least one oxo group may be substituted), an imidazolyl group, an isooxazolyl group, an oxazolyl group, a phenyl Cl-C6 alkyl group as described above, a phenyl group, an amino Cl-C6 alkyl group which may have a Cl-C6 alkyl group as a substituent as described later, a pyrrolidinyl Cl-C6 alkoxy group as described above, a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), for example, a 4-cyanophenyl group, 3-cyanophenyl group, 2-cyanophenyl group, 3,4-dicyanophenyl group, 2,4,6-tricyanophenyl group, 4-nitrophenyl group, 3-nitrophenyl group, 2-nitrophenyl group, 3,4-dinitrophenyl group, 2,4,6-trinitrophenyl group, 4-dimethylaminophenyl group, 3-methylaminophenyl group, 2-N-ethyl-N-methylaminophenyl group, 2,4-di(methylamino)phenyl group, 2,4,6-tri(methylamino)phenyl group, 4-dimethylamino sulfonylphenyl group, 3-methylamino sulfonylphenyl group, 2-N-ethyl-N-
methylaminosulfonylethyl group, 2,4-
di(methylaminosulfonylethyl)phenyl group, 2,4,6-
tri(methylaminosulfonylethyl)phenyl group, 4-
ethoxycarbonylphenyl group, 4-ethoxycarbonylphenyl
group, 3-methoxycarbonylphenyl group, 2-
propoxycarbonylphenyl group, 2,4-diethoxycarbonylphenyl
group, 2,4,6-triethoxycarbonylphenyl group, 4-
ethylthiophenyl group, 3-ethylthiophenyl group, 2-
ethylthiophenyl group, 3,4-dimethylthiophenyl group,
2,4,6-trimethylthiophenyl group, 3,4-
ethylenedioxyphenyl group, 3,4-methylenedioxyphenyl
group, 4-diisopropylaminomethylphenyl group, 3-
methylaminomethylphenyl group, 2-ethylaminomethylphenyl
group, 2,4-dimethylyaminomethylphenyl group, 2,4,6-
triethylaminomethylphenyl group, 4-phenoxyphenyl group,
3-phenoxyphenyl group, 2-phenoxyphenyl group, 2,4-
diphenoxophenyl group, 3,4,5-triphenoxophenyl group, 4-
benzylkoxyphenyl group, 3-benzylkoxyphenyl group, 2-
benzylkoxyphenyl group, 2,4-dibenzylkoxyphenyl group,
2,4,6-tribenzylkoxyphenyl group, 4-(2-oxc-1-
pyrrolidinyl)phenyl group, 4-(5-oxazolyl)phenyl group,
4-(5-isoaxazolyl)phenyl group, 4-(1-imidazolyl)phenyl
group, 4-benzylphenyl group, 3-benzylphenyl group, 2-
benzylphenyl group, 3,4-dibenzylphenyl group, 2,4,6-
tribenzylphenyl group, 4-biphenyl group, 3-biphenyl
group, 2-biphenyl group, 2,4-diphenylyphenyl group,
2,4,6-triphenylyphenyl group, 2-(2-imidazolyl)-4-
phenoxyphenyl group, 3-(2-oxazolyl)-4-benzylkoxyphenyl
group, 4-(3-isooxazolyl)-2-benzylphenyl or the like.

A phenyl group [wherein, on the phenyl ring, a halogen may be substituted] includes a phenyl group which may be substituted by 1 to 5 halogen atoms on the phenyl ring, for example, a phenyl group, 2-fluorophenyl group, 3-fluorophenyl group, 4-fluorophenyl group, 2-chlorophenyl group, 3-chlorophenyl group, 4-chlorophenyl group, 2-bromophenyl group, 3-bromophenyl group, 4-bromophenyl group, 2-iodophenyl group, 3-iodophenyl group, 4-iodophenyl group, 2,3-difluorophenyl group, 3,4-difluorophenyl group, 3,5-difluorophenyl group, 2,4-difluorophenyl group, 2,6-difluorophenyl group, 2,3-dichlorophenyl group, 3,4-dichlorophenyl group, 3,5-dichlorophenyl group, 2,4-dichlorophenyl group, 2,6-dichlorophenyl group, 3,4,5-trifluorophenyl group, 3,4,5-trichlorophenyl group, 2,4,6-trifluorophenyl group, 2,4,6-trichlorophenyl group, 2-fluoro-4-bromophenyl group, 4-chloro-3-fluorophenyl group, 2,3,4-trichlorophenyl group, 3,4,5-trifluorophenyl group, 2,4,6-tribromophenyl group, 2,3,4,5,6-pentafluorophenyl group or the like.

A phenyl C1-C6 alkoxy substituted C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a C1-C4 alkylendioxy group, a halogen atom, a cyano group, a phenyl group, a phenyl C1-C6 alkoxy group, a phenyl C2-C6 alkenyl group, a phenoxy group, a C1-C6 alkylthio
group, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) includes, in addition to a phenyl C1-C6 alkoxy substituted C1-C6 alkyl group as described above (wherein, on the phenyl group, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a phenyl C1-C6 alkoxy substituted C1-C6 alkyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents (preferably 1 or 2 substituents if the substituent is a C1-C4 alkylenedioxy group) selected from the group consisting of a straight or branched alkylenedioxy group containing 1 to 4 carbon atoms on the alkyl part as described above or later, a halogen atom, a cyano group, a phenyl group, a phenylalkoxy group having a straight or branched alkoxy containing 1 to 6 carbon atoms on the alkoxy part, a phenylethenyl group which is composed of a alkenyl group containing 2 to 6 carbon atoms and having at least 1 to 3 double bonds and includes both trans and cis forms, a phenoxy group, a straight or branched C1-C6 alkylthio group containing 1 to 6 carbon atoms, a halogen substituted or unsubstituted straight or branched C1-C6 alkyl group containing 1 to 6 carbon atoms and a halogen substituted or unsubstituted straight or branched C1-C6
alkoxy group containing 1 to 6 carbon atoms may be substituted), for example, a 4-cyanophenylmethoxymethyl group, 3-cyanophenylmethoxymethyl group, 2-cyanophenylmethoxymethyl group, 2,4-dicyanophenylmethoxymethyl group, 2,4,8-tricyanophenylmethoxymethyl group, 4-biphenylmethoxymethyl group, 3-biphenylmethoxymethyl group, 2-biphenylmethoxymethyl group, 2,4-diphenylphenyliethoxymethyl, 2,4,6-triphenylphenyliethoxymethyl group, 4-phenoxyphenyliethoxymethyl group, 3-phenoxyphenyliethoxymethyl group, 2-phenoxyphenyliethoxymethyl group, 3,4-diphenoxypyphenyliethoxymethyl group, 3,4,5-triphenoxypyphenyliethoxymethyl group, 4-methylthiophenyliethoxymethyl group, 3-ethylthiophenyliethoxymethyl group, 2-methylthiophenyliethoxymethyl group, 2,4-dimethylthiophenyliethoxymethyl group, 2,4,6-trimethylthiophenyliethoxymethyl group, 4-cyano-2-phenylphenyliethoxymethyl group, 3-phenoxy-4-methylthiophenyliethoxymethyl group, 3-trifluoromethyl-4-methylthiophenyliethoxymethyl group, 3-trifluoromethoxy-2-phenoxyphenyliethoxymethyl group, 25 3,4-methylenedioxyphenyliethoxymethyl group, 4-benzyloxyphenyliethoxymethyl group, 3,4-dibenzyloxyphenyliethoxymethyl group, 2,4,6-tribenzyloxyphenyliethoxymethyl group, 3-
benzyloxyphenylmethoxymethyl group, 2-
benzyloxyphenylmethoxymethyl group, 4-
styrylphenylmethoxymethyl group, 3-
styrylphenylmethoxymethyl group, 2-
5 styrylphenylmethoxymethyl group, 2,4-
distyrylphenylmethoxymethyl group, 2,4,6-
tristyrlylphenylmethoxymethyl group or the like.

A phenyl C1-C6 alkoxy group (wherein, on the
phenyl ring, at least one selected from the group
consisting of a cyano group, a phenyl group, a C1-C6
alkoxycarbonyl group, a phenoxy group, a C1-C6
alkylthio group, a halogen atom, a halogen substituted
or unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted) includes, in addition to a phenyl C1-C6
alkoxy group as described above (wherein, on the phenyl
ring, at least one selected from the group consisting
of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted), a C1-C6 alkoxy group substituted by 1 or
2 phenyl groups (wherein, on the phenyl ring, 1 to 5,
preferably 1 to 3 substituents selected from the group
consisting of a cyano group, a phenyl group, a C1-C6
alkoxycarbonyl group as described above, a phenoxy
group, a C1-C6 alkylthio group as described above, a
halogen atom, a halogen substituted or unsubstituted
C1-C6 alkyl group and a halogen substituted or
unsubstituted C1-C6 alkoxy group may be substituted), for example, a 4-cyanophenylmethoxy group, 3-
cyanobenzyloxy group, 2-cyanobenzyloxy group, 2,4-
dicyanobenzyloxy group, 2,3,4-tricyanobenzyloxy group, 4-
biphenylmethoxy group, 3-biphenylmethoxy group, 2-
biphenylmethoxy group, 2,4-diphenylbenzyloxy group, 2,4,6-triphenylbenzyloxy group, 4-
methoxycarbonylbenzyloxy group, 3-
ethoxycarbonylbenzyloxy group, 2-
methoxycarbonylbenzyloxy group, 3,4-
diethoxycarbonylbenzyloxy group, 3,4,5-
trimethoxycarbonylbenzyloxy group, 3-phenoxybenzyloxy
group, 2-phenoxybenzyloxy group, 4-phenoxybenzyloxy
group, 2,4-diphenoxycarbonylbenzyloxy group, 2,4,6-
tri phenoxybenzyloxy group, 4-methylthiobenzyloxy group,
3-methylthiobenzyloxy group, 2-methylthiobenzyloxy
group, 3,4-dimethylthiobenzyloxy group, 2,5,6-
trimethylthiobenzyloxy group, 3-cyano-4-bibenzyl
group, 4-ethoxycarbonyl-3-phenoxybenzyloxy group, 3-
methylthio-4-ethylbenzyloxy group, di(4-
trifluoromethoxyphenyl)methoxy group, di(4-
trifluoromethylphenyl)methoxy group, di(4-
chlorophenyl)methoxy group, di(3-methoxyphenyl)methoxy

group, di(2-methylphenyl)methoxy group, di(2,4-
dimethoxyphenyl)methoxy group, di(3,4-
dimethylphenyl)methoxy group, di(2,4,6-
trimethoxyphenyl)methoxy group, di(3,4,5-
trifluoromethylphenyl)methoxy group, di(2,4,6-
trifluorophenyl)methoxy group, 1-(4-
trifluoronethoxyphenyl)-1-(2,4-dichlorophenyl)methoxy
or the like.

A phenyl C2-C6 alkenyloxy group (wherein, on
the phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted) includes a group composed of a phenyl
group unsubstituted or substituted by 1 to 5,
preferably 1 to 3 substituents selected from the group
consisting of a halogen atom, a halogen C1-C6 alkyl
group and a halogen substituted or unsubstituted C1-C6
alkoxy group and an alkenyl group containing 2 to 6
carbon atoms and having at least 1 to 3 double bonds.
The phenyl C2-C6 alkenyloxy group includes both trans
and cis forms. Such a phenyl C2-C6 alkenyloxy group
includes a 2-phenylvinyloxy group, 3-phenyl-2-
propenyloxy group (common name: cinnamylloxy group), 4-
phenyl-2-butenyloxy group, 4-phenyl-3-butenyloxy group,
4-phenyl-1,3-buta dienyloxy group, 5-phenyl-1,3,5-
hexatrienyloxy group, 3-(2-fluorophenyl)-2-propenyloxy
group, 3-(3-fluorophenyl)-2-propenyloxy group, 3-(4-
difluorophenyl)-2-propenyloxy group, 3-(2,3-
difluorophenyl)-2-propenyloxy group, 3-(2,3,4,5,6-
pentafluorophenyl)-2-propenyloxy group, 3-(2,4-
difluorophenyl)-2-propenyloxy group, 3-(3,4-
difluorophenyl)-2-propenyloxy group, 3-(3,5-
difluorophenyl)-2-propenyloxy group, 3-(2-chlorophenyl)-2-propenyloxy group, 3-(3-chlorophenyl)-2-propenyloxy group, 3-(4-chlorophenyl)-2-propenyloxy group, 3-(2,3-dichlorophenyl)-2-propenyloxy group, 3-(2,4-dichlorophenyl)-2-propenyloxy group, 3-(3,4-dichlorophenyl)-2-propenyloxy group, 3-(3,5-dichlorophenyl)-2-propenyloxy group, 3-(2-bromophenyl)-2-propenyloxy group, 3-(3-bromophenyl)-2-propenyloxy group, 3-(4-bromophenyl)-2-propenyloxy group, 3-(2-methylphenyl)-2-propenyloxy group, 3-(3-methylphenyl)-2-propenyloxy group, 3-(4-methylphenyl)-2-propenyloxy group, 3-(2-trifluoromethylphenyl)-2-propenyloxy group, 3-(2-fluoro-4-bromophenyl)-2-propenyloxy group, 3-(4-chloro-3-fluorophenyl)-2-propenyloxy group, 3-(2,3,4-trichlorophenyl)-2-propenyloxy group, 3-(2,4,6-trichlorophenyl)-2-propenyloxy group, 3-(4-isopropylphenyl)-2-propenyloxy group, 3-(4-n-butylphenyl)-2-propenyloxy group, 3-(2,4-dimethylphenyl)-2-propenyloxy group, 3-(2,3,4-dimethylphenyl)-2-propenyloxy group, 3-(2,6-dimethylphenyl)-2-propenyloxy group, 3-(3,5-dimethylphenyl)-2-propenyloxy group, 3-(2,5-dimethylphenyl)-2-propenyloxy group, 3-(2,4,6-trimethylphenyl)-2-propenyloxy group, 3-(3,5,25-ditrifluoromethylphenyl)-2-propenyloxy group, 3-(4-n-butoxyphenyl)-2-propenyloxy group, 3-(2,4-dimethoxyphenyl)-2-propenyloxy group, 3-(2,3-dimethoxyphenyl)-2-propenyloxy group, 3-(2,6-
dimethoxyphenyl)-2-propenyloxy group, 3-(3,5-dimethoxyphenyl)-2-propenyloxy group, 3-(2,5-dimethoxyphenyl)-2-propenyloxy group, 3-(3,5-difluoromethoxyphenyl)-2-propenyloxy group, 3-(3-chloro-4-methoxyphenyl)-2-propenyloxy group, 3-(2-chloro-4-trifluoromethoxyphenyl)-2-propenyloxy group, 3-(3-methyl-4-fluorophenyl)-2-propenyloxy group, 3-(4-bromo-3-trifluoromethylphenyl)-2-propenyloxy group, 3-(3-trifluoromethylphenyl)-2-propenyloxy group, 3-(4-trifluoromethylphenyl)-2-propenyloxy group, 3-(2-trifluoromethoxyphenyl)-2-propenyloxy group, 3-(3-trifluoromethoxyphenyl)-2-propenyloxy group, 3-(4-trifluoromethoxyphenyl)-2-propenyloxy group, 3-(3-methoxyphenyl)2-propenyloxy group, 3-(4-methoxyphenyl)-2-propenyloxy group, 3-(3,4-dimethoxyphenyl)-2-propenyloxy group, 3-(3,5-dimethoxyphenyl)-2-propenyloxy group, 4-(4-chlorophenyl)-2-butenyloxy group, 5-(4-chlorophenyl)-2-pentenyloxy group, 4-(4-chlorophenyl)-3-butenyloxy group, 5-(4-chlorophenyl)-4-pentenyloxy group, 5-(4-chlorophenyl)-3-pentenyloxy group, 6-(4-chlorophenyl)-5-hexenyloxy group, 6-(4-chlorophenyl)-4-hexenyloxy group, 6-(4-chlorophenyl)-3-hexenyloxy group, 6-(4-chlorophenyl)-3-hexenyloxy group or the like.

A C1-C6 alkyl group which may have a hydroxide group as a substituent includes; in addition to a C1-C6 alkyl group as described above, a C1-C6
straight or branched alkyl group which may have 1 to 3 hydroxide groups, for example, a hydroxymethyl group, 2-hydroxyethyl group, 1-hydroxyethyl group, 3-hydroxypropyl group, 2,3-dihydroxypropyl group, 4-hydroxybutyl group, 3,4-dihydroxybutyl group, 1,1-dimethyl-2-hydroxyethyl group, 5-hydroxypentyl group, 6-hydroxyhexyl group, 2-methyl-3-hydroxypropyl group, 2,3,4-trihydroxybutyl group or the like.

A C1-C6 alkanoyl group includes a group derived from an aliphatic carboxylic acid containing 1 to 6 carbon atoms, examples of which include a formyl group, acetyl group, propionyl group, butyryl group, pentanoyl group, hexanoyl group or the like.

A phenyl C1-C6 alkoxy carbonyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) is a group composed of a phenyl C1-C6 alkoxy group which may be substituted by 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group as defined above and a carbonyl group, examples of which include a benzyloxy carbonyl group, 2-phenylethoxy carbonyl group, 3-phenylpropoxycarbonyl group, 2-phenylpropoxycarbonyl group, 4-
phenylbutoxycarbonyl group, 5-phenylpentoxycarbonyl group, 4-phenylpentoxycarbonyl group, 6-phenylhexyloxyxycarbonyl group, 2-fluorobenzylxloxyxycarbonyl group, 3-fluorobenzylxloxyxycarbonyl group, 4-

fluorobenzylxloxyxycarbonyl group, 2-(2-fluorophenyl)ethoxycarbonyl group, 2-(3-fluorophenyl)ethoxycarbonyl group, 2-(4-fluorophenyl)ethoxycarbonyl group, 2-chlorobenzylxloxyxycarbonyl group, 3-

chlorobenzylxloxyxycarbonyl group, 4-

chlorobenzylxloxyxycarbonyl group, 2-fluoro-4-bromobenzylxloxyxycarbonyl group, 4-chloro-3-fluorobenzylxloxyxycarbonyl group, 2,3,4-trichlorobenzylxloxyxycarbonyl group, 3,4,5-

trifluorobenzylxloxyxycarbonyl group, 2,3,4,5,6-pentafluorobenzylxloxyxycarbonyl group, 2,4,6-trichlorobenzylxloxyxycarbonyl group, 4-

isopropylbenzyloxyxycarbonyl group, 4-n-butylbenzyloxyxycarbonyl group, 4-methylbenzyloxyxycarbonyl group, 2-methylbenzyloxyxycarbonyl group, 3-methylbenzyloxyxycarbonyl group, 2,4-

dimethylbenzyloxyxycarbonyl group, 2,3-

dimethylbenzyloxyxycarbonyl group, 2,6-

dimethylbenzyloxyxycarbonyl group, 3,5-

dimethylbenzyloxyxycarbonyl group, 2,5-

dimethylbenzyloxyxycarbonyl group, 2,4,6-

dimethylbenzyloxyxycarbonyl group, 3,5-

ditrifluoromethylbenzyloxyxycarbonyl group, 4-
isopropoxybenzyloxy carbonyl group, 4-n-butoxybenzyloxy carbonyl group, 4-methoxybenzyloxy carbonyl group, 2-methoxybenzyloxy carbonyl group, 3-methoxybenzyloxy carbonyl group, 2,4-dimethoxybenzyloxy carbonyl group, 2,3-dimethoxybenzyloxy carbonyl group, 2,6-dimethoxybenzyloxy carbonyl group, 3,5-dimethoxybenzyloxy carbonyl group, 2,5-dimethoxybenzyloxy carbonyl group, 2,4,6-trimethoxybenzyloxy carbonyl group, 3,5-ditrifluoromethoxybenzyloxy carbonyl group, 2-isopropoxybenzyloxy carbonyl group, 3-chloro-4-methoxybenzyloxy carbonyl group, 2-chloro-4-trifluoromethoxybenzyloxy carbonyl group, 3-methyl-4-fluorobenzyloxy carbonyl group, 4-bromo-3-trifluoromethylbenzyloxy carbonyl group, 2-(2-chlorophenyl)ethoxycarbonyl group, 2-(3-chlorophenyl)ethoxycarbonyl group, 2-(4-chlorophenyl)ethoxycarbonyl group, 2-trifluoromethylbenzyloxy carbonyl group, 3-trifluoromethylbenzyloxy carbonyl group, 4-trifluoromethylbenzyloxy carbonyl group, 2-trifluoromethoxybenzyloxy carbonyl group, 3-trifluoromethoxybenzyloxy carbonyl group, 4-trifluoromethoxybenzyloxy carbonyl group, 2-(2-trifluoromethylphenyl)ethoxycarbonyl group, 2-(3-trifluoromethylphenyl)ethoxycarbonyl group, 2-(4-
trifluoromethylphenyl)ethoxycarbonyl group, 2-(2-trifluoromethoxyphenyl)ethoxycarbonyl group, 2-(3-trifluoromethoxyphenyl)ethoxycarbonyl group, 2-(4-trifluoromethoxyphenyl)ethoxycarbonyl group, 3-(2-trifluoromethylphenyl)propoxycarbonyl group, 3-(3-trifluoromethylphenyl)propoxycarbonyl group, 3-(4-trifluoromethylphenyl)propoxycarbonyl group, 3-(2-trifluoromethoxyphenyl)propoxycarbonyl group, 3-(3-trifluoromethoxyphenyl)propoxycarbonyl group, 3-(4-trifluoromethoxyphenyl)propoxycarbonyl group, 4-(3-trifluoromethylphenyl)butoxycarbonyl group, 5-(4-trifluoromethylphenyl)pentoxy carbonyl group, 4-(4-trifluoromethoxyphenyl)pentoxy carbonyl group, 5-(3-trifluoromethylphenylhexyloxy carbonyl group, 6-(4-trifluoromethylphenyl)hexyloxy carbonyl group, 6-(4-trifluoromethoxyphenyl)hexyloxy carbonyl group or the like.

An amino group which may have a group selected from the group consisting of a C1-C6 alkanoyl group and a C1-C6 alkyl group as a substituent includes an amino group which may have 1 or 2 groups selected from the group consisting of a C1-C6 alkanoyl group and a C1-C6 alkyl group as a substituent, for example, an amino group, methylamino group, ethylamino group, n-propylamino group, isopropylamino group, n-butyramino group, tert-butyramino group, n-pentyramino group, n-hexylamino group, dimethylamino group, diethylamino group, di-n-propylamino group, di-n-butyramino group,
di-n-pentylamino group, di-n-hexylamino group, N-
methyl-N-ethylamino group, N-ethyl-N-n-propylamino
group, N-methyl-N-n-butylamino group, N-methyl-N-n-
hexylamino group, N-methyl-N-acetylamino group,
acetylamino group, formylamino group, n-propionylamino
group, n-butyrylamino group, isobutyrylamino group, n-
pentanoylamino group, n-hexanoylamino group, N-ethyl-N-
acetylamino group or the like.

A 1,2,3,4-tetrahydroquinolyl group (wherein,
on the 1,2,3,4-tetrahydroquinoline ring, at least one
oxo group may be substituted as a substituent) includes
a 1,2,3,4-tetrahydroquinolyl group (wherein, wherein,
on the 1,2,3,4-tetrahydroquinoline ring, 1 or 2 oxo
groups may be substituted as a substituent), for
example, a 1,2,3,4-tetrahydro-1-quinolyl group,
1,2,3,4-tetrahydro-2-quinolyl group, 1,2,3,4-
tetrahydro-3-quinolyl group, 1,2,3,4-tetrahydro-4-
quinolyl group, 1,2,3,4-tetrahydro-5-quinolyl group,
1,2,3,4-tetrahydro-6-quinolyl group, 1,2,3,4-
tetrahydro-7-quinolyl group, 1,2,3,4-tetrahydro-8-
quinolyl group, 2-oxo-1,2,3,4-tetrahydro-1-quinolyl
group, 4-oxo-1,2,3,4-tetrahydro-1-quinolyl group, 2,4-
dio xo-1,2,3,4-tetrahydro-1-quinolyl group, 2-oxo-
1,2,3,4-tetrahydro-6-quinolyl group, 2-oxo-1,2,3,4-
tetrahydro-4-quinolyl group, 2-oxo-1,2,3,4-tetrahydro-
7-quinolyl group, 2-oxo-1,2,3,4-tetrahydro-8-quinolyl
group, 2-oxo-1,2,3,4-tetrahydro-5-quinolyl group, 2-
oxo-1,2,3,4-tetrahydro-3-quinolyl group or the like.
A C1-C6 alkylsulfonyl group is a group composed of an alkyl group containing 1 to 6 carbon atoms and a sulfonyl group, examples of which include a methanesulfonyl group, ethanesulfonyl group, n-propanesulfonyl group and n-butanesulfonyl group, n-pentanesulfonyl group, n-hexanesulfonyl group or the like.

A C3-C8 cycloalkyl group is a three-membered, four-membered, five-membered, six-membered, seven-membered or eight-membered cyclic alkyl group containing 3 to 8 carbon atoms, examples of which include a cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group, 3,4-dimethylcyclopentyl group, 3,3-dimethylcyclohexyl group or the like.

A C1-C6 alkylthio group is a linear or branched alkylthio group containing 1 to 6 carbon atoms, examples of which include a methylthio group, ethylthio group, n-propylthio group, isopropylthio group, n-butylthio group, isobutylthio group, tert-butylthio group, sec-butylthio group, n-pentylthio group, neopentylthio group, n-hexylthio group, isohexylthio group, 3-methylpentylthio group or the like.

A phenylsulfonyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted)
is a phenylsulfonyl group unsubstituted or having 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, a halogen substituted or unsubstituted C1-C6 alkoxy group as defined above, examples of which include a phenylsulfonyl group, 2-fluorophenylsulfonyl group, 3-fluorophenylsulfonyl group, 4-fluorophenylsulfonyl group, 2-chlorophenylsulfonyl group, 3-chlorophenylsulfonyl group, 4-chlorophenylsulfonyl group, 2-bromophenylsulfonyl group, 3-bromophenylsulfonyl group, 4-bromophenylsulfonyl group, 2-iodophenylsulfonyl group, 3-iodophenylsulfonyl group, 4-iodophenylsulfonyl group, 2,3-difluorophenylsulfonyl group, 3,4-difluorophenylsulfonyl group, 3,5-difluorophenylsulfonyl group, 2,4-difluorophenylsulfonyl group, 2,6-difluorophenylsulfonyl group, 2,3-dichlorophenylsulfonyl group, 3,4-dichlorophenylsulfonyl group, 3,5-dichlorophenylsulfonyl group, 2,4-dichlorophenylsulfonyl group, 2,6-dichlorophenylsulfonyl group, 3,4,5-trifluorophenylsulfonyl group, 3,4,5-trichlorophenylsulfonyl group, 2,4,6-trifluorophenylsulfonyl group, 2,4,6-trichlorophenylsulfonyl group, 2-fluoro-4-bromophenylsulfonyl group, 4-chloro-3-
fluorophenylsulfonyl group, 2,3,4-
trichlorophenylsulfonyl group, 3,4,5-
trifluorophenylsulfonyl group, 2,3,4,5,6-
pentafluorophenylsulfonyl group, 2,4,6-
trimethylphenylsulfonyl group, 4-n-butylphenylsulfonyl
group, 2,4-dimethylphenylsulfonyl group, 2,3-
dimethylphenylsulfonyl group, 2,6-
dimethylphenylsulfonyl group, 3,5-
dimethylphenylsulfonyl group, 2,5-
dimethylphenylsulfonyl group, 3,5-
ditrifluoromethylphenylsulfonyl group, 4-n-
butoxyphenylsulfonyl group, 2,4-dimethoxyphenylsulfonyl
group, 2,3-dimethoxyphenylsulfonyl group, 2,6-
dimethoxyphenylsulfonyl group, 3,5-
dimethoxyphenylsulfonyl group, 2,5-
dimethoxyphenylsulfonyl group, 2,4,6-
trimethoxyphenylsulfonyl group, 3,5-
ditrifluoromethoxyphenylsulfonyl group, 3-chloro-4-
dimethoxyphenylsulfonyl group, 2-chloro-4-
trifluoromethoxyphenylsulfonyl group, 3-methyl-4-
fluorophenylsulfonyl group, 4-bromo-3-
trifluoromethylphenylsulfonyl group, 2-
methylphenylsulfonyl group, 3-methylphenylsulfonyl
group, 4-methylphenylsulfonyl group, 2-methyl-3-
chlorophenylsulfonyl group, 3-methyl-4-
chlorophenylsulfonyl group, 2-chloro-4-
methylphenylsulfonyl group, 2-methyl-3-
fluorophenylsulfonyl group, 2-
trifluoromethylphenylsulfonyl group, 3-
trifluoromethylphenylsulfonyl group, 4-
trifluoromethylphenylsulfonyl group, 2-
pentafluoroethylphenylsulfonyl group, 3-
pentafluoroethylphenylsulfonyl group, 4-
pentafluoroethylphenylsulfonyl group, 2-
isopropylphenylsulfonyl group, 3-
isopropylphenylsulfonyl group, 4-
isopropylphenylsulfonyl group, 2-tert-
butylphenylsulfonyl group, 3-tert-butylphenylsulfonyl
group, 4-tert-butylphenylsulfonyl group, 2-sec-
butylphenylsulfonyl group, 3-sec-butylphenylsulfonyl
group, 4-sec-butylphenylsulfonyl group, 2-n-
heptafluoropropylphenylsulfonyl group, 3-n-
heptafluoropropylphenylsulfonyl group, 4-n-
heptafluoropropylphenylsulfonyl group, 4-n-
pentylphenylsulfonyl group, 4-n-hexylphenylsulfonyl
group, 2-methoxyphenylsulfonyl group, 3-
methoxyphenylsulfonyl group, 4-methoxyphenylsulfonyl
group, 3-chloro-2-methoxyphenylsulfonyl group, 2-
fluoro-3-methoxyphenylsulfonyl group, 2-fluoro-4-
methoxyphenylsulfonyl group, 2,6-
dimethoxyphenylsulfonyl group, 2,3,4-
trifluorophenylsulfonyl group, 2,4,6-
trifluorophenylsulfonyl group, 2-
trifluoromethoxyphenylsulfonyl group, 3-
trifluoromethoxyphenylsulfonyl group, 4-
trifluoromethoxyphenylsulfonyl group, 3-fluoro-2-
trifluoromethoxyphenylsulfonyl group, 2-fluoro-3-
trifluoromethoxyphenylsulfonyl group, 3-fluoro-4-
trifluoromethoxyphenylsulfonyl group, 3-chloro-2-
trifluoromethoxyphenylsulfonyl group, 2-chloro-3-
trifluoromethoxyphenylsulfonyl group, 3-chloro-4-
trifluoromethoxyphenylsulfonyl group, 2-
pentafluoroethoxyphenylsulfonyl group, 3-
pentafluoroethoxyphenylsulfonyl group, 4-
pentafluoroethoxyphenylsulfonyl group, 3-chloro-2-
pentafluoroethoxyphenylsulfonyl group, 2-chloro-3-
pentafluoroethoxyphenylsulfonyl group, 3-Chloro-4-
pentafluoroethoxyphenylsulfonyl group, 2-
isopropoxyphenylsulfonyl group, 3-
isopropoxyphenylsulfonyl group, 4-
isopropoxyphenylsulfonyl group, 2-tert-
butoxyphenylsulfonyl group, 3-tert-butoxyphenylsulfonyl
group, 4-tert-butoxyphenylsulfonyl group, 2-sec-
butoxyphenylsulfonyl group, 3-sec-butoxyphenylsulfonyl
group, 4-sec-butoxyphenylsulfonyl group, 2-n-
heptafluoropropoxyphenylsulfonyl group, 3-n-
heptafluoropropoxyphenylsulfonyl group, 4-n-
heptafluoropropoxyphenylsulfonyl group, 4-n-
pentoxyphenylsulfonyl group, 4-n-hexyloxyphenylsulfonyl
group or the like.

An amino substituted Cl-C6 alkoxy group which
may have Cl-C6 alkyl group(s) as substituent includes an
amino-Cl-C6 alkoxy group which may have 1 or 2 Cl-C6
alkyl groups as a substituent, for example, an
aminomethoxy group, 2-aminomethoxy group, 1-aminomethoxy group, 3-aminopropoxy group, 4-aminobutoxy group, 5-aminopentylxoxy group, 6-aminohexylxoxy group, 2-methyl-3-aminopropoxy group, 1,1-dimethyl-2-aminomethoxy group, ethylaminomethoxy group, 1-(propylamino)ethoxy group, 2-(methylamino)ethoxy group, 3-(isopropylamino)propoxy group, 4-(n-butyramino)butoxy group, 5-(n-pentylamino)pentylox group, 6-(n-hexylamino)hexylox group, dimethylaminomethoxy group, 3-dimethylaminopropoxy group, (N-ethyl-N-propylamino)methoxy group, 2-(N-methyl-N-hexylamino)ethoxy group or the like.

A phenyl group wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, a halogen substituted or unsubstituted C1-C6 alkoxy group, an amino group which may have substituent(s) selected from the group consisting of a C1-C6 alkanoyl group and a C1-C6 alkyl group as substituent, a C1-C6 alkoxy carbonyl group, a phenyl group, a phenoxy group wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group (may be substituted), an aminosulfonyl group, a 1,2,3,4-tetrahydroquinolyl group wherein, on the 1,2,3,4-tetrahydroquinoline ring, at least one oxo group may be
substituted as a substituent), a C1-C6 alkylsulfonyl group, C3-C6 cycloalkyl group, a nitro group, a cyano group, a C1-C6 alkylthio group, a phenylsulfonyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted ), a hydroxy group substituted C1-C6 alkyl group and a group:

\[
\begin{align*}
\text{O} & \quad R^{11} \\
W_1 & \quad R^{12}
\end{align*}
\]

(wherein, \( W \) represents a C1 to C6 alkylene group, and \( R^{11} \) and \( R^{12} \) are identical or different and each represent a C1-C6 alkoxy group) may be substituted as a substituent, includes a phenyl group which may be substituted at the 2 to 6 positions of the phenyl ring by 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, a halogen substituted or unsubstituted C1-C6 alkoxy group, an amino group which may have 1 or 2 substituents selected from the group consisting of a C1-C6 alkanoyl group and a C1-C6 alkyl group as a substituent, a C1-C6 alkoxy carbonyl group, a phenyl group, a phenoxy group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted
C1-C6 alkyl group and a halogen substituted or
unsubstituted C1-C6 alkoxy group may be substituted),
an aminosulfonyl group, a 1,2,3,4-tetrahydroquinolyl
group (wherein, on the 1,2,3,4-tetrahydroquinoline ring,
1 to 2 oxo groups may be substituted as a substituent),
a C1-C6 alkylsulfonyl group, C3-C8 cycloalkyl group, a
nitro group, a cyano group, a C1-C6 alkylthio group, a
phenylsulfonyl group (wherein, on the phenyl ring, 1 to
5, preferably 1 to 3 substituents selected from the
group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group and a
halogen substituted or unsubstituted C1-C6 alkoxy group
may be substituted), a hydroxyl group substituted C1-
C6 alkyl group and a group:

\[
\begin{align*}
W_1 & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad
\end{align*}
\]

(wherein, \(W\) represents a C1 to C6 alkylene group, and
\(R^{11}\) and \(R^{12}\) are identical or different and each represent
a C1-C6 alkoxy group) as described above.

A hydroxyl group substituted C1-C6 linear or
branched alkyl group having 1 to 3 hydroxyl groups, for
example, a hydroxymethyl group, 2-hydroxyethyl group,
1-hydroxyethyl group, 3-hydroxypropyl group, 2,3-
dihydroxypropyl group, 4-hydroxybutyl group, 3,4-
dihydroxybutyl group, 1,1-dimethyl-2-hydroxyethyl group,
5-hydroxypentyl group, 6-hydroxyhexyl group, 2-methyl-3-hydroxypropyl group, 2,3,4-trihydroxybutyl group or the like.

A halogen substituted or unsubstituted C1-C10 alkoxy group includes, in addition to a halogen substituted or unsubstituted C1-C6 alkoxy group as described above, a C1-C10 alkoxy group substituted by 1 to 7 C1-C10 alkoxy groups and halogen atoms, for example, a heptyloxy group, octyloxy group, nonyloxy group, decyloxy group, 7-fluoroheptyloxy group, 7,7,6-trifluoroheptyloxy group, 7,7,6,6,5-heptafluoroheptyloxy group, 8-chlorooctyloxy group, 8,8-dibromooctyloxy group, 6,7,8-trifluorooctyloxy group, 8,8,8,7,7,6,6-heptafluoroctyloxy group, 8,8,8,7,7-pentachlorooctyloxy group, 9-iodononyloxy group, 9,9-dibromononyloxy group, 9,9,9,8,8-pentachlorononyloxy group, 9,9,9,8,8,7,7-heptafluorononyloxy group, 10-chlorodecyloxy group, 10,10-dibromodecyloxy group, 10,10,10,9-tetrachlorodecyloxy group, 10,10,10,9,9,8,8-heptafluorodecyloxy group or the like.

A phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a C1-C4 alkylenedioxy group, a phenyl group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent) is a phenyl C1-C6 alkyl
group unsubstituted or substituted on the phenyl ring consisting the alkyl group by 1 to 5, preferably 1 to 3 substituents (preferably 1 or 2 substituents if the substituent is a C1-C4 alkylenedioxy group) selected from the group consisting of a C1-C4 alkylenedioxy group, a phenyl group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group, examples of which include a benzyl group, 1-phenethyl group, 2-phenethyl group, 3-phenylpropyl group, 2-phenylpropyl group, 4-phenylbutyl group, 5-phenylpentyl group, 4-phenylpentyl group, 6-phenylhexyl group; 2,3-methylenedioxybenzyl group, 3,4-methylenedioxybenzyl group, 3-phenylbenzyl group, 2-phenylbenzyl group, 4-phenylbenzyl group, 3,4-diphenylbenzyl group, 2,4,6-triphenylbenzyl group, 2-fluorobenzyl group, 3-fluorobenzyl group, 4-fluorobenzyl group, 2-chlorobenzyl group, 3-chlorobenzyl group, 4-chlorobenzyl group, 2-bromobenzyl group, 3-bromobenzyl group, 4-bromobenzyl group, 2-iodobenzyl group, 3-iodobenzyl group, 4-iodobenzyl group, 2,3-difluorobenzyl group, 3,4-difluorobenzyl group, 3,5-difluorobenzyl group, 2,4-difluorobenzyl group, 2,6-difluorobenzyl group, 2,3-dichlorobenzyl group, 3,4-dichlorobenzyl group, 3,5-dichlorobenzyl group, 2,4-dichlorobenzyl group, 2,6-dichlorobenzyl group, 2-fluoro-4-bromobenzyl group, 4-chloro-3-fluorobenzyl group, 2,3,4-trichlorobenzyl group, 3,4,5-
trifluorobenzyl group, 2,4,6-trichlorobenzyl group, 4-ethylbenzyl group, 4-sec-butylbenzyl group, 4-isopropylbenzyl group, 4-n-butylbenzyl group, 4-methylbenzyl group, 2-methylbenzyl group, 3-methylbenzyl group, 2,4-dimethylbenzyl group, 2,3-dimethylbenzyl group, 2,6-dimethylbenzyl group, 3,5-dimethylbenzyl group, 2,5-dimethylbenzyl group, 2,4,6-trimethylbenzyl group, 3,5-ditrifluoromethylbenzyl group, 2,3,4,5,6-pentafluorobenzyl group, 4-isoproxybenzyl group, 4-n-butoxybenzyl group, 4-tert-butoxybenzyl group, 4-methoxybenzyl group, 2-methoxybenzyl group, 3-methoxybenzyl group, 2,4-dimethoxybenzyl group, 2,3-dimethoxybenzyl group, 2,6-dimethoxybenzyl group, 3,5-dimethoxybenzyl group, 2,5-dimethoxybenzyl group, 2,4,6-trimethoxybenzyl group, 3,5-ditrifluoromethoxybenzyl group, 2-isoproxybenzyl group, 3-chloro-4-methoxybenzyl group, 2-chloro-4-trifluoromethoxybenzyl group, 3-methyl-4-fluorobenzyl group, 4-bromo-3-trifluoromethylbenzyl group, 2-trifluoromethylbenzyl group, 3-trifluoromethylbenzyl group, 4-trifluoromethylbenzyl group, 2-pentafluoroethylbenzyl group, 3-pentafluoroethylbenzyl group, 4-pentafluoroethylbenzyl group, 2-trifluoromethoxybenzyl group, 3-trifluoromethoxybenzyl group, 4-trifluoromethoxybenzyl group, 2-pentafluoroethoxybenzyl group, 3-pentafluoroethoxybenzyl group, 4-pentafluoroethoxybenzyl group, 2-[2-
trifluoromethylphenyl)ethyl group, 2-(3-
trifluoromethylphenyl)ethyl group, 2-(4-
trifluoromethylphenyl)ethyl group, 2-(2-
trifluoromethoxyphenyl)ethyl group, 1-(3-
trifluoromethoxyphenyl)ethyl group, 2-(4-
trifluoromethoxyphenyl)ethyl group, 2-(2-
pentafluoroethoxyphenyl)ethyl group, 2-(3-
pentafluoroethoxyphenyl)ethyl group, 2-(4-
pentafluoroethoxyphenyl)ethyl group, 3-(2-
trifluoromethylphenyl)propyl group, 3-(3-
trifluoromethylphenyl)propyl group, 3-(4-
trifluoromethylphenyl)propyl group, 3-(2-
trifluoromethoxyphenyl)propyl group, 3-(3-
trifluoromethoxyphenyl)propyl group, 3-(4-
trifluoromethoxyphenyl)propyl group, 3-(3-
pentafluoroethoxyphenyl)propyl group, 3-(4-
pentafluoroethoxyphenyl)propyl group, 4-(3-
pentafluoroethoxyphenyl)butyl group, 5-(4-
trifluoromethylphenyl)pentyl group, 4-(4-
trifluoromethylphenyl)pentyl group, 4-(4-
trifluoromethoxyphenyl)pentyl group, 6-(3-
trifluoromethylphenyl)hexyl group, 6-(4-
trifluoromethylphenyl)hexyl group, 6-(4-
trifluoromethoxyphenyl)hexyl group, 4-(4-
chlorophenyl)butyl group or the like.

A phenyl C1-C6 alkyl group [wherein, on the
phenyl ring, at least one selected from the group
consisting of a C1-C4 alkylenedioxy group, a phenyl
group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a group -N(=R'11A)R'11A (wherein R'11A and R'11B are identical or different, and each represent a hydrogen atom, C1-C6 alkyl group or phenyl group, and R'11A and R'11B may be bound to each other through or not through a nitrogen, oxygen or sulfur atom to form five to seven-membered saturated heterocyclic ring together with the nitrogen atom adjacent thereto), a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a phenyl C1-C6 alkoxy group, an amino group substituted C1-C6 alkoxy group which may have C1-C6 alkyl group(s) as a substituent, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent; includes, in addition to a phenyl C1-C6 alkyl group as described above (wherein, on the phenyl ring, at least one selected from the group consisting of a C1-C6 alkylenedioxy group, a phenyl group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy
group may be substituted as a substituent; a phenyl C1-C6 alkyl group wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents (preferably 1 or 2 substituents if the substituent is a C1-C4 alkylenedioxy group) selected from the group consisting of a C1-C4 alkylenedioxy group, a phenyl group as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted linear or branched alkyl group containing 1 to 6 carbon atoms, a halogen substituted or unsubstituted linear or branched alkoxy group containing 1 to 6 carbon atoms may be substituted), a group—N (R\textsuperscript{11A})R\textsuperscript{12A} (wherein R\textsuperscript{11A} and R\textsuperscript{12A} are identical or different, and each represent a hydrogen atom, a C1-C6 alkyl group as described above or a phenyl group, and R\textsuperscript{11A} and R\textsuperscript{12A} as described later may be bound to each other through or not through a nitrogen, oxygen or sulfur atom to form five to seven-membered saturated heterocyclic ring together with the nitrogen atom adjacent thereto), a phenoxy group as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted linear or branched alkyl group containing 1 to 6 carbon atoms, a halogen substituted or unsubstituted linear or branched alkoxy group containing 1 to 6 carbon atoms may be substituted), a phenyl C1-C6 alkoxy group as
described above, an amino group substituted C1-C6 alkoxy group which may have a C1-C6 alkyl group as a substituent as described above, a halogen atom as described above, a halogen substituted or unsubstituted C1-C6 alkyl group as described above and a halogen atom as described above, a halogen substituted or unsubstituted C1-C10 alkoxy group as described above may be substituted], for example, a 4-(4-trifluoromethylphenyl)benzyl group, 4-(4-trifluoromethoxyphenyl)benzyl group, 4-(4-chlorophenyl)benzyl group, 4-(4-trifluoromethylphenoxy)benzyl group, 4-(4-trifluoromethoxyphenoxy)benzyl group, 4-(4-chlorophenoxy)benzyl group, 4-phenoxybenzyl group, 3-phenoxybenzyl group, 2-phenoxybenzyl group, 2,4-diphenoxynbenzyl group, 2,4,6-triphenoxynbenzyl group, 4-benzyloxybenzyl group, 3-benzyloxybenzyl group, 2-benzyloxybenzyl group, 3,4-dibenzylbenzyl group, 3,4,5-tribenzyloxybenzyl group, 4-octyloxybenzyl group.

3-nonyloxybenzyl group, 2-decyloxybenzyl group, 4-heptyloxybenzyl group, 2,4-dioctyloxybenzyl group, 3,4,6-trioctyloxybenzyl group, 4-(8,8,8-trifluorooctyloxy)benzyl group, 4-dimethylaminobenzyl group, 4-diphenylaminobenzyl group, 4-(3-dimethylaminoproxy)benzyl group, 4-di-n-buty laminobenzyl group, 3-(N-methyl-N-ethylamino)benzyl group, 2-(N-methyl-N-phenylamino)benzyl group, 2,4,6-methylaminobenzyl group, 3-(3-}
dimethylaminopropoxy)benzyl group, 2,4-di-n-
butylaminobenzyl group, 4-(2-methylaminooethoxy)benzyl
group, 2-(4-methylaminobutoxy)benzyl group, 4-(2-
dimethylaminooethoxy)benzyl group, 2,3-
diethylaminomethoxybenzyl group, 2,4,6-tri(2-
dimethylaminooethoxy)benzyl group, 2-phenoxy-3-
phenylbenzyl group, 4-octyloxy-3-trifluoromethoxybenzyl
group, 4-benzyloxy-2-dimethylaminobenzyl group, 4-(1-
pyrrolidinyl)benzyl group, 4-(1-piperidyl)benzyl group
or the like.

A benzofuryl C1-C6 alkyl group [wherein, on
the benzofuran ring, at least one selected from the
group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group and a
halogen substituted or unsubstituted C1-C6 alkoxy group
may be substituted] includes a benzofuryl C1-C6 alkyl
group [wherein, on the benzofuran ring, 1 to 3
substituents selected from the group consisting of a
halogen atom as described above, a halogen substituted
or unsubstituted C1-C6 alkyl group as described above
and a halogen substituted or unsubstituted C1-C6 alkoxy
group as described above may be substituted], for
example, a (2-, 3-, 4-, 5-, 6- or 7-)benzofurymethyl
group, 1-(2-benzofuryl)ethyl group, 2-(3-
benzofuryl)ethyl group, 3-(4-benzofuryl)propyl group,
2-(5-benzofuryl)propyl group, 2-(6-benzofuryl)propyl
group, 4-(7-benzofuryl)butyl group, 5-(2-
benzofuryl)pentyl group, 4-(3-benzofuryl)pentyl group,
6-(4-benzofuryl)hexyl group, 2-methyl-3-(5-benzofuryl)propyl group, 1,1-dimethyl-2-(5-benzofuryl)ethyl group, (5-chloro-2-benzofuryl)methyl group, 2-(5-trifluoromethoxybenzofuryl)methyl group, 2-(5-trifluoromethylbenzofuryl)methyl group, (6-trifluoromethylbenzofuryl)methyl group, 2-(5-methylbenzofuryl)methyl group, 2-(5-methoxybenzofuryl)methyl group, (5,6-dibromo-2-benzofuryl)methyl group, (3,5,6-trifluoro-2-benzofuryl)methyl group, 2-(5,6-dimethylbenzofuryl)methyl group, 2-(5,7-dimethoxybenzofuryl)methyl group, 2-(5,6,7-trimethylbenzofuryl)methyl group, 2-(3,5,6-trimethoxybenzofuryl)methyl group, 2-(5-trifluoromethyl-6-chlorobenzofuryl)methyl group, 2-(5-trifluoromethoxy-6-methoxybenzofuryl)methyl group or the like.

A phenylsulfonyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) is a phenylsulfonyl group unsubstituted or having 1 to 5, preferably 1 to 3 substituents (preferably 1 or 2 substituents if the substituent is a C1-C4 alkylene dioxy group) selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, a halogen substituted
or unsubstituted C1-C6 alkoxy group and a C1-C4 alkylendioxy group as defined above, for example, a phenylsulfonyl group, 2-fluorophenylsulfonyl group, 3-fluorophenylsulfonyl group, 4-fluorophenylsulfonyl group, 2-chlorophenylsulfonyl group, 3-chlorophenylsulfonyl group, 4-chlorophenylsulfonyl group, 2-bromophenylsulfonyl group, 3-bromophenylsulfonyl group, 4-bromophenylsulfonyl group, 2-iodophenylsulfonyl group, 3-iodophenylsulfonyl group, 4-iodophenylsulfonyl group, 2,3-difluorophenylsulfonyl group, 3,4-difluorophenylsulfonyl group, 3,5-difluorophenylsulfonyl group, 2,4-difluorophenylsulfonyl group, 2,6-difluorophenylsulfonyl group, 2,3-dichlorophenylsulfonyl group, 3,4-dichlorophenylsulfonyl group, 3,5-dichlorophenylsulfonyl group, 2,4-dichlorophenylsulfonyl group, 2,6-dichlorophenylsulfonyl group, 2,3,4,5-tetrafluorophenylsulfonyl group, 3,4,5,6-tetrafluorophenylsulfonyl group, 2,4,6-trifluorophenylsulfonyl group, 2,4,6-trichlorophenylsulfonyl group, 2-fluoro-4-bromophenylsulfonyl group, 4-chloro-3-fluorophenylsulfonyl group, 2,3,4-trichlorophenylsulfonyl group, 3,4,5-trifluorophenylsulfonyl group, 2,3,4,5,6-pentafluorophenylsulfonyl group, 2,4,6-
trimethylphenylsulfonyl group, 4-n-butylyphenylsulfonyl group, 2,4-dimethylphenylsulfonyl group, 2,3-
dimethylphenylsulfonyl group, 2,6-
dimethylphenylsulfonyl group, 3,5-
dimethylphenylsulfonyl group, 2,5-
dimethylphenylsulfonyl group, 3,5-
ditrifluoromethylphenylsulfonyl group, 4-n-
butoxyphenylsulfonyl group, 2,4-dimethoxyphenylsulfonyl group, 2,3-dimethoxyphenylsulfonyl group, 2,6-
dimethoxyphenylsulfonyl group, 3,5-
dimethoxyphenylsulfonyl group, 2,5-
dimethoxyphenylsulfonyl group, 2,4,6-
trimethoxyphenylsulfonyl group, 3,5-
ditrifluoromethoxyphenylsulfonyl group, 3-chloro-4-
dimethoxyphenylsulfonyl group, 2-chloro-4-
trifluoromethoxyphenylsulfonyl group, 3-methyl-4-
fluorophenylsulfonyl group, 4-bromo-3-
trifluoromethylphenylsulfonyl group, 2-
methylphenylsulfonyl group, 3-methylphenylsulfonyl group, 4-methylphenylsulfonyl group, 2-methyl-3-
chlorophenylsulfonyl group, 3-methyl-4-
chlorophenylsulfonyl group, 2-chloro-4-
methylphenylsulfonyl group, 2-methyl-3-
fluorophenylsulfonyl group, 2-
trifluoromethylphenylsulfonyl group, 3-
trifluoromethylphenylsulfonyl group, 4-
trifluoromethylphenylsulfonyl group, 2-
pentafluoroethylphenylsulfonyl group, 3-
pentafluoroethylphenylsulfonyl group, 4-
pentafluoroethylphenylsulfonyl group, 2-
isopropylphenylsulfonyl group, 3-
isopropylphenylsulfonyl group, 4-
isopropylphenylsulfonyl group, 2-tert-
butyliphenylsulfonyl group, 3-tert-butyliphenylsulfonyl group, 4-tert-butyliphenylsulfonyl group, 2-sec-
butyliphenylsulfonyl group, 3-sec-butyliphenylsulfonyl group, 4-sec-butyliphenylsulfonyl group, 2-n-
heptafluoropropylphenylsulfonyl group, 3-n-
heptafluoropropylphenylsulfonyl group, 4-n-
heptafluoropropylphenylsulfonyl group, 4-n-
pentyliphenylsulfonyl group, 4-n-hexylphenylsulfonyl group, 2-methoxyphenylsulfonyl group, 3-
methoxyphenylsulfonyl group, 4-methoxyphenylsulfonyl group, 3-chloro-2-methoxyphenylsulfonyl group, 2-
fluoro-3-methoxyphenylsulfonyl group, 2-fluoro-4-
methoxyphenylsulfonyl group, 2,6-
dimethoxyphenylsulfonyl group, 2,3,4-
trifluorophenylsulfonyl group, 2,4,6-
trifluorophenylsulfonyl group, 2-
trifluoromethoxyphenylsulfonyl group, 3-
trifluoromethoxyphenylsulfonyl group, 4-
trifluoromethoxyphenylsulfonyl group, 3-fluoro-2-
trifluoromethoxyphenylsulfonyl group, 2-fluoro-3-
trifluoromethoxyphenylsulfonyl group, 3-fluoro-4-
trifluoromethoxyphenylsulfonyl group, 3-chloro-2-
trifluoromethoxyphenylsulfonyl group, 2-chloro-3-
trifluoromethoxyphenylsulfonyle group, 3-chloro-4-
trifluoromethoxyphenylsulfonyle group, 2-
pentafluoroethoxyphenylsulfonyle group, 3-
pentafluoroethoxyphenylsulfonyle group, 4-
5 pentafluoroethoxyphenylsulfonyle group, 3-chloro-2-
pentafluoroethoxyphenylsulfonyle group, 2-chloro-3-
pentafluoroethoxyphenylsulfonyle group, 3-chloro-4-
pentafluoroethoxyphenylsulfonyle group, 2-
isopropoxyphenylsulfonyle group, 3-
10 isopropoxyphenylsulfonyle group, 4-
isopropoxyphenylsulfonyle group, 2-tert-
butoxyphenylsulfonyle group, 3-tert-butoxyphenylsulfonyle group, 4-tert-butoxyphenylsulfonyle group, 2-sec-
butoxyphenylsulfonyle group, 3-sec-butoxyphenylsulfonyle group, 4-sec-butoxyphenylsulfonyle group, 2-n-
heptafluoropropanylphenylsulfonyle group, 3-n-
heptafluoropropanylphenylsulfonyle group, 4-n-
heptafluoropropanylphenylsulfonyle group, 4-n-
pentoxyphenylsulfonyle group, 4-n-hexyloxyphenylsulfonyle group, 2,3-methylenedioxyphenylsulfonyle group, 3,4-
methylenedioxyphenylsulfonyle group, or the like.

A phenoxy carbonyl group [wherein, on the
phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted Cl-C6 alkyl group and a halogen
substituted or unsubstituted Cl-C6 alkoxy group may be
substituted] includes a phenoxy carbonyl group (wherein,
on the phenyl ring, 1 to 5, preferably 1 to 3
substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), for example, a phenoxy carbonyl group, 2-fluorophenoxy carbonyl group, 3-fluorophenoxy carbonyl group, 2,3,4,5,6-pentafluorophenoxy carbonyl group, 4-fluorophenoxy carbonyl group, 2-chlorophenoxy carbonyl group, 3-chlorophenoxy carbonyl group, 4-chlorophenoxy carbonyl group, 2,3-dichlorophenoxy carbonyl group, 3,4-dichlorophenoxy carbonyl group, 3,5-dichlorophenoxy carbonyl group, 2-bromophenoxy carbonyl group, 3-bromophenoxy carbonyl group, 4-bromophenoxy carbonyl group, 2-methylphenoxy carbonyl group, 3-methylphenoxy carbonyl group, 4-methylphenoxy carbonyl group, 2-ethylphenoxy carbonyl group, 3-ethylphenoxy carbonyl group, 4-ethylphenoxy carbonyl group, 4-n-propylphenoxy carbonyl group, 4-n-butylphenoxy carbonyl group, 2,3-dimethylphenoxy carbonyl group, 3,4,5-trimethylphenoxy carbonyl group, 4-n-pentylphenoxy carbonyl group, 4-n-hexylphenoxy carbonyl group, 2-fluoro-4-bromophenoxy carbonyl group, 4-chloro-3-fluorophenoxy carbonyl group, 2,3,4-trichlorophenoxy carbonyl group, 2,4,6-trichlorophenoxy carbonyl group, 4-isopropylphenoxy carbonyl group, 4-n-
butylphenoxy carbonyl group, 2,4-dimethylphenoxy carbonyl group, 2,3-dimethylphenoxy carbonyl group, 2,6-dimethylphenoxy carbonyl group, 3,5-dimethylphenoxy carbonyl group, 2,5-dimethylphenoxy carbonyl group, 2,4,6-trimethylphenoxy carbonyl group, 3,5-ditrifluoromethylphenoxy carbonyl group, 4-n-butoxyphenoxy carbonyl group, 2,4-dimethoxyphenoxy carbonyl group, 2,3-dimethoxyphenoxy carbonyl group, 2,6-dimethoxyphenoxy carbonyl group, 3,5-dimethoxyphenoxy carbonyl group, 2,5-dimethoxyphenoxy carbonyl group, 3,5-ditrifluoromethoxy phenoxy carbonyl group, 3-chloro-4-methoxyphenoxy carbonyl group, 2-chloro-4-trifluoromethoxy phenoxy carbonyl group, 3-methyl-4-fluorophenoxy carbonyl group, 4-bromo-3-trifluoromethyl phenoxy carbonyl group, 2-trifluoromethyl phenoxy carbonyl group, 3-trifluoromethyl phenoxy carbonyl group, 4-trifluoromethyl phenoxy carbonyl group, 2-pentafluoroethyl phenoxy carbonyl group, 3-pentafluoroethyl phenoxy carbonyl group, 4-pentafluoroethyl phenoxy carbonyl group, 2-methoxyphenoxy carbonyl group, 3-methoxyphenoxy carbonyl group, 4-methoxyphenoxy carbonyl group, 2-ethoxyphenoxy carbonyl group, 3-ethoxyphenoxy carbonyl group, 4-ethoxyphenoxy carbonyl group, 4-n-
propoxyphenoxy carbonyl group, 4-tert-butoxyphenoxy carbonyl group, 4-n-butoxyphenoxy carbonyl group, 2,3-dimethoxyphenoxy carbonyl group, 3,4,5-trimethoxyphenoxy carbonyl group, 4-n-pentoxyphenoxy carbonyl group, 4-n-hexyloxy phenoxy carbonyl group, 2-trifluoromethoxy phenoxy carbonyl group, 3-trifluoromethoxy phenoxy carbonyl group, 4-trifluoromethoxy phenoxy carbonyl group, 2-pentafluoroethoxyphenoxy carbonyl group, 3-pentafluoroethoxyphenoxy carbonyl group, 4-pentafluoroethoxyphenoxy carbonyl group or the like.

A C1-C6 alkoxy substituted C1-C6 alkyl group is a group consisting of a C1-C6 alkyl group and a C1-C6 alkoxy group, both as described above, examples of which include a methoxymethyl group, 2-methoxyethyl group, 3-methoxypropyl group, 4-methoxybutyl group, 5-methoxypentyl group, 6-methoxyhexyl group, ethoxymethyl group, 2-ethoxyethyl group, 3-ethoxypropyl group, 2-isoproxyethyl group, tert-butoxymethyl group, pentyloxymethyl group, hexyloxymethyl group, 2-(tert-butoxy)ethyl group, 3-(tert-butoxy)propyl group, 5-(tert-butoxy)hexyl group, 4-(tert-butoxy)butyl group or the like.

A C2-C6 alkenyl group includes a vinyl group, 2-propenyl group, 3-butenyl group, 2-butenyl group, 4-pentenyl group, 3-pentenyl group, 5-hexenyl group, 4-hexenyl group, 3-hexenyl group or the like.
A C1-C6 alkoxy substituted C2-C6 alkanoyl group is a group consisting of a C1-C6 alkyl group and a C2-C6 alkanoyl group, both as described above, examples of which include a 2-methoxyacetyl group, 2-methoxypropionyl group, 3-methoxypropionyl group, 4-methoxybutyryl group, 5-methoxypentanoyl group, 6-methoxypyranoyl group, 2-ethoxyacetyl group, 2-ethoxypropionyl group, 3-ethoxypropionyl group, 2-isopropoxypropionyl group, 2-(tert-butoxy)acetyl group, 2-pentyloxyacetyl group, 2-hexyloxyacetyl group, 2-(tert-butoxy)propionyl group, 3-(tert-butoxy)propionyl group, 6-(tert-butoxy)hexanoyl group, 4-(tert-butoxy)butyryl group or the like.

A C3-C9 cycloalkyl substituted C1-C6 alkyl group is a group consisting of a cyclic alkyl group containing 3 to 8 carbon atoms and an alkyl group containing 1 to 6 carbon atoms, examples of which are cyclopropylmethyl group, 2-cyclopropylethyl group, 3-cyclopropylpropyl group, 4-cyclopropylbutyl group, 5-cyclopropylpentyl group, 6-cyclopropylhexyl group, cyclobutylmethyl group, 2-cyclobutylethyl group, 3-cyclobutylpropyl group, 4-cyclobutylbutyl group, 5-cyclobutylpentyl group, 6-cyclobutylhexyl group, cyclopentylmethyl group, 2-cyclopentylethyl group, 3-cyclopentylpropyl group, 4-cyclopentylbutyl group, 5-cyclopentylpentyl group, 6-cyclopentylhexyl group, cyclohexylmethyl group, 2-cyclohexylethyl group, 3-cyclohexylpropyl group, 4-cyclohexylbutyl group, 5-
cyclohexylpentyl group, 6-cyclohexylhexyl group, cycloheptylmethyl group, 2-cycloheptyl ethyl group, 3-cycloheptyl propyl group, 4-cycloheptylbutyl group, 5-cycloheptylpentyl group, 6-cycloheptylhexyl group, cyclooctylmethyl group, 2-cyclooctylethyl group, 3-cyclooctyl propyl group, 4-cyclooctylbutyl group, 5-cyclooctylpentyl group, 6-cyclooctylhexyl group or the like.

A pyridyl C1-C6 alkyl group includes a 2-pyridylmethyl group, 2-(3-pyridyl)ethyl group, 1-(4-pyridyl)ethyl group, 3-(2-pyridyl)propyl group, 4-(3-pyridyl)butyl, 5-(4-pyridyl)pentyl group, 6-(2-pyridyl)hexyl group, 2-methyl-3-(3-pyridyl)propyl group, 1,1-dimethyl-2-(2-pyridyl)ethyl group or the like.

An imidazolyl C1-C6 alkyl group (wherein, on the imidazole ring, a phenyl group may be substituted) includes an imidazolyl C1-C6 alkyl group (wherein, on the imidazole ring, 1 to 2 phenyl groups may be substituted), for example, a 4-imidazolylmethyl group, 2-(4-imidazolyl)ethyl group, 3-(2-imidazolyl)propyl group, 4-(1-imidazolyl)butyl group, 5-(5-imidazolyl)pentyl group, 6-(4-imidazolyl)hexyl group, 2,5-diphenyl-1-imidazolylmethyl group, 2-phenyl-4-imidazolylmethyl group, 2-(2-phenyl-4-imidazolyl)ethyl group, 3-(2-phenyl-4-imidazolyl)propyl group, 4-(2-phenyl-5-imidazolyl)butyl group, 5-(2-phenyl-4-imidazolyl)pentyl group, 6-(2-phenyl-4-imidazolyl)hexyl group or the like.
A 1,2,3,4-tetrahydroquinolyl group (wherein, on the 1,2,3,4-tetrahydroquinoline ring, at least one substituted from the group consisting of an oxo group and a C1-C6 alkyl group may be substituted as a substituent) includes a 1,2,3,4-tetrahydroquinolyl group (wherein, on the 1,2,3,4-tetrahydroquinoline ring, 1 to 5 substituents selected from the group consisting of an oxo group and a C1-C6 alkyl group may be substituted), for example, a 1,2,3,4-tetrahydro-1-quinolyl group, 1,2,3,4-tetrahydro-2-quinolyl group, 1,2,3,4-tetrahydro-3-quinolyl group, 1,2,3,4-tetrahydro-4-quinolyl group, 1,2,3,4-tetrahydro-5-quinolyl group, 1,2,3,4-tetrahydro-6-quinolyl group, 1,2,3,4-tetrahydro-7-quinolyl group, 1,2,3,4-tetrahydro-8-quinolyl group, 2-oxo-1,2,3,4-tetrahydro-1-quinolyl group, 4-oxo-1,2,3,4-tetrahydro-1-quinolyl group, 2,4-dioxo-1,2,3,4-tetrahydro-1-quinolyl group, 2-oxo-1,2,3,4-tetrahydro-6-quinolyl group, 2-oxo-1,2,3,4-tetrahydro-4-quinolyl group, 2-oxo-1,2,3,4-tetrahydro-7-quinolyl group, 2-oxo-1,2,3,4-tetrahydro-8-quinolyl group, 2-oxo-1,2,3,4-tetrahydro-5-quinolyl group, 2-oxo-1,2,3,4-tetrahydro-3-quinolyl group, 2-methyl-1,2,3,4-tetrahydro-1-quinolyl group, 4-ethyl-1,2,3,4-tetrahydro-1-quinolyl group, 2,4-dimethyl-1,2,3,4-tetrahydro-1-quinolyl group, 1,5,6-trimethyl-1,2,3,4-tetrahydro-1-quinolyl group, 1,4,5,6-tetramethyl-2-oxo-1,2,3,4-tetrahydro-1-quinolyl group, 1-propyl-1,2,3,4-tetrahydro-6-quinolyl group, 5-n-
pentyl-1,2,3,4-tetrahydro-4-quinolyl group, 6-n-hexyl-1,2,3,4-tetrahydro-7-quinolyl group, 7-tert-butyl-1,2,3,4-tetrahydro-8-quinolyl group, 8-n-pentyl-1,2,3,4-tetrahydro-8-quinolyl group, 1-n-hexyl-2-oxo-1,2,3,4-tetrahydro-8-quinolyl group, 1-methyl-2-oxo-1,2,3,4-tetrahydro-5-quinolyl group, 3-ethyl-2-oxo-1,2,3,4-tetrahydro-3-quinolyl group or the like.

An amino group which may have Cl-C6 alkyl group(s) as substituent includes an amino group which may have 1 to 2 Cl-C6 alkyl groups as substituent, for example, an amino group, methylamino group, ethylamino group, n-propylamino group, isopropylamino group, n-butylamino group, tert-butylamino group, n-pentylamino group, n-hexylamino group, dimethylamino group, diethylamino group, di-n-propylamino group, di-n-butylamino group, di-n-pentylamino group, di-n-hexylamino group, N-methyl-N-ethylamino group, N-ethyl-N-n-propylamino group, N-methyl-N-n-butylamino group, N-methyl-N-n-hexylamino group or the like.

A cyano substituted C1-C6 alkyl group includes a cyanomethyl group, 2-cyanoethyl group, 1-cyanoethyl group, 3-cyanopropyl group, 4-cyano-butyl group, 5-cyanopentyl group, 6-cyano-hexyl group, 2-methyl-3-cyanopropyl group, 1,1-dimethyl-2-cyanoethyl group or the like.

A furyl substituted C1-C6 alkyl group includes a 2-furylmethyl group, 3-furylmethyl group, 2-(2-furyl)ethyl group, 1-(3-furyl)ethyl group, 3-(2-
furyl)propyl group, 3-(3-furyl)propyl group, 4-(2-furyl)butyl group, 4-(3-furyl)butyl group, 5-(2-furyl)pentyl group, 5-(3-furyl)pentyl group, 6-(2-furyl)hexyl group, 6-(3-furyl)hexyl group or the like.

A piperazinyl substituted C1-C6 alkyl group [wherein, on the piperazine ring, at least one phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted] includes a piperazinyl substituted C1 to C6 alkyl group [wherein, on the piperazine ring, 1 to 3 phenyl groups as substituent (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted], for example, a 1-

1-piperazinylmethyl group, 2-(2-piperazinyl)ethyl group, 1-(1-piperazinyl)ethyl group, 3-(1-piperazinyl)propyl group, 4-(1-piperazinyl)butyl group, 5-(2-piperazinyl)pentyl group, 6-(1-piperazinyl)hexyl group, 2-(4-phenyl-1-piperazinyl)ethyl group, 3-(4-phenyl-1-

1-piperazinyl)propyl group, 4-(4-phenyl-1-piperazinyl)butyl group, 5-(4-phenyl-1-piperazinyl)pentyl group, 6-(4-phenyl-1-piperazinyl)hexyl group, 2-(4-(2-fluorophenyl)-1-
piperazinyl)ethyl group, 3-(4-(2-fluorophenyl)-1-
piperazinyl)propyl group, 4-(4-(2,3-difluorophenyl)-1-
piperazinyl)butyl group, 5-(4-(2-fluorophenyl)-1-
piperazinyl)pentyl group, 6-(4-(4-fluorophenyl)-1-
piperazinyl)hexyl group, 3-(4-(3-fluorophenyl)-1-
piperazinyl)propyl group, 4-(4-(3-fluorophenyl)-1-
piperazinyl)butyl group, 5-(4-(3-fluorophenyl)-1-
piperazinyl)pentyl group, 3-(4-(4-fluorophenyl)-1-
piperazinyl)propyl group, 4-(4-(fluorophenyl)-1-
piperazinyl)butyl group, 5-(4-(4-fluorophenyl)-1-
piperazinyl)pentyl group, 6-(4-(fluorophenyl)-1-
piperazinyl)hexyl group, 2-(4-(2,3-dichlorophenyl)-1-
piperazinyl)ethyl group, 3-(4-(2-chlorophenyl)-1-
piperazinyl)propyl group, 4-(4-(2-chlorophenyl)-1-
piperazinyl)butyl group, 5-(4-(2,4,6-trichlorophenyl)-
1-piperazinyl)pentyl group, 6-(4-(2-chlorophenyl)-1-
piperazinyl)hexyl group, 2-(4-(3-chlorophenyl)-1-
piperazinyl)ethyl group, 3-(4-(3-chlorophenyl)-1-
piperazinyl)propyl group, 4-(4-(3-chlorophenyl)-1-
piperazinyl)butyl group, 5-(4-(2,3,4,5,6-
pentafluorophenyl)-1-piperazinyl)pentyl group, 6-(4-(3-
chloro-4-methylphenyl)-1-piperazinyl)hexyl group, 2-(4-
(4-chlorophenyl)-1-piperazinyl)ethyl group, 3-(4-(4-
chlorophenyl)-1-piperazinyl)propyl group, 4-(4-(4-
chloro-3-methoxyphenyl)-1-piperazinyl)butyl group, 5-
(4-(4-chlorophenyl)-1-piperazinyl)pentyl group, 6-(4-
(4-chlorophenyl)-1-piperazinyl)hexyl group, 2-(4-(2-
methylphenyl)-1-piperazinyl)methyl group, 2-(4-(2,4-
dimethylphenyl)-1-piperazinyl)methyl group, 2-(4-
(2,4,6-trimethylphenyl)-1-piperazinyl)methyl group, 2-
(4-(2-trifluoromethylphenyl)-1-piperazinyl)ethyl group,
3-(4-(3,5-ditrifluoromethylphenyl)-1-piperazinyl)propyl
group, 4-(4-(2-trifluoromethylphenyl)-1-
piperazinyl)butyl group, 5-(4-(2-
trifluoromethylphenyl)-1-piperazinyl)pentyl group, 6-
(4-(2-trifluoromethylphenyl)-1-piperazinyl)hexyl group,
3-(4-(3-trifluoromethylphenyl)-1-piperazinyl)propyl
group, 4-(4-(3-trifluoromethylphenyl)-1-
piperazinyl)butyl group, 5-(4-(3-
trifluoromethylphenyl)-1-piperazinyl)pentyl group, 3-
(4-(4-(3-trifluoromethylphenyl)-1-piperazinyl)propyl group,
4-(4-(4-trifluoromethylphenyl)-1-piperazinyl)butyl
15
group, 5-(4-(4-trifluoromethylphenyl)-1-
piperazinyl)pentyl group, 6-(4-(4-
trifluoromethylphenyl)-1-piperazinyl)hexyl group, 2-(4-
(3,5-ditrifluoromethoxyphenyl)-1-piperazinyl)ethyl
group, 2-(4-(2-methoxyphenyl)-1-piperazinyl)methyl
20
group, 2-(4-(2,4-dimethoxyphenyl)-1-piperazinyl)methyl
group, 2-(4-(2,4,6-trimethoxyphenyl)-1-
piperazinyl)methyl group, 3-(4-(2-
trifluoromethoxyphenyl)-1-piperazinyl)propyl group, 4-
(4-(2-trifluoromethoxyphenyl)-1-piperazinyl)butyl group,
25 5-(4-(2-trifluoromethoxyphenyl)-1-piperazinyl)pentyl
group, 6-(4-(2-trifluoromethoxyphenyl)-1-
piperazinyl)hexyl group, 3-(4-(3-
trifluoromethoxyphenyl)-1-piperazinyl)propyl group, 4-
(4-(3-trifluoromethoxyphenyl)-1-piperazinyl)butyl group,
5-(4-(3-trifluoromethoxyphenyl)-1-piperazinyl)pentyl
4-(4-(4-trifluoromethoxyphenyl)-1-
piperazinyl)propyl group, 4-(4-(4-
trifluoromethoxyphenyl)-1-piperazinyl)butyl group, 5-
(4-(4-trifluoromethoxyphenyl)-1-piperazinyl)pentyl
group, 6-(4-(4-trifluoromethoxyphenyl)-1-
piperazinyl)hexyl group, 2,4-diphenyl-1-
piperazinylmethyl group, (2,4,5-triphenyl-1-
piperadiny)methyl group or the like.

R² and R¹⁵, R¹¹² and R¹¹⁵, or R¹¹² and R¹¹⁵ may bind
to each other directly or through a nitrogen, oxygen or
sulfur atom, so as to form a 5-7 membered saturated
heterocyclic ring group together with the nitrogen atom
adjacent thereto. Examples of the 5-7 membered
saturated heterocyclic ring group may include a
pyrrolidinyl group, a piperazyl group, a piperidyl
group, a morpholino group, a thiomorpholino group, and
a homopiperazinyl group.

R² and R¹⁵ may bind to each other directly or
through a nitrogen, oxygen or sulfur atom, so as to
form a 1,2,3,4-tetrahydroisoquinolyl group, an
isoindolyl group, or the above described 5-7 membered
saturated heterocyclic ring together with the nitrogen
atom adjacent thereto. On the a group or ring, at
least one selected from the group consisting of the
following groups may be substituted: a halogen atom, a
halogen substituted or unsubstituted C1-C6 alkyl group.
a halogen substituted or unsubstituted C1-C6 alkoxy group, a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a phenyl group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], a benzoyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], a pyridyl C1-C6 alkyl group, a C3-C8 cycloalkyl group, a phenyl C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a C1-C4 alkylenedioxy group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], a piperidyl C1-C6 alkyl group, a piperidyl group, a phenyl C1-C6 alkoxy group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], a phenoxy group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted
C1-C6 alkoxy group may be substituted), an amino group wherein at least one selected from the group consisting of a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], a C1-C6 alkyl group, and a phenyl C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] may be substituted as a substituent, a benzoazolyl group, a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), and a benzimidazolyl group. As such substituents, 1 to 3 groups selected from the following groups, each of which is described above or below, may be substituted: a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, a halogen substituted or unsubstituted C1-C6 alkoxy group, a phenyl group [wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a phenyl group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group,
and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted], a benzoyl group [wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted], a pyridyl Cl-C6 alkyl group, a C3-C8 cycloalkyl group, a phenyl Cl-C6 alkyl group [wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a Cl-C4 alkylenedioxy group, a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted, and in a case where the substituent is a Cl-C4 alkylenedioxy group, 1 or 2 groups are preferably substituted], a piperidyl Cl-C6 alkyl group, a piperidyl group, a phenyl Cl-C6 alkoxy group [wherein, or the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted], a phenoxy group [wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted], an amino group.
wherein 1 or 2 groups selected from the group consisting of a phenyl group [wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted], a Cl-C6 alkyl group, and a phenyl Cl-C6 alkyl group [wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted] may be substituted as a substituent, a benzoxazolyl group, a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted linear or branched alkyl group containing 1 to 6 carbon atoms, and a halogen substituted or unsubstituted linear or branched alkoxy group containing 1 to 6 carbon atoms, may be substituted), and a benzimidazolyl group.

\( R^{118} \) and \( R^{128} \) may bind to each other directly or through a nitrogen, oxygen or sulfur atom, so as to form the above described 5-7 membered saturated heterocyclic ring together with the nitrogen atom adjacent thereto. On the a 5-7 membered saturated heterocyclic ring, at least one selected from the group
consisting of a C1-C6 alkoxy carbonyl group and an amino group [wherein, on the amino group, at least one selected from the group consisting of a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) and a C1-C6 alkyl group may be substituted] may be substituted. An example of the substituent may be a group selected from the group consisting of a C1-C6 alkoxy carbonyl group and an amino group [wherein, on the amino group, 1 or 2 groups selected from the group consisting of a phenyl group (wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) and a C1-C6 alkyl group may be substituted], which are described above or below. Such 1 to 3 substituents may be substituted on the heterocyclic ring.

The term phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a phenyl group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] is used herein to mean an
unsubstituted phenyl group or the above defined phenyl group, which comprises 1 to 5 substituents, and preferably 1 to 3 substituents selected from the group consisting of a phenyl group, a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group. Examples of the phenyl group may include a phenyl group, a 2-phenylphenyl group, a 3-phenylphenyl group, a 4-phenylphenyl group, a 2,3-diphenylphenyl group, a 2,4,6-triphenylphenyl group, a 2-fluorophenyl group, a 3-fluorophenyl group, a 4-fluorophenyl group, a 2-chlorophenyl group, a 3-chlorophenyl group, a 4-chlorophenyl group, a 2-bromophenyl group, a 3-bromophenyl group, a 4-bromophenyl group, a 2-iodophenyl group, a 3-iodophenyl group, a 4-iodophenyl group, a 2,3-difluorophenyl group, a 3,4-difluorophenyl group, a 3,5-difluorophenyl group, a 2,4-difluorophenyl group, a 2,6-difluorophenyl group, a 2,3-dichlorophenyl group, a 3,4-dichlorophenyl group, a 3,5-dichlorophenyl group, a 2,4-dichlorophenyl group, a 2,6-dichlorophenyl group, a 3,4,5-trifluorophenyl group, a 3,4,5-trichlorophenyl group, a 2,4,6-trifluorophenyl group, a 2,4,6-trichlorophenyl group, a 2-fluoro-4-bromophenyl group, a 4-chloro-3-fluorophenyl group, a 2,3,4-trichlorophenyl group, a 3,4,5-trifluorophenyl group, a 2,3,4,5,6-pentafluorophenyl group, a 2,4,6-trimethylphenyl group, a 4-n-butylphenyl group, a 2,4-dimethylphenyl group, a 2,3-dimethylphenyl group, a
2,6-dimethylphenyl group, a 3,5-dimethylphenyl group, a 2,5-dimethylphenyl group, a 3,5-ditri fluoromethylphenyl group, a 4-n-butoxyphenyl group, a 2,4-dimethoxyphenyl group, a 2,3-dimethoxyphenyl group, a 2,6-dimethoxyphenyl group, a 3,5-dimethoxyphenyl group, a 2,5-dimethoxyphenyl group, a 2,4,6-trimethoxyphenyl group, a 3,5-ditri fluoromethoxyphenyl group, a 3-chloro-4-methoxyphenyl group, a 2-chloro-4-trifluoromethoxyphenyl group, a 3-methyl-4-fluorophenyl group, a 4-bromo-3-trifluoromethylphenyl group, a 2-methylphenyl group, a 3-methylphenyl group, a 4-methylphenyl group, a 2-methyl-3-chlorophenyl group, a 3-methyl-4-chlorophenyl group, a 2-chloro-4-methylphenyl group, a 2-methyl-3-fluorophenyl group, a 2-trifluoromethylphenyl group, a 3-trifluoromethylphenyl group, a 4-trifluoromethylphenyl group, a 2-pentafluoroethylphenyl group, a 3-pentafluoroethylphenyl group, a 4-pentafluoroethylphenyl group, a 2-isopropylphenyl group, a 3-isopropylphenyl group, a 4-isopropylphenyl group, a 2-tert-butylphenyl group, a 3-tert-butylphenyl group, a 4-tert-butylphenyl group, a 2-sec-butylphenyl group, a 3-sec-butylphenyl group, a 4-sec-butylphenyl group, a 2-n-heptafluoropropylphenyl group, a 3-n-heptafluoropropylphenyl group, a 4-n-heptafluoropropylphenyl group, a 4-n-pentylphenyl group, a 4-n-hexylphenyl group, a 2-methoxyphenyl group, a 3-methoxyphenyl group, a 4-methoxyphenyl group, a 3-
chloro-2-methoxyphenyl group, a 2-fluoro-3-
methoxyphenyl group, a 2-fluoro-4-methoxyphenyl group, a 2,6-dimethoxyphenyl group, a 2,3,4-trifluorophenyl group, a 2,4,6-trifluorophenyl group, a 2-
trifluoromethoxyphenyl group, a 3-
trifluoromethoxyphenyl group, a 4-
trifluoromethoxyphenyl group, a 3-fluoro-2-
trifluoromethoxyphenyl group, a 2-fluoro-3-
trifluoromethoxyphenyl group, a 3-fluoro-4-
trifluoromethoxyphenyl group, a 3-chloro-2-
trifluoromethoxyphenyl group, a 2-chloro-3-
trifluoromethoxyphenyl group, a 3-chloro-4-
trifluoromethoxyphenyl group, a 2-
pentafluoroethoxyphenyl group, a 3-
pentafluoroethoxyphenyl group, a 4-
pentafluoroethoxyphenyl group, a 3-chloro-2-
pentafluoroethoxyphenyl group, a 2-chloro-3-
pentafluoroethoxyphenyl group, a 3-chloro-4-
pentafluoroethoxyphenyl group, a 2-isopropoxyphenyl group, a 3-isopropoxyphenyl group, a 4-isopropoxyphenyl group, a 2-tert-butoxyphenyl group, a 3-tert-butoxyphenyl group, a 4-tert-butoxyphenyl group, a 2-
sec-butoxyphenyl group, a 3-sec-butoxyphenyl group, a 4-sec-butoxyphenyl group, a 2-n-
heptafluoroisopropoxyphenyl group, a 3-n-
heptafluoroisopropoxyphenyl group, a 4-n-
heptafluoroisopropoxyphenyl group, a 4-n-pentoxyphenyl group, and a 4-n-hexyloxyphenyl group.
The term phenyl C1-C6 alkoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) is used herein to mean the above defined phenyl C1-C6 alkoxy group, wherein 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted. Examples of the phenyl C1-C6 alkoxy group may include a benzylxoy group, a 2-phenylethoxy group, a 3-phenylpropoxy group, a 2-phenylpropoxy group, a 4-phenylbutoxy group, a 5-phenylpentox group, a 4-phenylpentox group, a 6-phenylhexyloxy group, a 2-fluorobenzylxoy group, a 3-fluorobenzylxoy group, a 4-fluorobenzylxoy group, a 2-(2-fluorophenyl)ethoxy group, a 2-(3-fluorophenyl)ethoxy group, a 2-(4-fluorophenyl)ethoxy group, a 2-chlorobenzylxoy group, a 3-chlorobenzylxoy group, a 4-chlorobenzylxoy group, a 2-fluoro-4-bromobenzylxoy group, a 4-chloro-3-fluorobenzylxoy group, a 2-chloro-4-fluorobenzylxoy group, a 3,4-dichlorobenzylxoy group, a 3,5-dichlorobenzylxoy group, a 2,3-dichlorobenzylxoy group, a 2,5-dichlorobenzylxoy group, a 2,3,4-trichlorobenzylxoy group, a 3,4,5-trifluorobenzylxoy group, a 2,3,4,5,6-
pentafluorobenzyl group, a 2,4,6-trichlorobenzyl group, a 4-propylbenzyl group, a 4-n-butylbenzyl group, a 4-methylbenzyl group, a 2-methylbenzyl group, a 3-methylbenzyl group, a 2,4-dimethylbenzyl group, a 2,3-dimethylbenzyl group, a 2,6-dimethylbenzyl group, a 3,5-dimethylbenzyl group, a 2,5-dimethylbenzyl group, a 2,4,6-trimethylbenzyl group, a 4-ethylbenzyl group, a 4-isopropylbenzyl group, a 3,5-dimethoxybenzyl group, a 4-isopropoxybenzyl group, a 4-n-butoxybenzyl group, a 4-methoxybenzyl group, a 2-methoxybenzyl group, a 3-methoxybenzyl group, a 2,4-dimethoxybenzyl group, a 2,3-dimethoxybenzyl group, a 2,6-dimethoxybenzyl group, a 3,5-dimethoxybenzyl group, a 2,5-dimethoxybenzyl group, a 2,4,6-trimethoxybenzyl group, a 3,5-difluoromethoxybenzyl group, a 4-isopropoxybenzyl group, a 3-chloro-4-methoxybenzyl group, a 2-chloro-4-trifluoromethoxybenzyl group, a 3-methyl-4-fluorobenzyl group, a 4-bromo-3-trifluoromethylbenzyl group, a 2-(2-chlorophenyl)ethoxy group, a 2-(3-chlorophenyl)ethoxy group, a 2-(4-chlorophenyl)ethoxy group, a 2-trifluoromethylbenzyl group, a 3-trifluoromethylbenzyl group, a 4-trifluoromethylbenzyl group, a 2-
trifluoromethoxybenzyloxy group, a 3-
trifluoromethoxybenzyloxy group, a 4-
trifluoromethoxybenzyloxy group, a 2-(2-
trifluoromethylphenyl)ethoxy group, a 2-(3-
trifluoromethylphenyl)ethoxy group, a 2-(4-
trifluoromethylphenyl)ethoxy group, a 2-(2-
trifluoromethylphenyl)propoxy group, a 3-(3-
trifluoromethylphenyl)propoxy group, a 3-(4-
trifluoromethylphenyl)propoxy group, a 3-(2-
trifluoromethoxyphenyl)propoxy group, a 3-(3-
trifluoromethoxyphenyl)propoxy group, a 3-(4-
trifluoromethoxyphenyl)propoxy group, a 4-(3-
trifluoromethylphenyl)butoxy group, a 5-(4-
trifluoromethylphenyl)pentoxy group, a 4-(4-
trifluoromethylphenyl)pentoxy group, a 4-(4-
trifluoromethoxyphenyl)pentoxy group, a 6-(3-
trifluoromethylphenyl)hexyloxy group, a 6-(4-
trifluoromethylphenyl)hexyloxy group, and a 6-(4-
trifluoromethoxyphenyl)hexyloxy group.

The term phenoxy group [wherein, on the
phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted] is used herein to mean an unsubstituted
phenoxyl group or the above-defined phenoxyl group, which comprises 1 to 5 substituents, and preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group. Examples of the phenoxyl group may include a phenoxyl group, a 2-fluorophenoxyl group, a 3-fluorophenoxyl group, a 4-fluorophenoxyl group, a 2-chlorophenoxyl group, a 3-chlorophenoxyl group, a 4-chlorophenoxyl group, a 2-bromophenoxyl group, a 3-bromophenoxyl group, a 4-bromophenoxyl group, a 2-iodophenoxyl group, a 3-iodophenoxyl group, a 4-iodophenoxyl group, a 2,3-difluorophenoxyl group, a 3,4-difluorophenoxyl group, a 3,5-difluorophenoxyl group, a 2,4-difluorophenoxyl group, a 2,6-difluorophenoxyl group, a 2,3-dichlorophenoxyl group, a 3,4-dichlorophenoxyl group, a 3,5-dichlorophenoxyl group, a 2,4-dichlorophenoxyl group, a 2,6-dichlorophenoxyl group, a 3,4,5-trifluorophenoxyl group, a 3,4,5-trichlorophenoxyl group, a 2,4,6-trifluorophenoxyl group, a 2,4,6-trichlorophenoxyl group, a 2-fluoro-4-bromophenoxyl group, a 4-chloro-3-fluorophenoxyl group, a 2,3,4-trichlorophenoxyl group, a 3,4,5-trifluorophenoxyl group, a 2,3,4,5,6-pentafluorophenoxyl group, a 2,4,6-trimethylphenoxyl group, a 4-n-butylphenoxyl group, a 2,4-dimethylphenoxyl group, a 2,3-dimethylphenoxyl group, a 2,6-dimethylphenoxyl group, a 3,5-dimethylphenoxyl group, a
2,5-dimethylphenoxy group, a 3,5-
ditrifluoromethylphenoxy group, a 4-n-butoxyphenoxy
group, a 2,4-dimethoxyphenoxy group, a 2,3-
dimethoxyphenoxy group, a 2,6-dimethoxyphenoxy group, a
3,5-dimethoxyphenoxy group, a 2,5-dimethoxyphenoxy
group, a 2,4,6-trimethoxyphenoxy group, a 3,5-
ditrifluoromethoxyphenoxy group, a 3-chloro-4-
methoxyphenoxy group, a 2-chloro-4-
trifluoromethoxyphenoxy group, a 3-methyl-4-
fluorophenoxy group, a 4-bromo-3-trifluoromethylphenoxy
group, a 2-methylphenoxy group, a 3-methylphenoxy group,
a 4-methylphenoxy group, a 2-methyl-3-chlorophenoxy
group, a 3-methyl-4-chlorophenoxy group, a 2-chloro-4-
methylphenoxy group, a 2-methyl-3-fluorophenoxy group,
a 2-trifluoromethylphenoxy group, a 3-
trifluoromethylphenoxy group, a 4-
trifluoromethylphenoxy group, a 2-
pentafluoroethylphenoxy group, a 3-
pentafluoroethylphenoxy group, a 4-
pentafluoroethylphenoxy group, a 2-isopropylphenoxy
group, a 3-isopropylphenoxy group, a 4-isopropylphenoxy
group, a 2-tert-butylphenoxy group, a 3-tert-
butylphenoxy group, a 4-tert-butylphenoxy group, a 2-
sec-butylphenoxy group, a 3-sec-butylphenoxy group, a
4-sec-butylphenoxy group, a 2-n-
heptafluoropropylphenoxy group, a 3-n-
heptafluoropropylphenoxy group, a 4-n-
heptafluoropropylphenoxy group, a 4-n-pentylphenoxy
group, a 4-n-hexylphenoxy group, a 2-methoxyphenoxy
group, a 3-methoxyphenoxy group, a 4-methoxyphenoxy
group, a 3-chloro-2-methoxyphenoxy group, a 2-fluoro-3-
methoxyphenoxy group, a 2-fluoro-4-methoxyphenoxy group,
a 2,6-dimethoxyphenoxy group, a 2,3,4-trifluorophenoxy
group, a 2,4,6-trifluorophenoxy group, a 2-
trifluoromethoxyphenoxy group, a 3-
trifluoromethoxyphenoxy group, a 4-
trifluoromethoxyphenoxy group, a 3-fluoro-2-
trifluoromethoxyphenoxy group, a 2-fluoro-3-
trifluoromethoxyphenoxy group, a 3-fluoro-4-
trifluoromethoxyphenoxy group, a 3-chloro-2-
trifluoromethoxyphenoxy group, a 2-chloro-3-
trifluoromethoxyphenoxy group, a 3-chloro-4-
trifluoromethoxyphenoxy group, a 2-
pentafluoroethoxyphenoxy group, a 3-
pentafluoroethoxyphenoxy group, a 4-
pentafluoroethoxyphenoxy group, a 3-chloro-2-
pentafluoroethoxyphenoxy group, a 2-chloro-3-
pentafluoroethoxyphenoxy group, a 3-chloro-4-
pentafluoroethoxyphenoxy group, a 2-isopropoxyphenoxy
group, a 3-isopropoxyphenoxy group, a 4-
isopropoxyphenoxy group, a 2-tert-butoxyphenoxy group,
a 3-tert-butoxyphenoxy group, a 4-tert-butoxyphenoxy
group, a 2-sec-butoxyphenoxy group, a 3-sec-
butoxyphenoxy group, a 4-sec-butoxyphenoxy group, a 2-
n-heptafluoropropoxyphenoxy group, a 3-n-
heptafluoropropoxyphenoxy group, a 4-n-
heptafluoropropoxyphenoxy group, a 4-n-pentoxyphenoxy group, and a 4-n-hexyloxyphenoxy group.

The term phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a C1-C4 alkylenedioxy group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) is used herein to mean an unsubstituted phenyl C1-C6 alkyl group, or a group wherein, on the phenyl ring constituting the group, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a C1-C4 alkylenedioxy group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted, with the proviso that, when the substituent is a C1-C4 alkylenedioxy group, 1 to 2 substituents are preferably substituted). Examples of the phenyl C1-C6 alkyl group may include a benzyl group, a 1-phenethyl group, a 2-phenethyl group, a 3-phenylpropyl group, a 2-phenylpropyl group, a 4-phenylbutyl group, a 5-phenylpentyl group, a 4-phenylpentyl group, a 6-phenylhexyl group, a 2,3-methylenedioxybenzyl group, a 3,4-methylenedioxybenzyl group, a 2-fluorobenzyl group, a 3-fluorobenzyl group, a 4-fluorobenzyl group, a 2-chlorobenzyl group, a 3-chlorobenzyl group, a 4-chlorobenzyl group, a 2-bromobenzyl group, a 3-bromobenzyl group, a 4-
bromobenzyl group, a 2-iodobenzyl group, a 3-iodobenzyl
group, a 4-iodobenzyl group, a 2,3-difluorobenzyl group,
a 3,4-difluorobenzyl group, a 3,5-difluorobenzyl group,
a 2,4-difluorobenzyl group, a 2,6-difluorobenzyl group,
a 2,3-dichlorobenzyl group, a 3,4-dichlorobenzyl group,
a 3,5-dichlorobenzyl group, a 2,4-dichlorobenzyl group,
a 2,6-dichlorobenzyl group, a 2-fluoro-4-bromobenzyl
group, a 4-chloro-3-fluorobenzyl group, a 2,3,4-
trichlorobenzyl group, a 3,4,5-trifluorobenzyl group, a
2,4,6-trichlorobenzyl group, a 4-isopropylbenzyl group,
a 4-n-butylbenzyl group, a 4-methylbenzyl group, a 2-
methylbenzyl group, a 3-methylbenzyl group, a 2,4-
dimethylbenzyl group, a 2,3-dimethylbenzyl group, a
2,6-dimethylbenzyl group, a 3,5-dimethylbenzyl group, a
2,5-dimethylbenzyl group, a 2,4,6-trimethylbenzyl group,
a 3,5-ditrifluoromethylbenzyl group, a 2,3,4,5,6-
pentafluorobenzyl group, a 4-isopropoxybenzyl group, a
4-n-butoxybenzyl group, a 4-methoxybenzyl group, a 2-
methoxybenzyl group, a 3-methoxybenzyl group, a 2,4-
dimethoxybenzyl group, a 2,3-dimethoxybenzyl group, a
2,6-dimethoxybenzyl group, a 3,5-dimethoxybenzyl group,
a 2,5-dimethoxybenzyl group, a 2,4,6-trimethoxybenzyl
group, a 3,5-ditrifluoromethoxybenzyl group, a 2-
isopropoxybenzyl group, a 3-chloro-4-methoxybenzyl
group, a 2-chloro-4-trifluoromethoxybenzyl group, a 3-
methyl-4-fluorobenzyl group, a 4-bromo-3-
trifluoromethylbenzyl group, a 2-trifluoromethylbenzyl
group, a 3-trifluoromethylbenzyl group, a 4-
trifluoromethylbenzyl group, a 2-pentafluoroethylbenzyl group, a 3-pentafluoroethylbenzyl group, a 4-pentafluoroethylbenzyl group, a 2-trifluoromethoxybenzyl group, a 3-trifluoromethoxybenzyl group, a 4-trifluoromethoxybenzyl group, a 2-pentafluoroethoxybenzyl group, a 3-pentafluoroethoxybenzyl group, a 4-pentafluoroethoxybenzyl group, a 2-(2-trifluoromethylphenyl)ethyl group, a 2-(3-trifluoromethylphenyl)ethyl group, a 2-(4-trifluoromethylphenyl)ethyl group, a 2-(2-trifluoromethoxyphenyl)ethyl group, a 2-(3-trifluoromethoxyphenyl)ethyl group, a 2-(4-trifluoromethoxyphenyl)ethyl group, a 2-(2-pentafluoroethoxyphenyl)ethyl group, a 2-(3-pentafluoroethoxyphenyl)ethyl group, a 2-(4-pentafluoroethoxyphenyl)ethyl group, a 3-(2-trifluoromethylphenyl)propyl group, a 3-(3-trifluoromethylphenyl)propyl group, a 3-(4-trifluoromethylphenyl)propyl group, a 3-(2-trifluoromethoxyphenyl)propyl group, a 3-(3-trifluoromethoxyphenyl)propyl group, a 3-(4-trifluoromethylphenyl)propyl group, a 3-(2-pentafluoroethoxyphenyl)propyl group, a 3-(4-pentafluoroethoxyphenyl)propyl group, a 4-(3-pentafluoroethoxyphenyl)butyl group, a 5-(4-trifluoromethylphenyl)pentyl group, a 4-(6-
trifluoromethylphenyl)pentyl group, a 4-(4-
trifluoromethoxyphenyl)pentyl group, a 6-(3-
trifluoromethylphenyl)hexyl group, a 6-(4-
trifluoromethylphenyl)hexyl group, and a 6-(4-
trifluoromethoxyphenyl)hexyl group.

Examples of the piperidyl Cl-C6 alkyl group
may include a piperidin-1-ylmethyl group, a piperidin-
2-ylethyl group, a piperidin-3-ylpropyl group, a
piperidin-4-ylbutyl group, a piperidin-1-ylpentyl group,
and a piperidin-2-ylhexyl group.

An amino group, wherein at least one selected
from the group consisting of a phenyl group [wherein,
on the phenyl ring, at least one selected from the
group consisting of a halogen atom, a halogen
substituted or unsubstituted Cl-C6 alkyl group, and a
halogen substituted or unsubstituted Cl-C6 alkoxy group
may be substituted], a Cl-C6 alkyl group, and a phenyl
Cl-C6 alkyl group [wherein, on the phenyl ring, at
least one selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted
Cl-C6 alkyl group, and a halogen substituted or
unsubstituted Cl-C6 alkoxy group may be substituted],
may be substituted as a substituent, may be an amino
group wherein 1 or 2 groups selected from the group
consisting of a phenyl group [wherein, on the phenyl
ring, 1 to 5 groups, and preferably 1 to 3 groups
selected from the group consisting of a halogen atom, a
halogen substituted or unsubstituted Cl-C6 alkyl group,
and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], a C1-C6 alkyl group, and a phenyl C1-C6 alkyl group [wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], may be substituted as substituents. Examples of the amino group may include an amino group, a methylamino group, a dimethylamino group, an ethylamino group, a diethylamino group, an n-propylamino group, an n-butylamino group, an n-pentylamino group, an n-hexylamino group, a phenylamino group, a (4-chlorophenyl)amino group, a (4-bromophenyl)amino group, a (2,4-dichlorophenyl)amino group, a (2,4,6-trichlorophenyl)amino group, a (2,3,4,5,6-pentafluorophenyl)amino group, a (4-fluorophenyl)amino group, a (4-iodophenyl)amino group, a (4-chlorophenyl)amino group, a (3-methylphenyl)amino group, a (2-trifluoromethylphenyl)amino group, a (3-trifluoromethylphenyl)amino group, a (4-trifluoromethylphenyl)amino group, a (3,4-dimethylphenyl)amino group, a (3,4,5-trimethylphenyl)amino group, a (2-methoxyphenyl)amino group, a (4-trifluoromethoxyphenyl)amino group, a (3-trifluoromethoxyphenyl)amino group, a (3,5-dimethoxyphenyl)amino group, a (2,5-dimethoxyphenyl)amino group, a (2,4,6-
trimethoxyphenyl)amino group, an N-methyl-N-(4-
trifluoromethylphenyl)amino group, an N-ethyl-N-(4-
trifluoromethoxyphenyl)amino group, a 1-phenethylamino
group, a 2-phenethylamino group, a 3-phenylpropylamino
group, a 2-phenylpropylamino group, a 4-
phenylbutylamino group, a 5-phenylpentylamino group, a
4-phenylpentylamino group, a 6-phenylhexylamino group,
a 2-fluorobenzylamino group, a 3-fluorobenzylamino
group, an N-phenyl-N-(4-fluorobenzyl)amino group, a 2-
chlorobenzylamino group, a 3-chlorobenzylamino group,
a 4-chlorobenzylamino group, a 2-bromobenzylamino group,
an N-methyl-N-(3-bromobenzyl)amino group, a 4-
bromobenzylamino group, a 2-iodobenzylamino group, a 3-
iodobenzylamino group, a 4-iodobenzylamino group, a
2,3-difluorobenzylamino group, a 3,4-
difluorobenzylamino group, a 3,5-difluorobenzylamino
group, a 2,4-difluorobenzylamino group, a 2,6-
difluorobenzylamino group, a 2,3-dichlorobenzylamino
group, a 3,4-dichlorobenzylamino group, a 3,5-
dichlorobenzylamino group, a 2,4-dichlorobenzylamino
group, a 2,6-dichlorobenzylamino group, a 2-fluoro-4-
bromobenzylamino group, a 4-chloro-3-fluorobenzylamino
group, a 2,3,4-trichlorobenzylamino group, a 3,4,5-
trifluorobenzylamino group, a 2,4,6-
trichlorobenzylamino group, a 4-isopropylbenzylamino
group, a 4-n-butylbenzylamino group, a 4-
methylbenzylamino group, a 2-methylbenzylamino group, a
3-methylbenzylamino group, a 2,4-dimethylbenzylamino
group, a 2,3-dimethylbenzylamino group, a 2,5-dimethylbenzylamino group, a 3,5-dimethylbenzylamino group, a 2,5-dimethylbenzylamino group, a 2,4,6(trimethylbenzylamino group, a 3,5-ditrifluoromethylbenzylamino group, a 2,3,4,5,6-pentafluorobenzylamino group, a 4-isopropoxybenzylamino group, a 4-n-butoxybenzylamino group, a 4-methoxybenzylamino group, a 2-methoxybenzylamino group, a 3-methoxybenzylamino group, a 2,4-dimethoxybenzylamino group, a 2,3-dimethoxybenzyl group, a 2,6-dimethoxybenzylamino group, a 3,5-dimethoxybenzylamino group, a 2,5-dimethoxybenzylamino group, a 2,4,6-trimethoxybenzylamino group, a 3,5-ditrifluoromethoxybenzylamino group, a 2-isopropoxybenzylamino group, a 3-chloro-4-methoxybenzylamino group, a 2-chloro-4-trifluoromethoxybenzylamino group, a 3-methyl-4-fluorobenzylamino group, a 4-bromo-3-trifluoromethylbenzylamino group, a 2-trifluoromethylbenzylamino group, a 3-trifluoromethylbenzylamino group, a 4-trifluoromethylbenzylamino group, a 2-pentafluoroethylbenzylamino group, a 3-pentafluoroethylbenzylamino group, a 4-pentafluoroethylbenzylamino group, a 2-trifluoromethoxybenzylamino group, a 3-trifluoromethoxybenzylamino group, a 4-trifluoromethoxybenzylamino group, a 2-
pentafluoroethoxybenzylamino group, a 3-
pentafluoroethoxybenzylamino group, a 4-
pentafluoroethoxybenzylamino group, a 2-(2-
trifluoromethylphenyl)ethylamino group, a 2-(3-
5 trifluoromethylphenyl)ethylamino group, a 2-(4-
trifluoromethylphenyl)ethylamino group, a 2-(2-
trifluoromethoxyphenyl)ethylamino group, a 2-(3-
trifluoromethoxyphenyl)ethylamino group, a 2-(4-
trifluoromethoxyphenyl)ethylamino group, a 2-(2-
10 pentafluoroethoxyphenyl)ethylamino group, a 2-(3-
pentafluoroethoxyphenyl)ethylamino group, a 2-(4-
pentafluoroethoxyphenyl)ethylamino group, a 3-(2-
trifluoromethylphenyl)propylamino group, a 3-(3-
trifluoromethylphenyl)propylamino group, a 3-(4-
15 trifluoromethylphenyl)propylamino group, a 3-(2-
trifluoromethoxyphenyl)propylamino group, a 3-(3-
trifluoromethoxyphenyl)propylamino group, a 3-(4-
trifluoromethoxyphenyl)propylamino group, a 3-(3-
20 pentafluoroethoxyphenyl)propylamino group, a 4-(3-
pentafluoroethoxyphenyl)butylamino group, a 5-(4-
trifluoromethylphenyl)pentylamino group, a 4-(4-
25 trifluoromethylphenyl)pentylamino group, a 4-(4-
trifluoromethoxyphenyl)pentylamino group, a 6-(3-
trifluoromethylphenyl)hexylamino group, a 6-(4-
trifluoromethylphenyl)hexylamino group, a 6-(4-
trifluoromethoxyphenyl)hexylamino group, an N-methyl-N-
phenylamino group, an N-methyl-N-benzylamino group, and
an N-phenyl-N-benzylamino group.

Examples of the carbamoyloxy group (wherein, on the amino group, at least one selected from the group consisting of a C1-C6 alkyl group and a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] may be substituted) may include carbamoyloxy groups such as a carbamoyloxy group, a phenylcarbamoyloxy group, a 2-fluorophenylcarbamoyloxy group, a 3-fluorophenylcarbamoyloxy group, a 4-fluorophenylcarbamoyloxy group, a 2-chlorophenylcarbamoyloxy group, a 3-chlorophenylcarbamoyloxy group, a 4-chlorophenylcarbamoyloxy group, a 2-bromophenylcarbamoyloxy group, a 3-bromophenylcarbamoyloxy group, a 4-bromophenylcarbamoyloxy group, a 2-iodophenylcarbamoyloxy group, a 3-iodophenylcarbamoyloxy group, a 4-iodophenylcarbamoyloxy group, a 2,3-difluorophenylcarbamoyloxy group, a 3,4-difluorophenylcarbamoyloxy group, a 3,5-difluorophenylcarbamoyloxy group, a 2,4-difluorophenylcarbamoyloxy group, a 2,6-difluorophenylcarbamoyloxy group, a 2,3-
dichlorophenylcarbamoyloxy group, a 3,4-
dichlorophenylcarbamoyloxy group, a 3,5-
dichlorophenylcarbamoyloxy group, a 2,4-
dichlorophenylcarbamoyloxy group, a 2,6-
dichlorophenylcarbamoyloxy group, a 3,4,5-
trifluorophenylcarbamoyloxy group, a 2,3,4,5,6-
pentafluorophenylcarbamoyloxy group, a 3,4,5-
trichlorophenylcarbamoyloxy group, a 2,4,6-
trifluorophenylcarbamoyloxy group, a 2,4,6-
trichlorophenylcarbamoyloxy group, a 2-
methylphenylcarbamoyloxy group, a 3-
methylphenylcarbamoyloxy group, a 4-
methylphenylcarbamoyloxy group, a 2-methyl-3-
chlorophenylcarbamoyloxy group, a 3-methyl-4-
chlorophenylcarbamoyloxy group, a 2-chloro-4-
methylphenylcarbamoyloxy group, a 2-methyl-3-
fluorophenylcarbamoyloxy group, a 2-
trifluoromethylphenylcarbamoyloxy group, a
methylcarbamoyloxy group, an ethylcarbamoyloxy group,
an n-propylcarbamoyloxy group, an n-butylcarbamoyloxy
group, an n-hexylcarbamoyloxy group, an n-
penylcarbamoyloxy group, an N-methyl-N-
phenylcarbamoyloxy group, an N,N-dimethylcarbamoyloxy
group, an N-methyl-N-ethylcarbamoyloxy group, an N-(2-
fluorophenyl)-N-methylcarbamoyloxy group, an N-(3-
fluorophenyl)-N-methylcarbamoyloxy group, an N-(4-
fluorophenyl)-N-methylcarbamoyloxy group, an N-(2-
chlorophenyl)-N-methylcarbamoyloxy group, an N-(3-chlorophenyl)-N-methylcarbamoyloxy group, an N-(4-chlorophenyl)-N-methylcarbamoyloxy group, an N-(4-bromophenyl)-N-methylcarbamoyloxy group, an N-(2-iodophenyl)-N-methylcarbamoyloxy group, an N-(3-iodophenyl)-N-methylcarbamoyloxy group, an N-(4-iodophenyl)-N-methylcarbamoyloxy group, an N-(2,3-difluorophenyl)-N-methylcarbamoyloxy group, an N-(3,4-difluorophenyl)-N-methylcarbamoyloxy group, an N-(3,5-difluorophenyl)-N-methylcarbamoyloxy group, an N-(2,4-difluorophenyl)-N-methylcarbamoyloxy group, an N-(2,6-difluorophenyl)-N-methylcarbamoyloxy group, an N-(2,3-dichlorophenyl)-N-methylcarbamoyloxy group, an N-(3,4-dichlorophenyl)-N-methylcarbamoyloxy group, an N-(3,5-dichlorophenyl)-N-methylcarbamoyloxy group, an N-(2,4-dichlorophenyl)-N-methylcarbamoyloxy group, an N-(2,6-dichlorophenyl)-N-methylcarbamoyloxy group, an N-(3,4,5-trifluorophenyl)-N-methylcarbamoyloxy group, an N-(3,4,5-trichlorophenyl)-N-methylcarbamoyloxy group, an N-(2,4,6-trifluorophenyl)-N-methylcarbamoyloxy group, an N-(2,4,6-trichlorophenyl)-N-methylcarbamoyloxy group, an N-(2-methylphenyl)-N-methylcarbamoyloxy group, an N-(3-methylphenyl)-N-methylcarbamoyloxy group, an N-(4-methylphenyl)-N-methylcarbamoyloxy group, an N-(2-methyl-3-chlorophenyl)-N-methylcarbamoyloxy group, an N-(3-methyl-4-chlorophenyl)-N-methylcarbamoyloxy group, an N-(2-chloro-4-methylphenyl)-N-methylcarbamoyloxy group, an N-(2-methyl-3-fluorophenyl)-N-...
methylcarbamoyloxy group, an N-(2-
trifluoromethylphenyl)-N-methylcarbamoyloxy group, an
N-(4-trifluoromethylphenyl)-N-methylcarbamoyloxy group,
an N-phenyl-N-phenylcarbamoyloxy group, an N-phenyl-N-
(2-fluorophenyl)carbamoyloxy group, an N-phenyl-N-(3-
fluorophenyl)carbamoyloxy group, an N-phenyl-N-(4-
fluorophenyl)carbamoyloxy group, an N-phenyl-N-(2-
chlorophenyl)carbamoyloxy group, an N-phenyl-N-(3-
chlorophenyl)carbamoyloxy group, an N-phenyl-N-(4-
chlorophenyl)carbamoyloxy group, an N-phenyl-N-(2-
chlorophenyl)carbamoyloxy group, an N-phenyl-N-(2-
bromophenyl)carbamoyloxy group, an N-phenyl-N-(3-
bromophenyl)carbamoyloxy group, an N-phenyl-N-(4-
bromophenyl)carbamoyloxy group, an N-phenyl-N-(2-
iodophenyl)carbamoyloxy group, an N-phenyl-N-(3-
iodophenyl)carbamoyloxy group, an N-phenyl-N-(2-
iodophenyl)carbamoyloxy group, an N-phenyl-N-(2,3-
difluorophenyl)carbamoyloxy group, an N-phenyl-N-(3,4-
difluorophenyl)carbamoyloxy group, an N-phenyl-N-(3,5-
difluorophenyl)carbamoyloxy group, an N-phenyl-N-(2,4-
difluorophenyl)carbamoyloxy group, an N-phenyl-N-(2,6-
difluorophenyl)carbamoyloxy group, an N-phenyl-N-(2,3-
dichlorophenyl)carbamoyloxy group, an N-phenyl-N-(3,4-
dichlorophenyl)carbamoyloxy group, an N-phenyl-N-(3,5-
dichlorophenyl)carbamoyloxy group, an N-phenyl-N-(2,4-
dichlorophenyl)carbamoyloxy group, an N-phenyl-N-(2,6-
dichlorophenyl)carbamoyloxy group, an N-phenyl-N-
(3,4,5-trifluorophenyl)carbamoyloxy group, an N-phenyl-
N-(3,4,5-trichlorophenyl)carbamoyloxy group, an N-
phenyl-N-(2,4,6-trifluorophenyl)carbamoyloxy group, an
N-phenyl-N-(2,4,6-trichlorophenyl)carbamoyloxy group,
an N-phenyl-N-(2-methylphenyl)carbamoyloxy group, an N-
phenyl-N-(3-methylphenyl)carbamoyloxy group, an N-
phenyl-N-(4-methylphenyl)carbamoyloxy group, an N-
phenyl-N-(2-methyl-3-chlorophenyl)carbamoyloxy group,
an N-phenyl-N-(3-methyl-4-chlorophenyl)carbamoyloxy
group, an N-phenyl-N-(2-chloro-4-methylphenyl)car-
bamoyloxy group, an N-phenyl-N-(2-methyl-3-fluorophenyl)carbamoyloxy group, an N-phenyl-N-(2-
trifluoromethylphenyl)carbamoyloxy group, an N-phenyl-
N-(3-trifluoromethylphenyl)carbamoyloxy group, an N-
phenyl-N-(4-trifluoromethylphenyl)carbamoyloxy group, a
2-pentafluoroethylphenylcarbamoyloxy group, a 3-
pentafluoroethylphenylcarbamoyloxy group,
a 4-pentafluoroethylphenylcarbamoyloxy group, a 2-
isopropylphenylcarbamoyloxy group, a 3-
isopropylphenylcarbamoyloxy group, a 4-
isopropylphenylcarbamoyloxy group, a 2-tert-
butylphenylcarbamoyloxy group, a 3-tert-
butylphenylcarbamoyloxy group, a 4-tert-
butylphenylcarbamoyloxy group, a 2-sec-
butylphenylcarbamoyloxy group, a 3-sec-
butylphenylcarbamoyloxy group,
a 4-sec-butylphenylcarbamoyloxy group, a 2-n-
heptafluoropropylphenylcarbamoyloxy group, a 3-n-
heptafluoropropylphenylcarbamoyloxy group, a 4-n-
heptafluoropropylphenylcarbamoyloxy group, a 4-n-
pentylphenylcarbamoyloxy group, a 4-n-hexylphenylcarbamoyloxy group, a 2,4-
dimethylphenylcarbamoyloxy group, a 2,4,6-
trimethylphenylcarbamoyloxy group, a 3,4-
dimethoxyphenylcarbamoyloxy group, a 3,4,5-
trimethoxyphenylcarbamoyloxy group, a 2-
methoxyphenylcarbamoyloxy group, a 3-
methoxyphenylcarbamoyloxy group, a 4-
methoxyphenylcarbamoyloxy group, a 2-methoxy-3-
chlorophenylcarbamoyloxy group, a 2-fluoro-3-
methoxyphenylcarbamoyloxy group, a 2-fluoro-4-
methoxyphenylcarbamoyloxy group, a 2,6-
dimethoxyphenylcarbamoyloxy group, a 2,3,4-
trifluorophenylcarbamoyloxy group, a 3,4,5-
trifluorophenylcarbamoyloxy group, a 2-
trifluoromethoxyphenylcarbamoyloxy group, a 3-
trifluoromethoxyphenylcarbamoyloxy group, a 4-
trifluoromethoxyphenylcarbamoyloxy group, a 2-
pentafluoroethoxyphenylcarbamoyloxy group, a 3-
pentafluoroethoxyphenylcarbamoyloxy group, a 4-
pentafluoroethoxyphenylcarbamoyloxy group, a 2-
isopropoxyphenylcarbamoyloxy group, a 3-
isopropoxyphenylcarbamoyloxy group, a 4-
isopropoxyphenylcarbamoyloxy group, a 2-tert-
butoxyphenylcarbamoyloxy group, a 3-tert-
butoxyphenylcarbamoyloxy group, a 4-tert-
butoxyphenylcarbamoyloxy group, a 2-sec-
butoxyphenylcarbamoyloxy group, a 3-sec-
butoxyphenylcarbamoyloxy group, a 4-sec-
butoxyphenylcarbamoyloxy group, a 2-n-
heptafluoropropoxyphenylcarbamoyloxy group, a 3-n-
heptafluoropropoxyphenylcarbamoyloxy group, a 4-n-
heptafluoropropoxyphenylcarbamoyloxy group, a 4-n-
pentyloxyphenylcarbamoyloxy group, and a 4-n-
hexyloxyphenylcarbamoyloxy group (wherein, on the amino
group, 1 or 2 groups selected from the group consisting
of a Cl-C6 alkyl group and a phenyl group [wherein, on
the phenyl ring, 1 to 5 groups, and preferably 1 to 3
groups selected from the group consisting of a halogen
atom, a halogen substituted or unsubstituted Cl-C6
alkyl group, and a halogen substituted or unsubstituted
Cl-C6 alkoxy group may be substituted] may be
substituted).

Examples of the halogen substituted or
unsubstituted Cl-C10 alkyl group may include: the above
described halogen substituted or unsubstituted Cl-C6
alkyl group; Cl-C10 alkyl groups such as a heptyl group,
an octyl group, a nonyl group, a decyl group, a 7-
fluoroheptyl group, a 7,7,6-trifluoroheptyl group, a
7,7,7,6,6,5,5-heptafluoroheptyl group, a 8-chlorooctyl
group, a 8,8-dibromoocetyl group, a 6,7,8-trifluoroocetyl
group, a 8,8,8,7,7,6,6-heptafluoroocetyl group, a
8,8,8,7,7,7-pentachlorooctyl group, a 9-iodononyl group,
a 9,9-dibromononyl group, a 9,9,9,8,8,8-pentachlorononyl
group, a 9,9,9,8,8,7,7-heptafluorononyl group, a 10-
chlorodecyl group, a 10,10-dibromodecyl group, a
10,10,10,9-tetrachlorodecyl group, and a 10,10,10,9,9,9,8,8-heptafluorodecyl group; and Cl-C10 alkyl groups wherein 1 to 7 halogen atoms are substituted.

In addition to the above described phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), examples of the phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a Cl-C6 alkylthio group, a cyano group, a phenoxy group, a Cl-C6 alkylthio group, a Cl-C6 alkanoyl group, a phenyl group, a phenyl Cl-C6 alkyl group, a halogen atom, a halogen substituted or unsubstituted Cl-C10 alkyl group, and a halogen substituted or unsubstituted Cl-C10 alkoxy group may be substituted) may further include phenyl groups such as a 4-cyanophenyl group, a 3-cyanophenyl group, a 2-cyanophenyl group, a 3,4-dicyanophenyl group, a 3,4,5-tricyanophenyl group, a 4-phenoxyphenyl group, a 3-phenoxyphenyl group, a 2-phenoxyphenyl group, a 3,4-diphenoxyphenyl group, a 2,4,6-triphenoxyphenyl group, a 4-methylthiophenyl group, a 3-methylthiophenyl group, a 2-methylthiophenyl group, a 3,4-dimethylthiophenyl group, a 2,4,6-trimethylthiophenyl group, a 4-acetylphenyl group, a 3-acetylphenyl group, a 2-acetylphenyl group, a 3,4-diacetylphenyl group, a
2,4,6-triacetylphe nyl group, a 4-biphenyl group, a 3-biphenyl group, a 2-biphenyl group, a 3,4-diphenylpheryl group, a 2,4,6-triphenylphenyl group, a 4-heptyloxyphenyl group, a 3-octyloxyphenyl group, a 2-nonyloxyphenyl group, a 4-decyloxyphenyl group, a 2,4-dihexyloxyphenyl group, a 2,4,6-trihexyloxyphenyl group, a 4-(7,7-dichlorohexyloxy)phenyl group, a 4-benzylphenyl group, a 3-benzylphenyl group, a 2-benzylphenyl group, a 2,4-dibenzylphenyl group, a 2,4,6-tribenzylphenyl group, a 4-octylphenyl group, a 4-heptylphenyl group, a 3-octylphenyl group, a 3-(8,8,8-trifluoroctyl)phenyl group, a 2-nonylphenyl group, a 4-decylphenyl group, a 2,4-dioctylphenyl group, a 2,4,6-trioctydiphenyl group, a 4-phenyl-3-chlorophenyl group, a 4-phenoxy-3-methylthiophenyl group, a 4-heptyloxy-3-trifluoromethoxyphenyl group, a 4-octyl-2-trifluoromethylphenyl group, a 4-benzyl-2-methylphenyl group, a 3,4-ethylenedioxyphenyl group, and a 3,4-methylenedioxyphenyl group [wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of the above described C1-C4 alkylenedioxy group, cyano group, phenoxy group, the above described C1-C6 alkylthio group, the above described C1-C6 alkanoyl group, phenyl group, the above described phenyl C1-C6 alkyl group, the above described halogen atom, the above described halogen substituted or unsubstituted C1-C6 alkyl group, and the above described halogen substituted or
unsubstituted C1-C6 alkoxy group may be substituted (in a case where the substituent is a C1-C4 alkylendioxy group, 1 or 2 groups are preferably substituted).

Examples of the carbamoyloxy substituted C1-C6 alkyl group (wherein, on the amino group, at least one selected from the group consisting of a C1-C6 alkyl group, a phenyl C1-C6 alkyl group, a C3-C8 cycloalkyl group, a naphthyl group, a 2,3-dihydro-1H-indenyl group, a 2,3-dihydrobenzofuryl group, and a phenyl group

[wherein, on the phenyl ring, at least one selected from the group consisting of a C1-C4 alkylendioxy group, a cyano group, a phenoxy group, a C1-C6 alkylthio group, a C1-C6 alkanoyl group, a phenyl group, a phenyl C1-C6 alkyl group, a halogen atom, a halogen substituted or unsubstituted C1-C10 alkyl group, and a halogen substituted or unsubstituted C1-C10 alkoxy group may be substituted], may be substituted), may include carbamoyloxy substituted C1-C6 alkyl groups such as a carbamoyloxyethyl group, a 2-carbamoyloxyethyl group, a 1-carbamoyloxyethyl group, a 3-carbamoyloxypropyl group, a 4-carbamoyloxybutyl group, a 5-carbamoyloxypentyl group, a 6-carbamoyloxyhexyl group, a phenylcarbamoyloxyethyl group, a 2-methylphenylcarbamoyloxyethyl group, a 3-methylphenylcarbamoyloxyethyl group, a 4-methylphenylcarbamoyloxyethyl group, a 2,3-dimethylphenylcarbamoyloxyethyl group, a 2,4-dimethylphenylcarbamoyloxyethyl group, a 2,6-
dimethylphenylcarbamoyloxyethyl group, a 2,4,6-trimethylphenylcarbamoyloxyethyl group, a 2-trifluoromethylphenylcarbamoyloxyethyl group, a 3-trifluoromethylphenylcarbamoyloxyethyl group, a 4-
5 trifluoromethylphenylcarbamoyloxyethyl group, a 2,3-ditrifluoromethylphenylcarbamoyloxyethyl group, a 2,4-ditrifluoromethylphenylcarbamoyloxyethyl group, a 2,6-ditrifluoromethylphenylcarbamoyloxyethyl group, a 2-pentafluoroethylphenylcarbamoyloxyethyl group, a 3-
10 pentafluoroethylphenylcarbamoyloxyethyl group, a 4-pentafluoroethylphenylcarbamoyloxyethyl group, a 2-(n-propylphenyl)carbamoyloxyethyl group, a 3-(n-propylphenyl)carbamoyloxyethyl group, a 4-(n-propylphenyl)carbamoyloxyethyl group, a 2-
15 (phenylcarbamoyloxy)ethyl group, a 2-(3-trifluoromethylphenylcarbamoyloxy)ethyl group, a 2-(4-trifluoromethylphenylcarbamoyloxy)ethyl group, a 2-(2,3-ditrifluoromethylphenylcarbamoyloxy)ethyl group, a 2-
20 (2,4-ditrifluoromethylphenylcarbamoyloxy)ethyl group, a 2-(2,6-ditrifluoromethylphenylcarbamoyloxy)ethyl group, a 2-(2-pentafluoroethylphenylcarbamoyloxy)ethyl group, a 2-(3-pentafluoroethylphenylcarbamoyloxy)ethyl group, a 2-(4-pentafluoroethylphenylcarbamoyloxy)ethyl group, a 3-(phenylcarbamoyloxy)propyl group, a 3-(3-
25 trifluoromethylphenylcarbamoyloxy)propyl group, a 3-(4-trifluoromethylphenylcarbamoyloxy)propyl group, a 3-
2-(2,3-ditrifluoromethylphenylcarbamoyloxy)propyl group, a 3-
3-(2,4-ditrifluoromethylphenylcarbamoyloxy)propyl group,
group, a 3-((2,6-dimethylphenyl)carbamoyloxy)-propyl group, a 3-(2-pentafluoroethylphenylcarbamoyloxy)propyl group, a 3-(3-pentafluoroethylphenylcarbamoyloxy)propyl group, a 4-(3-pentafluoroethylphenylcarbamoyloxy)propyl group, a 4-(1-trifluoromethylphenyl)carbamoyloxy)butyl group, a 5-(1-trifluoromethylphenyl)carbamoyloxy)pentyl group, a 6-(1-trifluoromethylphenyl)carbamoyloxy)hexyl group, a (2-fluorophenyl)carbamoyloxy)methyl group, a 2-(3-fluorophenyl)carbamoyloxy)ethyl group, a 1-(3-fluorophenyl)carbamoyloxy)ethyl group, a 3-(2-chlorophenyl)carbamoyloxy)propyl group, a 4-(3-chlorophenyl)carbamoyloxy)butyl group, a 5-(4-chlorophenyl)carbamoyloxy)pentyl group, a 6-(2-bromophenyl)carbamoyloxy)hexyl group, a (2-bromophenyl)carbamoyloxy)methyl group, a 2-(4-bromophenyl)carbamoyloxy)ethyl group, a 1-(2-iodophenyl)carbamoyloxy)ethyl group, a 3-(2-iodophenyl)carbamoyloxy)propyl group, a 4-(2-iodophenyl)carbamoyloxy)butyl group, a 5-(2,3-difluorophenyl)carbamoyloxy)pentyl group, a 6-(3,4-difluorophenyl)carbamoyloxy)hexyl group, a (3,5-difluorophenyl)carbamoyloxy)methyl group, a 2-(2,4-difluorophenyl)carbamoyloxy)ethyl group, a 1-(2,6-difluorophenyl)carbamoyloxy)ethyl group, a 3-(2,3-dichlorophenyl)carbamoyloxy)propyl group, a 4-(3,4-dichlorophenyl)carbamoyloxy)butyl group, a 5-(3,5-dichlorophenyl)carbamoyloxy)pentyl group, a 6-(2,4-
dichlorophenylcarbamoyloxy)hexyl group, a (2,6-
dichlorophenylcarbamoyloxy)methyl group, a 2-(3,4,5-
trifluorophenylcarbamoyloxy)ethyl group, a 1-
(2,3,4,5,6-pentafluorophenylcarbamoyloxy)ethyl group, a 
3-(3,4,5-trichlorophenylcarbamoyloxy)propyl group, a 4-
(2,4,6-trifluorophenylcarbamoyloxy)butyl group, a 5-
(2,4,6-trichlorophenylcarbamoyloxy)pentyl group, a (2-
methyl-3-chlorophenylcarbamoyloxy)methyl group, a (3-
methyl-4-chlorophenylcarbamoyloxy)methyl group, a (2-
chloro-4-methylphenylcarbamoyloxy)methyl group, a (2-
methyl-3-fluorophenylcarbamoyloxy)methyl group, an 
ethylcarbamoyloxymethyl group, an n-
butylcarbamoyloxymethyl group, an n-
hexylcarbamoyloxymethyl group, an n-
pentylcarbamoyloxymethyl group, an N-methyl-N-
phenylcarbamoyloxymethyl group, an N,N-
dimethylcarbamoyloxymethyl group, an N-methyl-N-
ethylcarbamoyloxymethyl group, a 2-(N-(2-fluorophenyl)-
N-methylcarbamoyloxy)ethyl group, a 1-(N-(3-
fluorophenyl)-N-methylcarbamoyloxy)ethyl group, a 3-(N-
(4-fluorophenyl)-N-methylcarbamoyloxy)propyl group, a 
4-(N-(2-chlorophenyl)-N-methylcarbamoyloxy)butyl group, 
a 5-(N-(3-chlorophenyl)-N-methylcarbamoyloxy)pentyl 
group, a 6-(N-(4-chlorophenyl)-N-
methylcarbamoyloxy)hexyl group, an (N-(-bromophenyl)-
N-methylcarbamoyloxy)methyl group, a 2-(N-(2-
iodophenyl)-N-methylcarbamoyloxy)ethyl group, a 1-(N-
(3-iodophenyl)-N-methylcarbamoyloxy)ethyl group, a 3-
(N-(4-iodophenyl)-N-methylcarbamoyloxy)propyl group, a 4-(N-(2,3-difluorophenyl)-N-methylcarbamoyloxy)butyl group, a 5-(N-(3,4-difluorophenyl)-N-methylcarbamoyloxy)pentyl group, a 6-(N-(3,5-difluorophenyl)-N-methylcarbamoyloxy)hexyl group, an (N-(2,4-difluorophenyl)-N-methylcarbamoyloxy)methyl group, a 2-(N-(2,6-difluorophenyl)-N-methylcarbamoyloxy)ethyl group, a 1-(N-(2,3-dichlorophenyl)-N-methylcarbamoyloxy)ethyl group, a 3-(N-(3,4-dichlorophenyl)-N-methylcarbamoyloxy)propyl group, an (N-(3,5-dichlorophenyl)-N-methylcarbamoyloxy)methyl group, a 4-(N-(2,4-dichlorophenyl)-N-methylcarbamoyloxy)butyl group, a 5-(N-(2,6-dichlorophenyl)-N-methylcarbamoyloxy)pentyl group, a 6-(N-(3,4,5-trifluorophenyl)-N-methylcarbamoyloxy)hexyl group, an (N-(3,4,5-trichlorophenyl)-N-methylcarbamoyloxy)methyl group, a 2-(N-(2,4,6-trifluorophenyl)-N-methylcarbamoyloxy)ethyl group, a 1-(N-(2,4,6-trichlorophenyl)-N-methylcarbamoyloxy)ethyl group, a 3-(N-(2-methylphenyl)-N-methylcarbamoyloxy)propyl group, a 4-(N-(3-methylphenyl)-N-methylcarbamoyloxy)butyl group, a 5-(N-(4-methylphenyl)-N-methylcarbamoyloxy)hexyl group, a 6-(N-(2-methyl-3-chlorophenyl)-N-methylcarbamoyloxy)hexyl group, an (N-(3-methyl-4-chlorophenyl)-N-methylcarbamoyloxy)methyl group, a 2-(N-(2-chloro-4-methylphenyl)-N-methylcarbamoyloxy)ethyl group, a 1-(N-(2-methyl-3-fluorophenyl)-N-methylcarbamoyloxy)ethyl group.
methylcarbamoyloxy)ethyl group, a 3-(N-(2-
trifluoromethylphenyl)-N-methylcarbamoyloxy)propyl
group, a 4-(N-(4-trifluoromethylphenyl)-N-
methylcarbamoyloxy)butyl group, a 2-(N-(4-
trifluoromethylphenyl)-N-methylcarbamoyloxy)ethyl group,
a 5-(N-phenyl-N-phenylcarbamoyloxy)pentyl group, a 6-
(N-phenyl-N-(2-fluorophenyl)carbamoyloxy)hexyl group,
an (N-phenyl-N-(3-fluorophenyl)carbamoyloxy)methyl
group, a 2-(N-phenyl-N-(4-fluorophenyl)-
carbamoyloxy)ethyl group, a 1-(N-phenyl-N-(2-
chlorophenyl)carbamoyloxy)ethyl group, a 1-(N-phenyl-N-
(3-chlorophenyl)carbamoyloxy)ethyl group, a 3-(N-
phenyl-N-(4-chlorophenyl)carbamoyloxy)propyl group, a
4-(N-phenyl-N-(2-bromophenyl)carbamoyloxy)butyl group,
a 5-(N-phenyl-N-(3-bromophenyl)carbamoyloxy)pentyl
group, a 6-(N-phenyl-N-(4-bromophenyl)-
carbamoyloxy)hexyl group, an (N-phenyl-N-(2-
iiodophenyl)carbamoyloxy)methyl group, a 1-(N-phenyl-N-
(3-iiodophenyl)carbamoyloxy)ethyl group, a 2-(N-phenyl-
N-(4-iiodophenyl)carbamoyloxy)ethyl group, a 1-(N-
phenyl-N-(2,3-difluorophenyl)carbamoyloxy)ethyl group,
a 3-(N-phenyl-N-(3,4-difluorophenyl)carbamoyloxy)propyl
group, a 4-(N-phenyl-N-(3,5-difluorophenyl)-
carbamoyloxy)butyl group, a 5-(N-phenyl-N-(2,4-
difluorophenyl)carbamoyloxy)pentyl group, a 6-(N-
phenyl-N-(2,6-difluorophenyl)carbamoyloxy)hexyl group,
an (N-phenyl-N-(2,3-dichlorophenyl)carbamoyloxy)methyl
group, a 2-(N-phenyl-N-(3,4-dichlorophenyl)-
carbamoyloxy)ethyl group, a 1-(N-phenyl-N-(3,5-dichlorophenyl)carbamoyloxy)ethyl group, a 3-(N-phenyl-N-(2,4-dichlorophenyl)carbamoyloxy)propyl group, a 4-(N-phenyl-N-(2,6-dichlorophenyl)carbamoyloxy)butyl group, a 5-(N-phenyl-N-(3,4,5-trifluorophenyl)carbamoyloxy)pentyl group, a 6-(N-phenyl-N-(3,4,5-trichlorophenyl)carbamoyloxy)hexyl group, an (N-phenyl-N-(2,4,6-trifluorophenyl)carbamoyloxy)methyl group, a 2-(N-phenyl-N-(2,4,6-trichlorophenyl)carbamoyloxy)ethyl group, a 1-(N-phenyl-N-(2-methylphenyl)carbamoyloxy)ethyl group, a 3-(N-phenyl-N-(3-methylphenyl)carbamoyloxy)propyl group, a 4-(N-phenyl-N-(4-methylphenyl)carbamoyloxy)butyl group, a 5-(N-phenyl-N-(2-methyl-3-chlorophenyl)carbamoyloxy)pentyl group, a 6-(N-phenyl-N-(3-methyl-4-chlorophenyl)carbamoyloxy)hexyl group, an (N-phenyl-N-(2-chloro-4-methylphenyl)carbamoyloxy)methyl group, an (N-phenyl-N-(2-methyl-3-fluorophenyl)carbamoyloxy)methyl group, a 2-(N-phenyl-N-(2-trifluoromethylphenyl)carbamoyloxy)ethyl group, a 1-(N-phenyl-N-(3-trifluoromethylphenyl)carbamoyloxy)ethyl group, a 3-(N-phenyl-N-(4-trifluoromethylphenyl)carbamoyloxy)propyl group, a 2-isopropylphenylcarbamoyloxy)methyl group, a 3-isopropylphenylcarbamoyloxy)methyl group, a 4-isopropylphenylcarbamoyloxy)methyl group, a 2-tert-butylphenylcarbamoyloxy)methyl group, a 4-n-butylphenylcarbamoyloxy)methyl group, a 2-methyl-4-chlorophenylcarbamoyloxy)methyl group, a 3-tert-
butylphenylcarbamoyloxyethyl group, a 4-tert-
butylphenylcarbamoyloxyethyl group, a 2-sec-
butylphenylcarbamoyloxyethyl group, a 3-sec-
butylphenylcarbamoyloxyethyl group, a 4-sec-
butylphenylcarbamoyloxyethyl group, a 4-
pentylphenylcarbamoyloxyethyl group, a 4-
hexylphenylcarbamoyloxyethyl group, a 3,4-
dimethoxyphenylcarbamoyloxyethyl group, a 3,4,5-
trimethoxyphenylcarbamoyloxyethyl group, a 2-
methoxyphenylcarbamoyloxyethyl group, a 3-
methoxyphenylcarbamoyloxyethyl group, a 4-
methoxyphenylcarbamoyloxyethyl group, a 2-methoxy-3-
chlorophenylcarbamoyloxyethyl group, a 2-(2-fluoro-3-
methoxyphenylcarbamoyloxy)ethyl group, a 1-(2-fluoro-4-
methoxyphenylcarbamoyloxy)ethyl group, a 3-(2,6-
dimethoxyphenylcarbamoyloxy)propyl group, a 4-(2,3,4-
trifluorophenylcarbamoyloxy)butyl group, a 5-(3,4,5-
trifluorophenylcarbamoyloxy)pentyl group, a 6-(2-
trifluoromethoxyphenylcarbamoyloxy)hexyl group, a 3-
trifluoromethoxyphenylcarbamoyloxyethyl group, a 4-
trifluoromethoxyphenylcarbamoyloxyethyl group, a 2-(4-
trifluoromethoxyphenylcarbamoyloxy)ethyl group, a 2-(N-
methyl-N-4-trifluoromethoxyphenyl)carbamoyloxy)ethyl
group, a 3-trifluoromethylphenylcarbamoyloxyethyl
group, a 4-trifluoromethylphenylcarbamoyloxyethyl
group, a 3-trifluoromethyl-4-
chlorophenylcarbamoyloxyethyl group, a 3,5-
ditrifluoromethoxyphenylcarbamoyloxyethyl group, a
2,4-dichlorophenylcarbamoyloxymethyl group, a 2-
chlorophenylcarbamoyloxymethyl group, a 3-
chlorophenylcarbamoyloxymethyl group, a 4-
chlorophenylcarbamoyloxymethyl group, a 3,5-
dichlorophenylcarbamoyloxymethyl group, a 3,4-
dichlorophenylcarbamoyloxymethyl group, a 2-
fluorophenylcarbamoyloxymethyl group, a 3-
fluorophenylcarbamoyloxymethyl group, a 4-
fluorophenylcarbamoyloxymethyl group, a 2-
pentafluoroethoxyphenylcarbamoyloxymethyl group, a 3-
pentafluoroethoxyphenylcarbamoyloxymethyl group, an 4-
pentafluoroethoxyphenylcarbamoyloxymethyl group, a 2-
isopropoxyphenylcarbamoyloxymethyl group, a 3-
isopropoxyphenylcarbamoyloxymethyl group, a 4-
isopropoxyphenylcarbamoyloxymethyl group, a 2-tert-
butoxyphenylcarbamoyloxymethyl group, a 4-n-
butoxyphenylcarbamoyloxymethyl group, a 3-
methoxyphenylcarbamoyloxymethyl group, a 4-
methoxyphenylcarbamoyloxymethyl group, a 4-
ethxyphenylcarbamoyloxymethyl group, a 3-tert-
butoxyphenylcarbamoyloxymethyl group, a 4-tert-
butoxyphenylcarbamoyloxymethyl group, a 2-sec-
butoxyphenylcarbamoyloxymethyl group, a 3-sec-
butoxyphenylcarbamoyloxymethyl group, a 4-sec-
butoxyphenylcarbamoyloxymethyl group, a 2-n-
heptafluoropropoxyphenylcarbamoyloxymethyl group, a 3-
n-heptafluoropropoxyphenylcarbamoyloxymethyl group, a 4-n-heptafluoropropoxyphenylcarbamoyloxymethyl group, a
4-n-pentloxyphenylcarbamoyloxymethyl group, a 4-n-
hexyloxyphenylcarbamoyloxymethyl group, a 4-
cyanophenylcarbamoyloxymethyl group, an (N-methyl-N-(3-
cyano phenyl)carbamoyloxy)methyl group, a 2-
cyanophenylcarbamoyloxymethyl group, a 3,4-
dicyanophenylcarbamoyloxymethyl group, a 3,4,5-
tricyanophenylcarbamoyloxymethyl group, a 4-
phenoxyphenylcarbamoyloxymethyl group, an (N-methyl-N-
(3-phenoxyphenyl)carbamoyloxy)methyl group, a 2-
phenoxyphenylcarbamoyloxymethyl group, a 3,4-
diphenoxophenylcarbamoyloxymethyl group, a 2,4,6-
triphenoxophenylcarbamoyloxymethyl group, a 4-
methylthiophenylcarbamoyloxymethyl group, an (N-methyl-
N-(4-methylthiophenyl)carbamoyloxy)methyl group, a 3-
methylthiophenylcarbamoyloxymethyl group, a 2-
methylthiophenylcarbamoyloxymethyl group, a 3,4-
dimethylthiophenylcarbamoyloxymethyl group, a 2,4,6-
trimethylthiophenylcarbamoyloxymethyl group, a 4-
acetylphenylcarbamoyloxymethyl group, a 3-
acetylphenylcarbamoyloxymethyl group, a 2-
acetylphenylcarbamoyloxymethyl group, a 3,4-
diacetylphenylcarbamoyloxymethyl group, an (N-methyl-N-
(3,4-diacylphenyl)carbamoyloxy)methyl group, a 2,4,6-
triacetylphenylcarbamoyloxymethyl group, a 4-
biphenylcarbamoyloxymethyl group, a 3-
biphenylcarbamoyloxymethyl group, a 2-
biphenylcarbamoyloxymethyl group, an (N-methyl-N-(2-
biphenyl)carbamoyloxy)methyl group, a 3,4-
diphenylcarbamoyloxymethyl group, a 2,4,6-
triphenylphenylcarbamoyloxymethyl group, a 4-n-
heptyloxyphenylcarbamoyloxymethyl group, an (N-methyl-
N-4-(n-heptyloxyphenyl)carbamoyloxy)methyl group, a 3-
n-octyloxyphenylcarbamoyloxymethyl group, a 2-n-
nonyloxyphenylcarbamoyloxymethyl group, a 4-n-
decyloxyphenylcarbamoyloxymethyl group, a 2,4-di-n-
heptyloxyphenylcarbamoyloxymethyl group, a 2,4,6-tri-n-
heptyloxyphenylcarbamoyloxymethyl group, a 4-(7,7-
dichloroheptyloxy)phenylcarbamoyloxymethyl group, a 4-
benzylphenylcarbamoyloxymethyl group, an (N-methyl-N-
(4-benzylphenyl)carbamoyloxy)methyl group, a 3-
benzylphenylcarbamoyloxymethyl group, a 2-
benzylphenylcarbamoyloxymethyl group, a 2,4-
dibenzylphenylcarbamoyloxymethyl group, a 2,4,6-
tribenzylphenylcarbamoyloxymethyl group, a 4-n-
ocetylphenylcarbamoyloxymethyl group, an (N-methyl-N-(4-
n-octylphenyl)carbamoyloxy)methyl group, a 3-n-
heptylphenylcarbamoyloxymethyl group, a 2-n-
ocetylphenylcarbamoyloxymethyl group, a 3-(8,8,3-
trifluorooctyl)phenylcarbamoyloxymethyl group, a 4-n-
nonylphenylcarbamoyloxymethyl group, a 3-n-
decylphenylcarbamoyloxymethyl group, a 2,4-di-n-
ocetylphenylcarbamoyloxymethyl group, a 2,4,6-tri-n-
ocetylphenylcarbamoyloxymethyl group, a 4-phenyl-3-
chlorophenylcarbamoyloxymethyl group, a 4-phenoxy-3-
methylthiophenylcarbamoyloxymethyl group, a 4-n-
heptyloxy-3-trifluoromethoxyphenylcarbamoyloxymethyl
group, a 4-n-octyl-2-trifluoromethylphenyl-
carbamoxyoxymethyl group, a 4-benzyl-2-
methylphenylcarbamoxyoxymethyl group, a 3,4-
ethylendioxyphenylcarbamoxyoxymethyl group, a 3,4-
5 methylenedioxyphenylcarbamoxyoxymethyl group, a
benzylcarbamoxyoxymethyl group, a 2-
phenylethylcarbamoxyoxymethyl group, a
cyclohexylcarbamoxyoxymethyl group, a 1-
naphthylcarbamoxyoxymethyl group, a 2-
10 naphthylcarbamoxyoxymethyl group, a 5-(2,3-dihydro-1H-
indenyl)carbamoxyoxymethyl group, a 5-(2,3-
dihydrobenzofuryl)carbamoxyoxymethyl group, an (N-
methyl-N-(3,4-methylenedioxyphenyl)carbamoxyloxy)methyl
15 group, an (N-methyl-N-benzylcarbamoxyloxy)methyl
group, an (N-methyl-N-(2-phenylethyl)carbamoxyloxy)methyl
group, an (N-methyl-N-cyclohexylcarbamoxyloxy)methyl
group, an (N-methyl-N-(1-naphthyl)carbamoxyloxy)methyl
group, an (N-methyl-N-(2-naphthyl)carbamoxyloxy)methyl
group, an (N-methyl-N-(5-(2,3-dihydro-1H-indenyl))-
carbamoxyloxy)methyl group, and an (N-methyl-N-(2,3-
dihydro-5-benzofuryl)carbamoxyloxy)methyl group (wherein,
on the amino group, 1 or 2 groups selected from the
following groups may be substituted: a C1-C6 alkyl
group, the above described phenyl C1-C6 alkyl group,
the above described C3-C8 cycloalkyl group, naphthyl
group, 2,3-dihydro-1H-indenyl group, 2,3-
dihydrobenzofuryl group, and the above described phenyl
group (wherein, on the phenyl ring, 1 to 5 groups, and
preferably 1 to 3 groups selected from the group consisting of a C1-C4 alkylenedioxy group, a cyano group, a phenoxy group, a C1-C6 alkylthio group, a C1-C6 alkanoyl group, a phenyl group, a phenyl C1-C6 alkyl group, a halogen atom, a halogen substituted or unsubstituted C1-C10 alkyl group, and a halogen substituted or unsubstituted C1-C10 alkoxy group may be substituted (in a case where the substituent is a C1-C4 alkylenedioxy group, 1 or 2 groups are preferably substituted)).

Examples of the C1-C6 alkanoyl substituted C1-C6 alkyl group may include an acetylmethyl group, a 2-propionylethyl group, a 1-buthyrylethyl group, a 2-acetylethyl group, a 3-acetylpropyl group, a 4-acetylbutyl group, a 4-isobuthyrylbutil group, a 5-pentanoylpentyl group, a 6-acetylhexyl group, a 6-tert-butylcarbonylhexyl group, a 1,1-dimethyl-2-hexanoylethyl group, and a 2-methyl-3-acetylpropyl group.

In addition to the above described phenoxy C1-C6 alkyl group (wherein, on the phenyl ring at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), examples of the phenoxy C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the following groups may be substituted: a halogen atom; a C1-C4 alkylenedioxy
group; a C1-C6 alkoxy carbonyl group; a phenyl group; a phenoxy group; a pyrrolyl group; a benzothiazolyl group; a 1,2,4-triazolyl group; an imidazolyl group; an isoxazolyl group; a benzoxazolyl group; a benzotriazolyl group; a cyano group; a nitro group; a C2-C6 alkenyl group; a C1-C6 alkanoyl group; a C1-C6 alkoxy carbonyl substituted C1-C6 alkyl group; a C1-C6 alkanoyl substituted C1-C6 alkyl group; a group - N(R₁₁⁰);R₁₁² (wherein R₁₁⁰ and R₁₁², which may be identical or different, each represent a hydrogen atom, a C1-C6 alkyl group, a C1-C6 alkanoyl group, or a phenyl group, and R₁₁⁰ and R₁₁² may bind to each other adjacent thereto directly or through a nitrogen, oxygen or sulfur atom, so as to form a 5-7 membered saturated heterocyclic ring together with the nitrogen atom, wherein, on the heterocyclic ring, at least one selected from the group consisting of a C1-C6 alkoxy carbonyl group and an amino group (wherein, on the amino group, at least one selected from a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) and a C1-C6 alkyl group may be substituted) may be substituted); a phenyl C1-C6 alkoxy group; a phenyl C1-C6 alkyl group; a C1-C6 alkylthio group; a C3-C6 cycloalkyl group; a halogen substituted or unsubstituted C1-C6 alkyl group; and a halogen
substituted or unsubstituted C1-C6 alkoxy group), may further include phenoxy C1-C6 alkyl groups such as a 3,4-methylenedioxyphenoxyethyl group, a 3,4-ethylenedioxyphenoxyethyl group, a 4-ethoxycarbonylphenoxyethyl group, a 3-methoxycarbonylphenoxyethyl group, a 2-ethoxycarbonylphenoxyethyl group, a 2,4-diethoxycarbonylphenoxyethyl group, a 2,4,6-triethoxycarbonylphenoxyethyl group, a 2-ethoxycarbonyl-4-methylphenoxyethyl group, a 2-methoxycarbonyl-4-methoxyphenoxyethyl group, a 2-methoxycarbonyl-3-methoxyphenoxyethyl group, a 2-(4-ethoxycarbonylphenoxy)ethyl group, a 4-cyanophenoxyethyl group, a 3-cyanophenoxyethyl group, a 2-cyanophenoxyethyl group, a 2,4-dicyanophenoxyethyl group, a 2,4,6-tricyanophenoxyethyl group, a 2-(4-cyanophenoxy)ethyl group, a 4-nitrophenoxyethyl group, a 3-nitrophenoxyethyl group, a 2-nitrophenoxyethyl group, a 2,4,6-trinitrophenoxyethyl group, a 2-(4-nitrophenoxy)ethyl group, a 4-allylphenoxyethyl group, a 3-allylphenoxyethyl group, a 2-allylphenoxyethyl group, a 3,4-diallylphenoxyethyl group, a 3,4,5-triallylphenoxyethyl group, a 2-(4-allylphenoxy)ethyl group, a 2-(3-allylphenoxy)ethyl group, a 3-diethylaminophenoxyethyl group, a 3-anilinophenoxyethyl group, a 4-
acetylamino phenoxymethyl group, a 2,4,6-
tri(diethylamino)phenoxymethyl group, a 2-
anilinophenoxymethyl group, a 2,4-
diacetylamino phenoxymethyl group, a 2-(3-
diethylaminophenoxy)ethyl group, a 2-(3-
anilinophenoxy)ethyl group, a 2-(4-(2-
acetyl ethyl)phenoxy)ethyl group, a 4-(2-
acetyl ethyl)phenoxy methyl group, a 3-
acetylmethyl phenoxymethyl group, 2-(3-
acetylpropyl)phenoxymethyl group, a 2,4-di(2-
acetyl ethyl)phenoxymethyl group, a 2,4,6-tri(2-
acetyl ethyl)phenoxymethyl group, a 4-
methoxy carbonylmethyl phenoxymethyl group, a 3-
ethoxy carbonylmethyl phenoxymethyl group, a 2-
methoxy carbonylmethyl phenoxymethyl group, a 2,6-
dimethoxy carbonylmethyl phenoxymethyl group, a 2,4,6-
trimethoxy carbonylmethyl phenoxymethyl group, a 2-(4-
methoxy carbonylmethyl phenoxo)ethyl group, a 4-
propionyl phenoxymethyl group, a 4-acetyl phenoxymethyl

20 group, a 3-propionyl phenoxymethyl group, a 2-
acetylphenoxymethyl group, a 2,4-
dipropionyl phenoxymethyl group, a 2,4,6-
tri acetyl phenoxymethyl group, a 2-(4-
propionyl phenoxy)ethyl group, a 2-benzyl phenoxymethyl

group, a 3-benzyl phenoxymethyl group, a 4-
benzyl phenoxymethyl group, a 2,3-dibenzyl phenoxymethyl
group, a 3,4,5-tribenzyl phenoxymethyl group, a 4-
methyl thiophenoxymethyl group, a 3-

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methylthiophenoxyethyl group, a 2-
methylthiophenoxyethyl group, a 2,4-
dimethylthiophenoxyethyl group, a 2,4,6-
trimethylthiophenoxyethyl group, a 2-(4-
methylthiophenoxy)ethyl group, a 4-
cyclopentyloxyphenoxymethyl group, a 3-
cyclohexylphenoxymethyl group, a 4-
cyclohexylphenoxymethyl group, a 2-
cyloheptylphenoxymethyl group, a 2,4-
dicyclopentyloxyphenoxymethyl group, a 2,4-cyclopentyl-6-
cylooctylphenoxymethyl group, a 2-(4-
cylohexylphenoxo)ethyl group, a 2-(4-
cylopentyloxyphenoxymethyl group, a 2-(4-octyl-
octyloxyphenoxymethyl group, a 2-(4-a-
octyloxyphenoxo)ethyl group, a 4-phenylphenoxymethyl
group, a 3-phenylphenoxymethyl group, a 2-
phenylphenoxymethyl group, a 2,4-diphenylphenoxymethyl
group, a 2,4,6-triphenylphenoxymethyl group, a 2-(4-
phenylphenoxo)ethyl group, a 4-phenoxyphenoxymethyl
group, a 3-phenoxyphenoxymethyl group, a 2-
phenoxyphenoxymethyl group, a 2,4-
diphenoxyphenoxymethyl group, a 2,4,6-
triphenoxyphenoxymethyl group, a 2-(3-
phenoxyphenoxo)ethyl group, a 4-benzylxyloxyphenoxymethyl
group, a 3-benzylxyloxyphenoxymethyl group, a 2-
benzylxyloxyphenoxymethyl group, a 2,4-
dibenzylxyloxyphenoxymethyl group, a 2,4,6-
tribenzylxyloxyphenoxymethyl group, a 2-14-
benzyloxyphenoxy)ethyl group, a 2,4-
dibenzyl)phenoxy)methyl group, a 2,4,6-
tribenzylphenoxy)methyl group, a 2-(4-
benzylphenoxy)ethyl group, a 4-(1-
pyrrolyl)phenoxy)methyl group, a 3-(1-
pyrrolyl)phenoxy)methyl group, a 2-(1-
pyrrolyl)phenoxy)methyl group, a 2,4-di(1-
pyrrolyl)phenoxy)methyl group, a 2,4,6-tri(1-
pyrrolyl)phenoxy)methyl group, a 2-(2-
benzothiazolyl)phenoxy)methyl group, a 2-(2-
benzothiazolyl)phenoxy)methyl group, a 3-(2-
benzothiazolyl)phenoxy)methyl group, a 2,4,6-tri(5-
benzothiazolyl)phenoxy)methyl group, a 2,4-di(6-
benzothiazolyl)phenoxy)methyl group, a 4-(1,1,2,4-
triazolyl)phenoxy)methyl group, a 3-(1,1,2,4-
triazolyl)phenoxy)methyl group, a 2-(1,1,2,4-
triazolyl)phenoxy)methyl group, a 4-(3,1,2,4-
triazolyl)phenoxy)methyl group, a 2,4-di(5,1,2,4-
triazolyl)phenoxy)methyl group, a 2,4,6-tri(1,1,2,4-
triazolyl)phenoxy)methyl group, a 4-(5-
isoazolyl)phenoxy)methyl group, a 3-(3-
isoazolyl)phenoxy)methyl group, a 2-(4-
isoazolyl)phenoxy)methyl group, a 2-(5-
isoazolyl)phenoxy)methyl group, a 2,4-di(5-
isoazolyl)phenoxy)methyl group, a 2,4,6-tri(5-
isoazolyl)phenoxy)methyl group, a 4-(1-
imidazolyl)phenoxy)methyl group, a 3-(2-
imidazolyl)phenoxy)methyl group, a 2-(4-
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imidazolyl)phenoxyethyl group, a 2,4-di(1-
imidazolyl)phenoxyethyl group, a 2,4,6-tri(1-
imidazolyl)phenoxyethyl group, a 4-(1-
benzotriazolyl)phenoxyethyl group, a 3-(1-
benzotriazolyl)phenoxyethyl group, a 2-(1-
benzotriazolyl)phenoxyethyl group, a 2-(1-
benzotriazolyl)phenoxyethyl group, a 2,4-di(1-
benzotriazolyl)phenoxyethyl group, a 2,4,6-tri(1-
benzotriazolyl)phenoxyethyl group, a 4-(8-
benzimidazolyl)phenoxyethyl group, a 3-(5-
benzimidazolyl)phenoxyethyl group, a 2-(2-
benzimidazolyl)phenoxyethyl group, a 2-(1-
benzotriazolyl)phenoxyethyl group, a 2,4-di(2-
benzimidazolyl)phenoxyethyl group, a 2,4,6-tri(2-
benzimidazolyl)phenoxyethyl group, a 4-(4-tert-
butoxycarbonyl-1-piperazinyl)phenoxyethyl group, a 2-
(4-(4-(4-N-(4-chlorophenyl)-N-methylamino))-1-
piperidyl)phenoxyethyl group, a 2-(4-(1,2,4-
triazolyl)phenoxyethyl group, a 2-(2-(5-
isoazolyl)phenoxyethyl group, a 2-(2-methoxy-4-
allylphenoxy)ethyl group, a 2-(2-fluoro-4-
nitrophenoxy)ethyl group, a 2-(2-ethoxy-5-
allylphenoxy)ethyl group, a 2-fluoro-4-
nitrophenoxyethyl group, a 2-methoxy-4-
allylphenoxyethyl group, a 2-ethoxy-5-
allylphenoxyethyl group, and a 2-methyl-4-
acetylphenoxyethyl group (wherein, on the phenyl ring,
1 to 5 groups, and preferably 1 to 3 groups selected
from the following groups may be substituted: a halogen atom; the above described Cl-C₄ alkylendioxy group; the above described Cl-C₆ alkoxy carbonyl group; a phenyl group; a phenoxy group; a pyrrolyl group; a benzothiazolyl group; a 1,2,4-triazolyl group; an imidazolyl group; an isoxazolyl group; a benzoxazolyl group; a benzotriazolyl group; a cyano group; a nitro group; the above described C2-C₆ alkenyl group; the above described Cl-C₆ alkanoyl group; the above described Cl-C₆ alkoxy carbonyl substituted Cl-C₆ alkyl group; the above described Cl-C₆ alkanoyl substituted Cl-C₆ alkyl group; a group -N(R¹¹¹)R¹²² (wherein R¹¹¹ and R¹²², which may be identical or different, each represent a hydrogen atom, the above described Cl-C₆ alkyl group, the above described Cl-C₆ alkanoyl group, or a phenyl group, and the above described R¹¹² and R¹²² may bind to each other adjacent thereto directly or through a nitrogen, oxygen or sulfur atom, so as to form a 5-7 membered saturated heterocyclic ring together with the nitrogen atom, wherein, on the heterocyclic ring, 1 to 3 groups selected from the group consisting of a Cl-C₆ alkoxy carbonyl group and an amino group (wherein, on the amino group, 1 or 2 groups selected from a phenyl group (wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C₆ alkyl group, and a halogen substituted or unsubstituted Cl-C₆ alkoxy group may be
substituted) and a C1-C6 alkyl group may be substituted] may be substituted); the above described phenyl C1-C6 alkoxy group; the above described phenyl C1-C6 alkyl group; the above described C1-C6 alkylthio group; the above described C3-C9 cycloalkyl group; the above described halogen substituted or unsubstituted C1-C6 alkyl group; and the above described halogen substituted or unsubstituted C1-C10 alkoxy group (in a case where the substituent is a C1-C4 alkylenedioxy group, 1 or 2 groups may be substituted).

Examples of the tetrahydropyranloxy C1-C5 alkyl group may include a (2-tetrahydropyranloxy)methyl group, a 2-(3-tetrahydropyranloxy)ethyl group, a 1-(4-tetrahydropyranloxy)ethyl group, a 2-(2-tetrahydropyranloxy)ethyl group, a 3-(2-tetrahydropyranloxy)propyl group, a 4-(2-tetrahydropyranloxy)butyl group, a 4-(3-tetrahydropyranloxy)butyl group, a 5-(2-tetrahydropyranloxy)pentyl group, a 6-(2-tetrahydropyranloxy)hexyl group, a 6-(2-tetrahydropyranloxy)hexyl group, a 1,1-dimethyl-2-(4-tetrahydropyranloxy)ethyl group, and a 2-methyl-3-(3-tetrahydropyranloxy)propyl group.

Examples of the furyl C1-C6 alkoxy substituted C1-C6 alkyl group (wherein, on the furan ring, at least one C1-C6 alkoxy carbonyl group may be substituted) may include furyl C1-C6 alkoxy substituted
C1-C6 alkyl groups such as a (2-furyl)methoxy)methyl group, a (2-(3-furyl)ethoxy)methyl group, a (3-(2-furyl)propoxy)methyl group, a (2-(3-furyl)propoxy)methyl group, a (4-(2-furyl)butoxy)methyl group, a (5-(2-furyl)pentoxy)methyl group, a (4-(2-furyl)pentoxy)methyl group, a (6-(3-furyl)hexyloxy)methyl group, a 2-(2-furyl)methoxy)ethyl group, a 1-(2-(3-furyl)ethoxy)ethyl group, a 3-(3-(2-furyl)propoxy)propyl group, a 4-(2-(3-furyl)propoxy)butyl group, a 5-(4-(2-furyl)butoxy)hexyl group, a 1,1-dimethyl-2-(5-(3-furyl)pentoxy)ethyl group, a 2-methyl-3-(4-(2-furyl)pentoxy)propyl group, a 2-(6-(3-furyl)hexyloxy)ethyl group, a (5-ethoxycarbonyl-2-furyl)methoxy)methyl group, a (4-methoxycarbonyl-2-furyl)methoxy)methyl group, a ((3-propoxycarbonyl-2-furyl)methoxy)methyl group, a ((3-propoxycarbonyl-2-furyl)methoxy)methyl group, a ((5-butoxycarbonyl-2-furyl)methoxy)methyl group, a (4-pentoxy)carbonyl-2-furyl)methoxy)methyl group, a (5-hexyloxy)carbonyl-2-furyl)methoxy)methyl group, a (3,5-diethoxycarbonyl-2-furyl)methoxy)methyl group, and a ((3,4,5-triethoxycarbonyl-2-furyl)methoxy)methyl group (wherein, on the furan ring, 1 to 3 C1-C6 alkoxy carbonyl groups may be substituted).

Examples of the C3-C8 cycloalkyl C1-C6 alkyl group may include a cyclohexylmethyl group, a 2-cyclopropylethyl group, a 1-cyclopentylethyl group, a 3-cyclobutylpropyl group, a 4-cyclohexylbutyl group, a 5-cycloheptylpentyl group, a 6-cyclooctylhexyl group, a
1,1-dimethyl-2-cyclohexylethyl group, and a 2-methyl-3-cyclohexylpropyl group.

Examples of the tetrazolyl C1-C6 alkoxy substituted C1-C6 alkyl group (wherein, on the tetrazole ring, a group selected from the group consisting of the following groups may be substituted: a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a phenyl C1-C6 alkyl group, and a C3-C8 cycloalkyl C1-C6 alkyl group), may include tetrazolyl C1-C6 alkoxy substituted C1-C6 alkyl groups such as a (5-tetrazolyl)methoxy)methyl group, a 12-(5-tetrazolyl)ethoxy)methyl group, a (3-(5-tetrazolyl)propoxy)methyl group, a (2-(5-tetrazolyl)propoxy)methyl group, a (4-(5-tetrazolyl)butoxy)methyl group, a (5-(5-tetrazolyl)pentoxy)methyl group, a (4-(1-tetrazolyl)pentoxy)methyl group, a (6-(5-tetrazolyl)hexyloxy)methyl group, a (2-(1-tetrazolyl)methoxy)ethyl group, a 1-(2-(5-tetrazolyl)ethoxy)ethyl group, a 3-(3-(1-tetrazolyl)propoxy)propyl group, a 4-(2-(5-tetrazolyl)propoxy)butyl group, a 5-(4-(1-tetrazolyl)butoxy)hexyl group, a 1,1-dimethyl-2-(5-(5-tetrazolyl)pentoxy)ethyl group, a 2-methyl-3-(4-(1-tetrazolyl)pentoxy)propyl group, a 2-(6-(5-
tetrazolyl)hexyloxy)methyl group, a ((1-(2-phenylethyl)-5-tetrazolyl)methoxy)methyl group, a ((1-cyclohexylmethyl-5-tetrazolyl)methoxy)methyl group, a ((5-benzyl-1-tetrazolyl)methoxy)methyl group, a ((1-cyclopentylmethyl-5-tetrazolyl)methoxy)methyl group, a ((5-(2-cyclohexylethyl)-1-tetrazolyl)methoxy)methyl group, a ((1-benzyl-5-tetrazolyl)methoxy)methyl group, a ((1-cycloheptylmethyl-5-tetrazolyl)methoxy)methyl group, a ((1-(3-phenylpropyl)-5-tetrazolyl)methoxy)methyl group, a ((1-phenyl-5-tetrazolyl)methoxymethyl group, a ((1-(4-trifluoromethoxyphenyl)-5-tetrazolyl)methoxymethyl group, a ((1-(4-trifluoromethylphenyl)-5-tetrazolyl)methoxy)methyl group, a ((1-(4-chlorophenyl)-5-tetrazolyl)methoxy)methyl group (wherein, on the tetrazole ring, a group selected from the group consisting of the following groups may be substituted: a phenyl group (wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted linear or branched alkyl group containing 1 to 6 carbon atoms, and a halogen substituted or unsubstituted linear or branched alkoxy group containing 1 to 6 carbon atoms, may be substituted), the above described phenyl C1-C6 alkyl group, and the above described C3-C8 cycloalkyl C1-C6 alkyl group).

Examples of the isoxazolyl C1-C6 alkoxy
substituted C1-C6 alkyl group (wherein, on the isoxazole ring, at least one C1-C6 alkyl group may be substituted) may include isoxazolyl C1-C6 alkoxy substituted C1-C6 alkyl groups such as a ((3-5 isoxazolyl)methoxy)methyl group, a (2-(4-isoxazolyl)ethoxy)methyl group, a (3-(5-isoxazolyl)propoxy)methyl group, a (2-(3-isoxazolyl)propoxy)methyl group, a (4-(4-isoxazolyl)butoxy)methyl group, a (5-(5-isoxazolyl)pentoxy)methyl group, a (4-(3-isoxazolyl)pentoxy)methyl group, a (6-(4-isoxazolyl)hexyloxy)methyl group, a (2-(5-isoxazolyl)methoxy)ethyl group, a 1-(2-(3-isoxazolyl)ethoxy)ethyl group, a 3-(3-(4-isoxazolyl)propoxy)propyl group, a 4-(2-(3-isoxazolyl)propoxy)butyl group, a 5-(4-(3-isoxazolyl)butoxy)hexyl group, a 1,1-dimethyl-2-(5-(4-isoxazolyl)pentoxy)ethyl group, a 2-methyl-3-(4-(5-isoxazolyl)pentoxy)propyl group, a 2-(6-(3-isoxazolyl)hexyloxy)ethyl group, a ((5-methyl-3-isoxazolyl)methoxy)methyl group, a ((4-ethyl-3-isoxazolyl)methoxy)methyl group, a ((3-n-propyl-4-isoxazolyl)methoxy)methyl group, a ((5-n-butyl-3-isoxazolyl)methoxy)methyl group, a ((4-n-pentyl-3-isoxazolyl)methoxy)methyl group, a ((3-n-hexyl-5-isoxazolyl)methoxy)methyl group, and a ((4,5-dimethyl-3-isoxazolyl)methoxy)methyl group (wherein, on the isoxazole ring, the above described 1 to 2 C1-C6 alkyl
groups may be substituted).

Examples of the benzothienyl C1-C6 alkoxy substituted C1-C6 alkyl group (wherein, on the benzothiophene ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may include benzothienyl C1-C6 alkoxy substituted C1-C6 alkyl groups such as a ((3-benzothienyl)methoxy)methyl group, a ((2-benzothienyl)ethoxy)methyl group, a (3-(4-benzothienyl)propoxy)methyl group, a (2-(5-benzothienyl)propoxy)methyl group, a (4-(6-benzothienyl)butoxy)methyl group, a (5-(7-benzothienyl)pentoxy)methyl group, a (4-(3-benzothienyl)pentoxy)methyl group, a (6-(2-benzothienyl)hexyloxy)methyl group, a 2-(4-benzothienyl)methoxy)ethyl group, a 1-(2-(5-benzothienyl)ethoxy)ethyl group, a 3-(3-(6-benzothienyl)propoxy)propyl group, a 4-(12-(7-benzothienyl)propoxy)butyl group, a 5-(4-(3-benzothienyl)butoxy)hexyl group, a 1,1-dimethyl-2-(5-(3-benzothienyl)pentoxy)ethyl group, a 2-methyl-3-(4-(5-benzothienyl)pentoxy)propyl group, a 2-(6-(3-benzothienyl)hexyloxy)ethyl group, a ((5-methyl-3-benzothienyl)methoxy)methyl group, a ((4-ethyl-3-benzothienyl)methoxy)methyl group, a ((5-chloro-3-benzothienyl)methoxy)methyl group, a ((6-methyl-3-
benzothienyl)methoxy)methyl group, a ((4-
trifluoromethyl-3-benzothienyl)methoxy)methyl group, a
((3-methoxy-5-benzothienyl)methoxy)methyl group, a ((5-
trifluoromethoxy-3-benzothienyl)methoxy)methyl group, a
((4,5-dichloro-3-benzothienyl)methoxy)methyl group, a
((2,4,5-trifluoromethyl-3-benzothienyl)methoxy)methyl group,
a ((4,5-dichloro-2-methyl-3-benzothienyl)methoxy)methyl
group, and a ((4,5-dichloro-2-methoxy-3-
benzothienyl)methoxy)methyl group (wherein, on the
benzothiophene ring, 1 to 3 groups selected from the
group consisting of the above described halogen atom,
the above described halogen substituted or
unsubstituted Cl-C6 alkyl group, and the above
described halogen substituted or unsubstituted Cl-C6
alkoxy group may be substituted).

Examples of the 1,3,4-oxadiazolyl Cl-C6
alkoxy substituted Cl-C6 alkyl group (wherein, on the
1,3,4-oxadiazole ring, a phenyl group may be
substituted [wherein, on the phenyl ring, at least one
selected from the group consisting of a halogen atom, a
halogen substituted or unsubstituted Cl-C6 alkyl group,
and a halogen substituted or unsubstituted Cl-C6 alkoxy
group may be substituted]) may include 1,3,4-
oxadiazolyl Cl-C6 alkoxy substituted Cl-C6 alkyl groups
such as a ((2-1,3,4-oxadiazolyl)methoxy)methyl group, a
(2-(2-1,3,4-oxadiazolyl)methoxy)methyl group, a (3-(2-
1,2,4-oxadiazolyl)propoxy)methyl group, a (2-(2-1,3,4-
oxadiazolyl)propoxy)methyl group, a (4-(2-1,3,4-

oxadiazolyl)butoxy)methyl group, a (5-(2-1,3,4-oxadiazolyl)pentoxy)methyl group, a (4-(2-1,3,4-oxadiazolyl)pentoxy)methyl group, a (6-(2-1,3,4-oxadiazolyl)hexyloxy)methyl group, a 2-(2-1,3,4-oxadiazolyl)methoxy)ethyl group, a 1-(2-1,3,4-oxadiazolyl)ethoxy)ethyl group, a 3-(2-1,3,4-oxadiazolyl)propoxy)propyl group, a 4-(2-1,3,4-oxadiazolyl)propoxy)butyl group, a 5-(2-1,3,4-oxadiazolyl)methoxy)pentyl group, a 6-(2-1,3,4-oxadiazolyl)butoxy)hexyl group, a 1,1-dimethyl-2-(2-1,3,4-oxadiazolyl)pentoxy)ethyl group, a 2-methyl-3-(2-1,3,4-oxadiazolyl)pentoxy)propyl group, a 2-(2-1,3,4-oxadiazolyl)hexyloxy)ethyl group, a (5-(4-methylphenyl)-2-1,3,4-oxadiazolyl)methoxymethyl group, a (5-(4-chlorophenyl)-2-1,3,4-oxadiazolyl)methoxymethyl group, a (5-(4-trifluoromethylphenyl)-2-1,3,4-oxadiazolyl)methoxymethyl group, a (5-(4-methoxyphenyl)-2-1,3,4-oxadiazolyl)methoxymethyl group, a (5-(4-trifluoromethoxyphenyl)-2-1,3,4-oxadiazolyl)methoxymethyl group, a (5-(2,4-dichlorophenyl)-2-1,3,4-oxadiazolyl)methoxymethyl group, a (5-(2,4,6-trimethylphenyl)-2-1,3,4-oxadiazolyl)methoxymethyl group, and a (5-(2,4-dimethoxyphenyl)-2-1,3,4-oxadiazolyl)methoxymethyl group (wherein, on the 1,3,4-oxadiazole ring, the above described phenyl group may be substituted (wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen
atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted).

Examples of the C2-C6 alkyloxy substituted
5 Cl-C6 alkyl group may include an ethynloxydimethyl group, a 2-(2-ethynloxy)ethyl group, a 1-(2-butynloxy)ethyl group, a 2-(3-butynloxy)ethyl group, a 3-(1-methyl-2-propynloxy)propyl group, a 4-(2-pentynloxy)butyl group, a 4-(2-hexynloxy)butyl group, a 5-(2-propynloxy)pentyl group, a 6-(2-propynloxy)hexyl group, a 6-(2-butynloxy)hexyl group, a 1,1-dimethyl-2-(2-propynloxy)ethyl group, and a 2-methyl-3-(2-propynloxy)propyl group.

Examples of the naphthyl Cl-C6 alkoxy substituted Cl-C6 alkyl group may include a (1-naphthyl)methoxymethyl group, a (2-(2-naphthyl)ethoxy)methyl group, a (3-(1-naphthyl)propoxy)methyl group, a (2-(2-naphthyl)propoxy)methyl group, a (4-(1-naphthyl)butoxy)methyl group, a (5-(2-naphthyl)pentoxy)methyl group, a (4-(1-naphthyl)pentoxy)methyl group, a (6-(1-naphthyl)hexyloxy)methyl group, a 2-(1-naphthyl)methoxy)ethyl group, a 1-(2-(2-naphthyl)ethoxy)ethyl group, a 3-(3-(1-naphthyl)propoxy)propyl group, a 4-(2-(2-naphthyl)propoxy)butyl group, a 5-(4-(1-
naphthyl)butoxy)pentyl group, a 6-(5-(2-
naphthyl)pentoxy)hexyl group, a 1,1-dimethyl-2-(4-(1-
naphthyl)pentoxy)ethyl group, and a 2-methyl-3-(6-(1-
naphthyl)hexyloxy)propyl group.

Examples of the 1,2,4-oxadiazolyl C1-C6
alkoxy substituted C1-C6 alkyl group [wherein, on the
1,2,4-oxadiazole ring, a phenyl group may be
substituted] may include 1,2,4-oxadiazolyl C1-C6 alkoxy
substituted C1-C6 alkyl groups such as a (3-(3-1,2,4-
oxadiazolyl)methoxy)methyl group, a (2-(5-1,2,4-
oxadiazolyl)ethoxy)methyl group, a (3-(3-1,2,4-
oxadiazolyl)propoxy)methyl group, a (2-(5-1,2,4-
oxadiazolyl)propoxy)methyl group, a (4-(3-1,2,4-
oxadiazolyl)butoxy)methyl group, a (5-(5-1,2,4-
oxadiazolyl)pent oxy)methyl group, a (4-(3-1,2,4-
oxadiazolyl)pent oxy)methyl group, a (6-(3-1,2,4-
oxadiazolyl)hexyloxy)methyl group, a 2-(5-1,2,4-
oxadiazolyl) methoxy)ethyl group, a 1-(2-(3-1,2,4-
oxadiazolyl)ethoxy)ethyl group, a 3-(3-(5-1,2,4-
oxadiazolyl)propoxy)propyl group, a 4-(2-(3-1,2,4-
oxadiazolyl)propoxy)butyl group, a 5-(3-1,2,4-
oxadiazolyl) methoxy)pentyl group, a 6-(4-(5-1,2,4-
oxadiazolyl)butoxy)hexyl group, a 1,1-dimethyl-2-(5-(3-
1,2,4-oxadiazolyl)pentoxy)ethyl group, a 2-methyl-3-(4-
5-1,2,4-oxadiazolyl)pentoxy)propyl group, a 2-(6-(3-
1,2,4-oxadiazolyl)hexyloxy)ethyl group, a (5-phenyl-3-
1,2,4-oxadiazolyl)methoxymethyl group, and a (3-phenyl-
5-1,2,4-oxadiazolyl)methoxymethyl group [wherein, on
the 1,2,4-oxadiazole ring, a phenyl group may be substituted].

Examples of the pyridyl C1-C6 alkoxy substituted C1-C6 alkyl group (wherein, on the pyridine ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may include pyridyl C1-C6 alkoxy substituted C1-C6 alkyl groups such as a (2-pyridyl)methoxymethyl group, a (2-(3-pyridyl)ethoxy)methyl group, a (3-(4-pyridyl)propoxy)methyl group, a (2-(2-pyridyl)propoxy)methyl group, a (4-(3-pyridyl)butoxy)methyl group, a (5-(4-pyridyl)pentoxy)methyl group, a (4-(2-pyridyl)pentoxy)methyl group, a (6-(3-pyridyl)hexyloxy)methyl group, a (2-(4-pyridyl)methoxy)ethyl group, a 1-(2-(2-pyridyl)ethoxy)ethyl group, a 3-(3-(3-pyridyl)propoxy)propyl group, a 4-(2-(4-pyridyl)propoxy)butyl group, a 5-(2-pyridyl)methoxy)pentyl group, a 6-(4-(2-pyridyl)butoxy)hexyl group, a 1,1-dimethyl-2-(5-(3-pyridyl)pentoxy)ethyl group, a 2-methyl-3-(4-(4-pyridyl)pentoxy)propyl group, a 2-(6-(2-pyridyl)hexyloxy)ethyl group, a (2-trifluoromethyl-5-pyridyl)methoxymethyl group, a (4-chloro-2-
pyridyl)methoxymethyl group, a (3-trifluoromethyl-2-pyridyl)methoxymethyl group, a (2-methoxy-4-pyridyl)methoxymethyl group, a (2-trifluoromethoxy-5-pyridyl)methoxymethyl group, a (2,4-dibromo-3-pyridyl)methoxymethyl group, a (2,4,6-trimethyl-5-pyridyl)methoxymethyl group, a (2,4-dimethoxy-5-pyridyl)methoxymethyl group, and a (2,4,6-trifluoro-3-pyridyl)methoxymethyl group (wherein, on the pyridine ring, 1 to 3 groups selected from the group consisting of the above described halogen atom, the above described halogen substituted or unsubstituted Cl-C6 alkyl group, and the above described halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted).

Examples of the thiazolyl Cl-C6 alkoxy substituted Cl-C6 alkyl group (wherein, on the thiazole ring, at least one selected from the group consisting of a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) and a lower alkyl group may be substituted), may include thiazolyl Cl-C6 alkoxy substituted Cl-C6 alkyl groups such as a (4-thiazolyl)methoxymethyl group, a (2-(2-thiazolyl)ethoxy)methyl group, a (3-(5-thiazolyl)propoxy)methyl group, a (2-(4-thiazolyl)propoxy)methyl group, a (4-(2-
thiazolyl)butoxy)methyl group, a (5-(4-
thiazolyl)pentoxy)methyl group, a (4-(5-
thiazolyl)pentoxy)methyl group, a (6-(4-
thiazolyl)hexyloxy)methyl group, a (2-(2-
thiazolyl)methoxy)ethyl group, a 1-(2-(5-
thiazolyl)ethoxy)ethyl group, a 3-(3-(4-
thiazolyl)propoxy)propyl group, a 4-(4-(2-
thiazolyl)propoxy)butyl group, a 5-(4-
thiazolyl)methoxy)pentyl group, a 6-(4-
thiazolyl)butoxy)hexyl group, a 1,1-dimethyl-2-(5-(4-
thiazolyl)pentoxy)ethyl group, a 2-methyl-3-(4-(2-
thiazolyl)pentoxy)propyl group, a 2-(6-(5-
thiazolyl)hexyloxy)ethyl group, a (2-(4-methylphenyl)-
4-thiazolyl)methoxymethyl group, a (2-(4-chlorophenyl)-
4-thiazolyl)methoxymethyl group, a (2-(4-
trifluoromethylphenyl)-4-thiazolyl)methoxymethyl group,
a (5-(4-methoxyphenyl)-4-thiazolyl)methoxymethyl group,
a (2-(4-trifluoromethoxyphenyl)-4-
thiazolyl)methoxymethyl group, a (5-(2,4-
dichlorophenyl)-2-thiazolyl)methoxymethyl group, a (4-
(2,4,6-trimethylphenyl)-2-thiazolyl)methoxymethyl group,
a (4-(2,4-dimethoxyphenyl)-2-thiazolyl)methoxymethyl
 group, a (2-methyl-4-thiazolyl)methoxymethyl group, a
(2,5-dimethyl-5-thiazolyl)methoxymethyl group, and a
(2-phenyl-4-methyl-5-thiazolyl)methoxymethyl group
[wherein, on the thiazole ring, 1 or 2 groups selected
from the group consisting of the above described phenyl
group (wherein, on the phenyl ring, 1 to 5 groups, and
preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted linear or branched C1-C6 alkyl group containing 1 to 6 carbon atoms, and a halogen substituted or unsubstituted linear or branched C1-C6 alkoxy group containing 1 to 6 carbon atoms, may be substituted] and a linear or branched alkyl group containing 1 to 6 carbon atoms, may be substituted].

Examples of the 1,2,3,4-tetraphydronaphthyl
C1-C6 alkoxy substituted C1-C6 alkyl group [wherein, on the 1,2,3,4-tetraphydronaphthylene ring, at least one C1-C6 alkyl group may be substituted] may include 1,2,3,4-tetraphydronaphthyl C1-C6 alkoxy substituted C1-C6 alkyl groups such as a (6-1,2,3,4-
tetraphydronaphthyl) methoxymethyl group, a (2-(2-
1,2,3,4-tetraphydronaphthyl) ethoxy)methyl group, a (3-
(3-1,2,3,4-tetraphydronaphthyl) propoxy)methyl group, a (2-(4-1,2,3,4-tetraphydronaphthyl) propoxy)methyl group, a (4-(5-1,2,3,4-tetraphydronaphthyl) butoxy)methyl group;
a (5-(6-1,2,3,4-tetraphydronaphthyl) pentoxy)methyl group, a (4-(6-1,2,3,4-tetraphydronaphthyl) pentoxy)methyl group, a (6-(5-1,2,3,4-tetraphydronaphthyl) hexyloxy)methyl group, a 2-(6-1,2,3,4-tetraphydronaphthyl) methoxy)ethyl group, a 1-(2-(6-1,2,3,4-
tetraphydronaphthyl) ethoxy)ethyl group, a 3-(3-(5-
1,2,3,4-tetraphydronaphthyl) propoxy)propyl group, a 4-
(2-(5-1,2,3,4-tetraphydronaphthyl) propoxy)butyl group, a 5-(4-(6-1,2,3,4-tetraphydronaphthyl) butoxy)pentyl group,
a 6-(5-(5-1,2,3,4-tetrahydronaphthyl)pentoxy)hexyl group, a 1,2-dimethyl-2-(4-(6-1,2,3,4-
tetrahydronaphthyl)pentoxy)ethyl group, a 2-methyl-3-
(6-(6-1,2,3,4-tetrahydronaphthyl)hexyloxy)propyl group.
5 a (1,1,4,4-tetramethyl-6-1,2,3,4-
tetrahydronaphthyl)methoxymethyl group, a (1,1,4-
trimethyl-6-1,2,3,4-tetrahydronaphthyl)methoxymethyl group, a (1,1-dimethyl-6-1,2,3,4-
tetrahydronaphthyl)methoxymethyl group, a (1,1-
dimethyl-7-1,2,3,4-tetrahydronaphthyl)methoxymethyl group, a (1-methyl-6-1,2,3,4-
tetrahydronaphthyl)methoxymethyl group, a (1,4-
dimethyl-6-1,2,3,4-tetrahydronaphthyl)methoxymethyl group, a (1,1,4,4-tetraethyl-6-1,2,3,4-
tetrahydronaphthyl)methoxymethyl group, a (1,1-dimethyl-4-ethyl-6-1,2,3,4-
tetrahydronaphthyl)methoxymethyl group, a (1,1-di-n-
propyl-6-1,2,3,4-tetrahydronaphthyl)methoxymethyl group, a (4,4-di-n-butyl-6-1,2,3,4-
tetrahydronaphthyl)methoxymethyl group, a (1-n-pentyl-
6-1,2,3,4-tetrahydronaphthyl)methoxymethyl group, a
(1,4-di-n-hexyl-6-1,2,3,4-
tetrahydronaphthyl)methoxymethyl group, and a (1-
methyl-5-n-propyl-4-ethyl-6-1,2,3,4-
tetrahydronaphthyl)methoxymethyl group [wherein, on the
1,2,3,4-tetrahydronaphthalene ring, the above described
1 to 4 C1-C6 alkyl groups may be substituted].

Examples of the carbamoyl C1-C6 alkoxy
substituted C1-C6 alkyl group [wherein, on the amino
group, at least one selected from the group consisting
of a C1-C6 cycloalkyl group and a phenyl group (wherein,
on the phenyl ring, at least one selected from the
group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a
halogen substituted or unsubstituted C1-C6 alkoxy group
may be substituted; may be substituted] may include
carbamoyl C1-C6 alkoxy substituted C1-C6 alkyl groups
such as a carbamoylmethoxymethyl group, a 2-
(carbamoylemethoxy)methyl group, a (3-
carbamoylpropoxy)methyl group, a (2-
carbamoylpropoxy)methyl group, a (4-
carbamoylbutoxy)methyl group, a (5-
carbamoylpent oxy)methyl group, a (4-
carbamoylpent oxy)methyl group, a (6-
carbamoylnonyloxy)methyl group, a (2-
carbamoylmethoxy)ethyl group, a 1-(2-
carbamoylemethoxy)ethyl group, a 3-(3-
carbamoylpropoxy)propyl group, a 4-(2-
carbamoylpropoxy)butyl group, a 5-
(carbamoylmethoxy)pentyl group, a 4-(2-
carbamoylpropoxy)butyl group, a 6-(4-
carbamoylbutoxy)hexyl group, a 1,1-dimethyl-2-(5-
carbamoylpent oxy)ethyl group, a 2-methyl-3-(4-
carbamoylpent oxy)propyl group, a 2-(6-
carbamoylnonyloxy)ethyl group, an (N-(4-
methylphenyl)carbamoyl)methoxymethyl group, an (N-(4-
chlorophenyl)carbamoyl)methoxymethyl group, an (N-(4-
trifluoromethylphenyl)carbamoyl)methoxymethyl group, an
(N-(4-methoxyphenyl)carbamoyl)methoxymethyl group, an
(N-(4-trifluoromethoxyphenyl)carbamoyl)methoxymethyl
group, an (N-(2,4-dichlorophenyl)-
carbamoyl)methoxymethyl group, an (N-(2,4,6-
trimethylphenyl)carbamoyl)methoxymethyl group, an (N-
(2,4-dimethoxyphenyl)carbamoyl)methoxymethyl group, an
(N-cyclohexylcarbamoyl)methoxymethyl group, an (N-
cyclopentylcarbamoyl)methoxymethyl group, an (N-
cycloheptylcarbamoyl)methoxymethyl group, an (N-
cyclooctylcarbamoyl)methoxymethyl group, an (N-
cyclobutylcarbamoyl)methoxymethyl group, an (N-
cycloprouplcarbamoyl)methoxymethyl group, an (N-
cyclopropyl-N-cyclohexylcarbamoyl)methoxymethyl group,
an (N,N-dicyclohexylcarbamoyl)methoxymethyl group, an
(N-cyclopropyl-N-(4-fluoromethylphenyl)carbamoyl)-
methoxymethyl group, and an (N-cyclohexyl-N-(4-
fluoromethylphenyl)carbamoyl)methoxymethyl group

(wherein, on the amino group, 1 or 2 groups selected
from the group consisting of the above described C3-C8
cycloalkyl group and the above described phenyl group
[wherein, on the phenyl ring, 1 to 5 groups, and
preferably 1 to 3 groups selected from the group

consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted] may be substituted)
Examples of the benzofuryl C1-C6 alkoxy substituted C1-C6 alkyl group [wherein, on the benzofuran ring, at least one cyano group may be substituted] may include benzofuryl C1-C6 alkoxy substituted C1-C6 alkyl groups such as a (2-benzofuryl)methoxymethyl group, a (2-(3-benzofuryl)ethoxy)methyl group, a (3-(4-benzofuryl)propoxy)methyl group, a (2-(5-benzofuryl)propoxy)methyl group, a (4-(6-benzofuryl)butoxy)methyl group, a (5-(7-benzofuryl)pentoxy)methyl group, a (4-(4-benzofuryl)pentoxy)methyl group, a (6-(3-benzofuryl)hexyloxy)methyl group, a (2-(2-benzofuryl)methoxy)ethyl group, a 1-(2-(3-benzofuryl)ethoxy)ethyl group, a 3-(3-(4-benzofuryl)propoxy)propyl group, a 4-(2-(5-benzofuryl)propoxy)butyl group, a 5-(4-(6-benzofuryl)butoxy)pentyl group, a 6-(5-(7-benzofuryl)pentoxy)hexyl group, a 1,1-dimethyl-2-(4-(2-benzofuryl)pentoxy)ethyl group, a 2-methyl-3-(6-(3-benzofuryl)hexyloxy)propyl group, a (7-cyano-2-benzofuryl)methoxymethyl group, a (6-cyano-2-benzofuryl)methoxymethyl group, a (5-cyano-2-benzofuryl)methoxymethyl group, a (4-cyano-2-benzofuryl)methoxymethyl group, a (3-cyano-2-benzofuryl)methoxymethyl group, a (2-cyano-5-benzofuryl)methoxymethyl group, a (6,7-dicyano-2-benzofuryl)methoxymethyl group, and a (3,4,5-tricyano-
2-benzofuryl)methoxymethyl group [wherein, on the benzofuran ring, 1 to 3 cyano groups may be substituted].

Examples of the C7-C10 alkoxy group may include an n-heptyloxy group, an n-octyloxy group, an n-nonyloxy group, an n-decyloxy group, a 5-methylhexyloxy group, a 4,4-dimethylpentylloxy group, a 6-methylheptyloxy group, and a 5,5,5-trimethylpentylloxy group.

Examples of the phenoxy group [wherein, on the phenyl ring, at least one selected from the group consisting of a pheryl C1-C6 alkoxy group, a C3-C6 cycloalkyl group, a C7-C10 alkoxy group, and a phenoxy group is substituted] may include phenoxy groups such as a 4-benzyloxyphenoxy group, a 4-cyclohexylphenoxy group, a 4-n-octyloxyphenoxy group, a 4-cyclopentylphenoxy group, a 3-phenoxyphenoxy group, a 3-benzyloxyphenoxy group, a 3-cyclohexylphenoxy group, a 3-n-octyloxyphenoxy group, a 3-cyclopentylphenoxy group, a 4-phenoxyphenoxy group, a 2-benzyloxyphenoxy group, a 2-cyclohexylphenoxy group, a 2-n-heptyloxyphenoxy group, a 2-cyclopentylphenoxy group, a 2-phenoxyphenoxy group, a 4-(2-phenoxyphenoxy)phenoxy group, a 4-cyclooctylphenoxy group, a 4-n-nonyloxyphenoxy group, a 4-cyclopropylphenoxy group, a 2,3-diphenoxyphenoxy group, a 4-(3-phenylpropoxy)phenoxy group, a 4-cycloheptylphenoxy group, a 4-n-decyloxyphenoxy group, a 4-
cyclobutylphenoxy group, a 2,4,6-triphenoxyphenoxy group, a 4-(4-phenylbutoxy)phenoxy group, a 2,4-dicyclohexylphenoxy group, a 2,4-di-n-octyloxyphenoxy group, a 2,4,6-tricyclopentylphenoxy group, a 3-phenoxy-4-benzylloxyphenoxy group, a 4-(5-phenylpentyl)phenoxy group, a 4-cyclohexyl-3-phenoxyphenoxy group, a 2,4,6-tri-n-octyloxyphenoxy group, a 4-cyclopentyl-2-benzylloxyphenoxy group, a 3-phenoxy-2-cyclohexylphenoxy group, a 4-(6-phenylhexyloxy)phenoxy group, a 3,4,5-tribenzyloxyphenoxy group, and a 2,4-dibenzylloxyphenoxy group, provided that, on the phenyl ring, 1 to 3 groups selected from the group consisting of the above described phenyl C1-C6 alkoxy group, the above described C3-C8 cycloalkyl group, the above described C7-C10 alkoxy group, and the above described phenoxy group, are substituted.

Examples of the 2,3-dihydrobenzofuryloxy group [wherein, on the 2,3-dihydrobenzofuran ring, at least one oxo group may be substituted] may include 2,3-dihydrobenzofuryloxy groups such as a (2-, 3-, 4-, 5-, 6- or 7-)2,3-dihydrobenzofuryloxy group, a 3-oxo-6-2,3-dihydrobenzofuryloxy group, and a 2-oxo-5-2,3-dihydrobenzofuryloxy group, provided that, on the 2,3-dihydrobenzofuran ring, 1 or 2 oxo groups may be substituted.

Examples of the benzothiazolyloxy group [wherein, on the benzothiazole ring, at least one C1-C6
alkyl group may be substituted) may include benzothiazolylloxy groups such as a (2-, 4-, 5-, 6- or 7-) benzothiazolylloxy group, a 2-methyl-5-
benzothiazolylloxy group, a 2-ethyl-5-benzothiazolylloxy group, a 2-n-propyl-5-benzothiazolylloxy group, a 2-
tert-butyl-5-benzothiazolylloxy group, a 2-n-pentyl-5-
benzothiazolylloxy group, a 2-n-hexyl-5-
benzothiazolylloxy group, a 2,5-dimethyl-6-
benzothiazolylloxy group, and a 4,5,6-trimethyl-2-
benzothiazolylloxy group, provided that, on the benzothiazole ring, the above described 1 to 3 C1-C6 alkyl groups may be substituted.

Examples of the furyl C1-C6 alkoxy group

[wherein, on the furan ring, at least one C1-C6
alkoxycarbonyl group may be substituted] may include furyl C1-C6 alkoxy groups such as a 12- or
3-) furylmethoxy group, a 2-((2- or 3-) furyl)ethoxy
group, a 1-((2- or 3-) furyl)ethoxy group, a 3-((2- or
3-) furyl)propoxy group, a 2-((2- or 3-) furyl)propoxy
group, a 4-((2- or 3-) furyl)butoxy group, a 5-((2- or
3-) furyl)pent oxy group, a 4-((2- or 3-) furyl)pent oxy
group, a 6-((2- or 3-) furyl)hexyloxy group, a 2-methyl-
3-((2- or 3-) furyl)propoxy group, a 1,1-dimethyl-2-((2-
or 3-) furyl)ethoxy group, a 2-ethoxycarbonyl-5-
furylmethoxy group, a 2-ethoxycarbonyl-5-furylmethoxy
group, a 2-methoxycarbonyl-4-furylmethoxy group, a 2-
propoxycarbonyl-3-furylmethoxy group, a 2-
butoxycarbonyl-5-furylmethoxy group, a 2-
pentylsuccoxybenzyl-5-furylethoxy group, a 2-
succtylsuccoxybenzyl-5-furylethoxy group, a 2,3-
diethoxycarbonyl-5-furylethoxy group, and a 2,3,4-
trimethoxycarbonyl-5-furylethoxy group, provided that,
on the furan ring, the above described 1 to 3 Cl-C6
alkoxy carbonyl groups may be substituted.

Examples of the tetrazolyl Cl-C6 alkoxy group
[wherein, on the tetrazole ring, at least one selected
from the group consisting of a phenyl Cl-C6 alkyl group
and a C3-C8 cycloalkyl Cl-C6 alkyl group may be
substituted] may include tetrazolyl Cl-C6 alkoxy groups
such as a (1-2 or 5-)tetrazolylmethoxy group, a 2-
((1-2 or 5-)tetrazolyl)ethoxy group, a 1-((1-2 or
5-)tetrazolyl)ethoxy group, a 3-((1-2 or
5-)tetrazolyl)propoxy group, a 2-((1-2 or
5-)tetrazolyl)propoxy group, a 4-((1-2 or
5-)tetrazolyl)butoxy group, a 5-((1-2 or
5-)tetrazolyl)pentoxy group, a 4-((1-2 or
5-)tetrazolyl)pentox group, a 6-((1-2 or
5-)tetrazolyl)hexyloxy group, a 2-methyl-3-((1-2 or
5-)tetrazolyl)propoxy group, a 1,1-dimethyl-2-((1-2 or
5-)tetrazolyl)ethoxy group, a 1-(2-phénylethyl)-5-
tetrazolylmethoxy group, a 1-cyclohexymethy1-5-
tetrazolylmethoxy group, a 5-benzyl-1-tetrazolylmethoxy
group, a 5-(2-cyclopentylethyl)-1-tetrazolylmethoxy
group, a 1-benzyl-5-tetrazolylmethoxy group, a 1-(3-
phenylpropyl)-5-tetrazolylmethoxy group, a 1-(4-
phenylbutyl)-5-tetrazolylmethoxy group, a 1-(5-
phenylpentyl)-5-tetrazolylmethoxy group, a 1-(6-
phenylhexyl)-5-tetrazolylmethoxy group, a 1-
cyclobutylmethyl-5-tetrazolylmethoxy group, a 1-(3-
cyclopropylpropyl)-5-tetrazolylmethoxy group, a 1-(4-
cycloheptylbutil)-5-tetrazolylmethoxy group, a 1-(5-
cyclooctylpentyl)-5-tetrazolylmethoxy group, and a 1-
(6-cyclohexylhexyl)-5-tetrazolylmethoxy group, provided
that, on the tetrazole ring, one group selected from
the group consisting of the above described phenyl Cl-
C6 alkyl group and the above described C3-C8 cycloalkyl
Cl-C6 alkyl group may be substituted.

Examples of the 1,2,4-oxadiazolyl Cl-C6
alkoxy group (wherein, on the 1,2,4-oxadizole ring, a
phenyl group may be substituted (wherein, on the phenyl
ring, at least one selected from the group consisting
of a halogen atom, a halogen substituted or
unsubstituted Cl-C6 alkyl group, and a halogen
substituted or unsubstituted Cl-C6 alkoxy group may be
substituted) may include 1,2,4-oxadiazolyl Cl-C6
alkoxy groups such as a (3- or 5-)1,2,4-
oxadiazolylmethoxy group, a 2-((3- or 5-)1,2,4-
oxadiazolyl)ethoxy group, a 1-((3- or 5-)1,2,4-
oxadiazolyl)ethoxy group, a 3-((3- or 5-)1,2,4-
oxadiazolyl)propoxy group, a 2-((3- or 5-)1,2,4-
oxadiazolyl)propoxy group, a 4-((3- or 5-)1,2,4-
oxadiazolyl)butoxy group, a 5-((3- or 5-)1,2,4-
oxadiazolyl)pentoxy group, a 4-((3- or 5-)1,2,4-
oxadiazolyl)pentoxy group, a 6-((3- or 5-)1,2,4-
oxadiazo[3-](3- or 5-){1,2,4-oxadiazo[3-]propoxy group, a 1, 1-dimethyl-2-
(3- or 5-){1,2,4-oxadiazo[3-]ethoxy group, a 3-(4-tert-
butylphenyl)-5-1,2,4-oxadiazo[3-]methoxy group, a 3-
phenyl-5-1,2,4-oxadiazo[3-]methoxy group, a 3-(4-
chlorophenyl)-5-1,2,4-oxadiazo[3-]methoxy group, a 3-(4-
trifluoromethylphenyl)-5-1,2,4-oxadiazo[3-]methoxy group,
a 5-(4-trifluoromethoxyphenyl)-3-1,2,4-
oxadiazo[3-]methoxy group, a 5-(4-methoxyphenyl)-3-
phenyl-5-1,2,4-oxadiazo[3-]methoxy group, a 5-(2,4-
dimethylphenyl)-5-1,2,4-oxadiazo[3-]methoxy group, a 3-
(2,4,6-trimethylphenyl)-5-1,2,4-oxadiazo[3-]methoxy group,
a 3-(2,4-dimethylphenyl)-5-1,2,4-
oxadiazo[3-]methoxy group, a 5-(2,4,6-trimethoxyphenyl)-
3-1,2,4-oxadiazo[3-]methoxy group, a 3-(2,4-
dibromophenyl)-5-1,2,4-oxadiazo[3-]methoxy group, a 3-
(2,4,6-trifluorophenyl)-5-1,2,4-oxadiazo[3-]methoxy group,
a 3-(3,5-dichlorophenyl)-5-1,2,4-
oxadiazo[3-]methoxy group, a 3-(2-methyl-5-
chlorophenyl)-5-1,2,4-oxadiazo[3-]methoxy group, a 3-(3-
methoxy-5-chlorophenyl)-5-1,2,4-oxadiazo[3-]methoxy
group, and a 3-(2,3,4,5,6-pentafluorophenyl)-5-1,2,4-
oxadiazo[3-]methoxy group, provided that, on the 1,2,4-
oxadiazo[3-] ring, the above described phenyl group may
be substituted (wherein, on the phenyl ring, 1 to 5
groups, and preferably 1 to 3 groups selected from the
group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a
halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted).

Examples of the benzothienyl Cl-C6 alkoxy group [wherein, on the benzothiophene ring, at least one halogen atom may be substituted] may include benzothienyl Cl-C6 alkoxy groups such as a (2-, 3-, 4-, 5-, 6- or 7-)benzothienylmethoxy group, a 2-(2-, 3-, 4-, 5-, 6- or 7-)benzothienyl)ethoxy group, a 1-(2-, 3-, 4-, 5-, 6- or 7-)benzothienyl)ethoxy group, a 3-, 4-, 5-, 6- or 7-)benzothienyl)propoxy group, a 2-(2-, 3-, 4-, 5-, 6- or 7-)benzothienyl)propoxy group, a 4-(2-, 3-, 4-, 5-, 6- or 7-)benzothienyl)butoxy group, a 5-(2-, 3-, 4-, 5-, 6- or 7-)benzothienyl)pent oxy group, a 4-(2-, 3-, 4-, 5-, 6- or 7-)benzothienyl)pent oxy group, a 6-(2-, 3-, 4-, 5-, 6- or 7-)benzothienyl)hexyloxy group, a 2-methyl-3-(2-, 3-, 4-, 5-, 6- or 7-)benzothienyl)propoxy group, a 1,1-dimethyl-2-(2-, 3-, 4-, 5-, 6- or 7-)benzothienyl)ethoxy group, a 5-chloro-3-

benzothienylmethoxy group, a 4-bromo-2-
benzothienylmethoxy group, a 6-fluoro-5-
benzothienylmethoxy group, a 7-iodo-4-1,2,4-
oxadiazolylmethoxy group, a 4,5-dichloro-3-
benzothienylmethoxy group, and a 3,4,5-trifluoro-2-
benzothienylmethoxy group, provided that, on the benzothiophene ring, 1 to 3 halogen atoms may be substituted.

Examples of the isoxazolyl Cl-C6 alkoxy group
{wherein, on the isoxazole ring, at least one Cl-C6 alkyl group may be substituted} may include isoxazolyl Cl-C6 alkoxy groups such as a {3-, 4- or
5-}isoxazolylmethoxy group, a 2-{3-, 4- or
5-}isoxazolylmethoxy group, a 1-{3-, 4- or
5-}isoxazolylmethoxy group, a 3-{3-, 4- or
5-}isoxazolylpropoxy group, a 2-{3-, 4- or
5-}isoxazolylpropoxy group, a 4-{3-, 4- or
5-}isoxazolylbutoxy group, a 5-{3-, 4- or
10 5-}isoxazolylpentoxy group, a 4-{3-, 4- or
5-}isoxazolylpentoxy group, a 6-{3-, 4- or
5-}isoxazolylhexyloxy group, a 2-methyl-3-{3-, 4- or
5-}isoxazolylpropoxy group, a 1,1-dimethyl-2-{3-, 4- or
5-}isoxazolylmethoxy group, a 3,5-dimethyl-4-
15 isoxazolylmethoxy group, a (3-methyl-5-
isoxazolyl)methoxy group, a (4-ethyl-5-
isoxazolyl)methoxy group, a (5-n-propyl-4-
isoxazolyl)methoxy group, a (3-tert-butyl-4-
isoxazolyl)methoxy group, a (4-n-pentyl-5-
isoxazolyl)methoxy group, and a (5-n-hexyl-5-
isoxazolyl) methoxy group, provided that, on the isoxazole ring, the above described 1 or 2 Cl-C6 alkyl groups may be substituted.

Examples of the 1,3,4-oxadiazolyl Cl-C6 alkoxy group {wherein, on the 1,3,4-oxadiazole ring, at least one phenyl group may be substituted} may include 1,3,4-oxadiazolyl Cl-C6
alkoxy groups such as a 2-1,3,4-oxadiazolylmethoxy group, a 2-(2-1,3,4-oxadiazolyl)ethoxy group, a 1-(2-1,3,4-oxadiazolyl)prooxy group, a 2-(2-1,3,4-oxadiazolyl)prooxy group, a 4-(2-1,3,4-oxadiazolyl)butoxy group, a 5-(2-1,3,4-oxadiazolyl)pentoxy group, a 4-(2-1,3,4-oxadiazolyl)pentoxy group, a 6-(2-1,3,4-oxadiazolyl)hexyloxy group, a 2-methyl-3-(2-1,3,4-isoxazolyl)prooxy group, a 1,1-dimethyl-2-(2-1,3,4-oxadiazolyl)ethoxy group, a 2-(4-methylphenyl)-5-1,3,4-oxadiazolylmethoxy group, a 3-phenyl-5-1,3,4-oxadiazolylmethoxy group, a 2-(4-ethylphenyl)-5-1,3,4-oxadiazolylmethoxy group, a 3-(4-n-propylphenyl)-5-1,3,4-oxadiazolylmethoxy group, a 3-(4-sec-butylphenyl)-5-1,3,4-oxadiazolylmethoxy group, a 3-(4-n-pentylphenyl)-5-1,3,4-oxadiazolylmethoxy group, a 3-(2,4-dimethylphenyl)-5-1,3,4-oxadiazolylmethoxy group, a 3-(2,4,6-trimethylphenyl)-5-1,3,4-oxadiazolylmethoxy group, a 3-(3-n-hexylphenyl)-5-1,3,4-oxadiazolylmethoxy group, a 3-(2-methylphenyl)-5-1,3,4-oxadiazolylmethoxy group, and a 3-(3-methylphenyl)-5-1,3,4-oxadiazolylmethoxy group, provided that, on the 1,3,4-oxadiazole ring, one phenyl group may be substituted

(wherein, on the phenyl ring, the above described 1 to 3 C1-C6 alkyl groups may be substituted).

Examples of the naphthyl C1-C6 alkoxy groups may include a (2- or 3-)naphthylmethoxy group, a 2-(2-
or 3-naphthyl)ethoxy group, a 1-(2- or 3-naphthyl)ethoxy group, a 3-((2- or 3-naphthyl)-propoxy group, a 2-((2- or 3-naphthyl)propoxy group, a 4-((2- or 3-naphthyl)butoxy group, a 5-((2- or 3-naphthyl)pentoxy group, a 4-((1- or 2-naphthyl)pentoxy group, a 6-((2- or 3-naphthyl)hexyloxy group, a 2-methyl-3-((2- or 3-naphthyl)propoxy group, and a 1,1-dimethyl-2-((2- or 3-naphthyl)ethoxy group.

Examples of the pyridyl Cl-C6 alkoxy group (wherein, on the pyridine ring, at least one halogen substituted or unsubstituted Cl-C6 alkyl group may be substituted) may include pyridyl Cl-C6 alkoxy groups such as a (1-, 2-, 3- or 4-)pyridylmethoxy group, a 2-((1-, 2-, 3- or 4-)pyridyl)ethoxy group, a 1-((1-, 2-, 3- or 4-)pyridyl)ethoxy group, a 3-((1-, 2-, 3- or 4-)pyridyl)propoxy group, a 2-((1-, 2-, 3- or 4-)pyridyl)propoxy group, a 4-((1-, 2-, 3- or 4-)pyridyl)butoxy group, a 5-((1-, 2-, 3- or 4-)pyridyl)pentoxy group, a 4-((1-, 2-, 3- or 4-)pyridyl)pentoxy group, a 6-((1-, 2-, 3- or 4-)pyridyl)hexyloxy group, a 2-methyl-3-((1-, 2-, 3- or 4-)pyridyl)propoxy group, a 1,1-dimethyl-2-((1-, 2-, 3- or 4-)pyridyl)ethoxy group, a 2-trifluoromethyl-5-pyridylmethoxy group, a 2-methyl-5-pyridylmethoxy group, a 2-ethyl-6-pyridylmethoxy group, a 3-n-propyl-2-pyridylmethoxy group, a 4-n-butyl-5-pyridylmethoxy group, a 3-n-penty1-4-pyridylmethoxy group, a 2-n-
hexyl-6-pyridylmethoxy group, a 2,3-ditrifluoromethyl-5-pyridylmethoxy group, a 3,4,5-tritrifluoromethyl-2-pyridylmethoxy group, a 2,4-dimethyl-5-pyridylmethoxy group, and a 3,4,5-trimethyl-2-pyridylmethoxy group, provided that, on the pyridine ring, 1 to 3 halogen substituted or unsubstituted C1-C6 alkyl groups may be substituted.

Examples of the thiazolyl C1-C6 alkoxy group (wherein, on the thiazole ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted)) may include thiazolyl C1-C6 alkoxy groups such as a (2-, 4- or 5-)thiazolylmethoxy group, a 2-((2-, 4- or 5-)thiazolyl)ethoxy group, a 1-((2-, 4- or 5-)thiazolyl)ethoxy group, a 3-((2-, 4- or 5-)thiazolyl)propoxy group, a 2-((2-, 4- or 5-)thiazolyl)propoxy group, a 4-((2-, 4- or 5-)thiazolyl)butoxy group, a 5-((2-, 4- or 5-)thiazolyl)pentoxy group, a 4-((2-, 4- or 5-)thiazolyl)pentoxy group, a 6-((2-, 4- or 5-)thiazolyl)hexyloxy group, a 2-methyl-3-((2-, 4- or 5-)thiazolyl)propoxy group, a 1,1-dimethyl-2-((2-, 4- or 5-)thiazolyl)ethoxy group, a 2-(4-trifluoromethylphenyl)-4-thiazolylmethoxy group, a 2-phenyl-4-thiazolylmethoxy group, a 2-(4-chlorophenyl)-
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4-thiazolylmethoxy group, a 2-(4-
trifluoromethylphenyl)-5-thiazolylmethoxy group, a 2-
(4-trifluoromethoxyphenyl)-4-thiazolylmethoxy group, a 5-
(4-methoxyphenyl)-3-thiazolylmethoxy group, a 5-(2,4-
dimethylphenyl)-2-thiazolylmethoxy group, a 4-(2,4,6-
dimethylphenyl)-2-thiazolylmethoxy group, a 2-(2,4-
dimethylphenyl)-5-thiazolylmethoxy group, a 2-(2,4,6-
dimethoxyphenyl)-4-thiazolylmethoxy group, a 2-(2,4-
dibromophenyl)-4-thiazolylmethoxy group, a 2-(2,4,6-
trifluorophenyl)-5-thiazolylmethoxy group, a 2-(3,5-
dichlorophenyl)-4-thiazolylmethoxy group, a 2-(2-
methyl-5-chlorophenyl)-4-thiazolylmethoxy group, a 2-
(3-methoxy-5-chlorophenyl)-4-thiazolylmethoxy group, a 2-
(2,3,4,5,6-pentafluorophenyl)-4-thiazolylmethoxy

group, and a 2,5-diphenyl-4-thiazolylmethoxy group,
provided that, on the thiazole ring, the above
described 1 or 2 phenyl groups may be substituted
(wherein, on the phenyl ring, 1 to 5 groups, and
preferably 1 to 3 groups selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted Cl-C6 alkyl group, and a halogen
substituted or unsubstituted Cl-C6 alkoxy group may be
substituted).

Examples of the 1,2,3,4-tetrahydronaphthyl

Cl-C6 alkoxy group (wherein, on the 1,2,3,4-
tetrahydronaphthalene ring, at least one Cl-C6 alkyl
group may be substituted) may include 1,2,3,4-
tetrahydronaphthyl Cl-C6 alkoxy groups such as a 1-,
2-, 5- or 6-)1,2,3,4-tetrahydronaphthylmethoxy group, a 2-((1-, 2-, 5- or 6-)1,2,3,4-tetrahydronaphthyl)ethoxy group, a 1-((1-, 2-, 5- or 6-)1,2,3,4-tetrahydronaphthyl)ethoxy group, a 3-((1-, 2-, 5- or 6-)1,2,3,4-tetrahydronaphthyl)ethoxy group, a 4-((1- or 2-)1,2,3,4-tetrahydronaphthyl)propoxy group, a 5-((1- or 2-)1,2,3,4-tetrahydronaphthyl)pentoxy group, a 6-((1-, 2-, 5- or 6-)1,2,3,4-tetrahydronaphthyl)pentoxy group, a 6-((1-, 2-, 5- or 6-)1,2,3,4-tetrahydronaphthyl)hexyloxy group, a 2-methyl-3-((1-, 2-, 5- or 6-)1,2,3,4-tetrahydronaphthyl)propoxy group, a 1,1-dimethyl-2-((1-, 2-, 5- or 6-)1,2,3,4-tetrahydronaphthyl)ethoxy group, a (1,1,4,4-tetramethyl-6-1,2,3,4-tetrahydronaphthyl)methoxy group, a (1,1,4-trimethyl-6-1,2,3,4-tetrahydronaphthyl)methoxy group, a (1,1-dimethyl-6-1,2,3,4-tetrahydronaphthyl)methoxy group, a (4,4-dimethyl-6-1,2,3,4-tetrahydronaphthyl)methoxy group, a (1-methyl-6-1,2,3,4-tetrahydronaphthyl)methoxy group, a (1,4-dimethyl-6-1,2,3,4-tetrahydronaphthyl)methoxy group, a (1,1,4,4-tetraethyl-6-1,2,3,4-tetrahydronaphthyl)methoxy group, a (1,1-dimethyl-4-ethyl-6-1,2,3,4-tetrahydronaphthyl)methoxy group, a (1,1-dimethyl-4-propyl-6-1,2,3,4-tetrahydronaphthyl)methoxy group, a (4,4-di-n-butyl-6-1,2,3,4-tetrahydronaphthyl)methoxy group, a (1-n-pentyl-6-1,2,3,4-tetrahydronaphthyl)methoxy group, a
(1,4-di-n-hexyl-6-1,2,3,4-tetrahydronaphthyl)methoxy group, and a (1-methyl-5-n-propyl-4-ethyl-6-1,2,3,4-tetrahydronaphthyl)methoxy group, provided that, on the 1,2,3,4-tetrahydronaphthalene ring, the above described 1 to 4 Cl-C6 alkyl groups may be substituted.

Examples of the phenoxy Cl-C6 alkoxy group (wherisin, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) may include phenoxy Cl-C6 alkoxy groups such as a phenoxymethoxy group, a 2-phenoxethoxy group, a 1-phenoxethoxy group, a 3-phenoxpropoxy group, a 2-phenoxpropoxy group, a 4-phenoxbutoxy group, a 5-phenoxpentoxy group, a 4-phenoxpentoxy group, a 6-phenoxhexyloxy group, a 2-methyl-3-phenoxpropoxy group, a 1,1-dimethyl-2-phenoxethoxy group, a 2-fluorophenoxyethoxy group, a 3-fluorophenoxyethoxy group, a 4-fluorophenoxyethoxy group, a 2-(2-fluorophenoxy)ethoxy group, a 2-(3-fluorophenoxy)ethoxy group, a 2-(4-fluorophenoxy)ethoxy group, a 2-chlorophenoxyethoxy group, a 3-chlorophenoxyethoxy group, a 4-chlorophenoxyethoxy group, a 2-fluoro-4-bromophenoxyethoxy group, a 4-chloro-3-fluorophenoxyethoxy group, a 2-chloro-4-fluorophenoxyethoxy group, a 3,4-dichlorophenoxyethoxy group, a 3,5-dichlorophenoxyethoxy group, a 2,3-
dichlorophenoxy group, a 2,5-
dichlorophenoxy group, a 2,3,4-
trichlorophenoxy group, a 3,4,5-
trifluorophenoxy group, a 2,3,4,5,6-
pentafluorophenoxy group, a 2,4,6-
trichlorophenoxy group, a 4-
isopropylphenoxy group, a 4-n-
butylphenoxy group, a 4-methylphenoxy group, a 2-methylphenoxy group, a 3-
methylphenoxy group, a 2,4-
dimethylphenoxy group, a 2,3-
dimethylphenoxy group, a 2,6-
dimethylphenoxy group, a 3,5-
dimethylphenoxy group, a 2,5-
dimethylphenoxy group, a 2,4,6-
trimethylphenoxy group, a 4-ethylphenoxy group, a 4-isopropylphenoxy group, a 3,5-
ditrifluoromethylphenoxy group, a 4-
isopropoxyphenoxy group, a 4-n-
butoxyphenoxy group, a 4-methoxyphenoxy group, a 2-methoxyphenoxy group, a 3-
methoxyphenoxy group, a 2,4-
dimethoxyphenoxy group, a 2,3-
dimethoxyphenoxy group, a 2,6-
dimethoxyphenoxy group, a 3,5-
dimethoxyphenoxy group, a 2,5-
dimethoxyphenoxy group, a 2,4,6-
trimethoxyphenoxy group, a 3,5-
ditrifluoromethoxyphenoxymethoxy group, a 2-isopropoxyphenoxymethoxy group, a 3-chloro-4-methoxyphenoxymethoxy group, a 2-chloro-4-trifluoromethoxyphenoxymethoxy group, a 3-methyl-4-fluorophenoxymethoxy group, a 4-bromo-3-trifluoromethylphenoxymethoxy group, a 2-(2-chlorophenoxy)ethoxy group, a 2-(3-chlorophenoxy)ethoxy group, a 2-(4-chlorophenoxy)ethoxy group, a 2-trifluoromethylphenoxymethoxy group, a 3-trifluoromethylphenoxymethoxy group, a 4-trifluoromethylphenoxymethoxy group, a 2-trifluoromethoxyphenoxymethoxy group, a 3-trifluoromethoxyphenoxymethoxy group, a 4-trifluoromethoxyphenoxymethoxy group, a 2-(2,5-trifluoromethylphenoxy)ethoxy group, a 2-(3-trifluoromethylphenoxy)ethoxy group, a 2-(4-trifluoromethylphenoxy)ethoxy group, a 2-(2-trifluoromethoxyphenoxy)ethoxy group, a 2-(3-trifluoromethoxyphenoxy)ethoxy group, a 2-(4-trifluoromethoxyphenoxy)ethoxy group, a 3-(2-trifluoromethylphenoxy)propoxy group, a 3-(3-trifluoromethylphenoxy)propoxy group, a 3-(4-trifluoromethylphenoxy)propoxy group, a 3-(2-trifluoromethylphenoxy)propoxy group, a 3-(3-trifluoromethoxyphenoxy)propoxy group, a 3-(4-trifluoromethoxyphenoxy)propoxy group, a 4-(3-trifluoromethylphenoxy)butoxy group, a 5-(4-trifluoromethylphenoxy)pentoxy group, a 4-(4-
trifluoromethylphenoxy)pentoxy group, a 4- (4-
trifluoromethoxyphenoxy)pentoxy group, a 6-
(3-
trifluoromethylphenoxy)hexyloxy group, a 6-
(4-
trifluoromethoxyphenoxy)hexyloxy group, and a 6-
(4-
trifluoromethoxyphenoxy)hexyloxy group, provided that,
on the phenyl ring, 1 to 5 groups, and preferably 1 to
3 groups selected from the group consisting of the
above described halogen atom, the above described
halogen substituted or unsubstituted Cl-C6 alkyl group,
and the above described halogen substituted or
unsubstituted Cl-C6 alkoxy group may be substituted.

Examples of the carbamoyl Cl-C6 alkoxy group
(wherein, on the amino group, at least one selected
from the group consisting of a C3-C8 cycloalkyl group
and a phenyl group (wherein, on the phenyl ring, at
least one selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted
Cl-C6 alkyl group, and a halogen substituted or
unsubstituted Cl-C6 alkoxy group may be substituted)
may be substituted] may include carbamoyl Cl-C6 alkoxy
groups such as a carbamoylmethoxy group, a 2-
carbamoylethoxy group, a 3-carbamoylpropoxy group, a 2-
carbamoylpropoxy group, a 4-carbamoylbutoxy group, a 5-
carbamoylpentoxy group, a 4-carbamoylpentoxy group, a
6-carbamoylhexyloxy group, a 2-methyl-3-
carbamoylpropoxy group, a 1,1-dimethyl-2-
carbamoylethoxy group, an (N-(4-
methylphenyl)carbamoyl)methoxy group, an (N-(4-
chlorophenyl)carbamoyl)methoxy group, an (N-(4-
trifluoromethylphenyl)carbamoyl)methoxy group, an (N-
(4-methoxyphenyl)carbamoyl)methoxy group, an (N-(4-
trifluoromethoxyphenyl)carbamoyl)methoxy group, an (N-
(2,4-dichlorophenyl)carbamoyl)methoxy group, an (N-
(2,4,6-trimethylphenyl)carbamoyl)methoxy group, an (N-
(2,4-dimethoxyphenyl)carbamoyl)methoxy group, an (N-
cyclohexyl)carbamoyl)methoxy group, an (N-
cyclopentyl)carbamoyl)methoxy group, an (N-
cycloheptyl)carbamoyl)methoxy group, an (N-
cyclooctyl)carbamoyl)methoxy group, an (N-
cyclobutyl)carbamoyl)methoxy group, an (N-
cyclopropyl)carbamoyl)methoxy group, an (N-cyclopropyl-
N-cyclohexyl)carbamoyl)methoxy group, an (N,N-
dicyclohexyl)carbamoyl)methoxy group, an (N-cyclopropyl-
N-(4-fluoromethylphenyl)carbamoyl)methoxy group, and an
(N-cyclohexyl-N-(4-fluoromethylphenyl)carbamoyl)methoxy
group, provided that, on the amino group, 1 or 2 groups
selected from the group consisting of the above
described C3-C6 cycloalkyl group and the above
described phenyl group (wherein, on the phenyl ring, 1
to 5 groups, and preferably 1 to 3 groups selected from
the group consisting of a halogen atom, a halogen
substituted or unsubstituted Cl-C6 alkyl group, and a
halogen substituted or unsubstituted Cl-C6 alkoxy group
may be substituted) may be substituted.

Examples of the benzofuryl Cl-C6 alkoxy group
(wherein, on the benzofuran ring, at least one cyano
group may be substituted) may include benzofuryl C1-C6 alkyl group such as a (2-benzofuryl)ethoxy group, a 2-(3-benzofuryl)ethoxy group, a 3-(4-benzofuryl)propoxy group, a 2-(5-benzofuryl)propoxy group, a 4-(6-benzofuryl)butoxy group, a 5-(7-benzofuryl)pentoxy group, a 4-(2-benzofuryl)pentoxy group, a 6-(3-benzofuryl)hexyloxy group, a 2-(2-benzofuryl)methoxy group, a 1,1-dimethyl-2-(2-benzofuryl)ethoxy group, a 2-methyl-3-(3-benzofuryl)propoxy group, a 7-cyano-2-benzofuryl)methoxy group, a (6-cyano-2-benzofuryl)methoxy group, a (5-cyano-2-benzofuryl)methoxy group, a (4-cyano-2-benzofuryl)methoxy group, a (3-cyano-2-benzofuryl)methoxy group, a (2-cyano-5-benzofuryl)methoxy group, and a (6,7-dicyano-2-benzofuryl)methoxy group, a (3,4,5-tricyano-2-benzofuryl)methoxy group, provided that, on the benzofuran ring, 1 to 3 cyano groups may be substituted.

Examples of the naphthoxy C1-C6 alkyl group

(wherein, on the naphthalene ring, at least one C1-C6 alkoxy group may be substituted) may include 
naphthoxy C1-C6 alkyl groups such as a (1- or 2-)
naphthoxymethyl group, a 2-((1- or 2-)naphthoxy)ethyl group, a 1-((1- or 2-)naphthoxy)ethyl group, a 3-((1- or 2-)naphthoxy)propyl group, a 2-((1- or 2-)naphthoxy)butyl group, a 5-((1- or 2-)naphthoxy)penty group, a 6-((1- or
2-naphthoxy)pentyl group, a 6-((1- or 2-naphthoxy)hexyl group, a 2-methyl-3-((1- or 2-naphthoxy)propyl group, a 1,1-dimethyl-2-((1- or 2-naphthoxy)ethyl group, a 2-(4-methoxy-1- naphthoxy)ethyl group, a (4-methoxy-1-naphthoxy)methyl group, a 2-(3-ethoxy-1-naphthoxy)ethyl group, a 2-n-propoxy-1-naphthoxymethyl group, a 5-tert-butoxy-2-naphthoxymethyl group, a 6-n-pentyloxy-3-naphthoxymethyl group, a 7-n-hexyloxy-4-naphthoxymethyl group, a 2-(2,4-dimethoxy-1-naphthoxy)ethyl group, and a 2-(1,2,3,4-tetramethoxy-5-naphthoxy)ethyl group, provided that, on the naphthalene ring, the above described 1 to 4 Cl-C6 alkoxy groups may be substituted.

Examples of the benzothiazolyloxy C1-C6 alkyl group (wherein, on the benzothiazole ring, at least one C1-C6 alkyl group may be substituted) may include benzothiazolyloxy C1-C6 alkyl groups such as a (2-, 4-, 5-, 6- or 7-)benzothiazolyloxyethyl group, a 2-((2-, 4-, 5-, 6- or 7-)benzothiazolyloxy)ethyl group, a 1-((2-, 4-, 5-, 6- or 7-)benzothiazolyloxy)ethyl group, a 3-((2-, 4-, 5-, 6- or 7-)benzothiazolyloxy)propyl group, a 2-((2-, 4-, 5-, 6- or 7-)benzothiazolyloxy)propyl group, a 4-((2-, 4-, 5-, 6- or 7-)benzothiazolyloxy)butyl group, a 5-((2-, 4-, 5-, 6- or 7-)benzothiazolyloxy)pentyl group, a 4-((2-, 4-, 5-, 6- or 7-)benzothiazolyloxy)pentyl group, a 6-((2-, 4-, 5-, 6- or 7-)benzothiazolyloxy)pentyl group.
6- or 7-)benzothiazolyloxy)hexyl group, a 2-methyl-3-
(2-, 4-, 5-, 6- or 7-)benzothiazolyloxy)propyl group,
a 1,1-dimethyl-2-(2-, 4-, 5-, 6- or
7-)benzothiazolyloxy)ethyl group, a 2-(2-methyl-5-
benzothiazolyloxy)ethyl group, a (2-methyl-5-
benzothiazolyloxy)methyl group, a 2-(4-ethyl-6-
benzothiazolyloxy)ethyl group, a (2-n-propyl-4-
benzothiazolyloxy)methyl group, a 5-tert-butyl-6-
benzothiazolyloxy)methyl group, a (6-n-pentyl-7-
benzothiazolyloxy)methyl group, a (7-n-hexyl-5-
benzothiazolyloxy)methyl group, a 2-(2,4-dimethyl-5-
benzothiazolyloxy)ethyl group, and a 2-(2,4,5-
trimethyl-7-benzothiazolyloxy)ethyl group, provided
that, on the benzothiazole ring, the above described 1
15 to 3 Cl-C6 alkyl groups may be substituted.

Examples of the quinolyloxy Cl-C6 alkyl group
(wherein, on the quinoline ring, at least one Cl-C6
alkyl group may be substituted) may include quinolyloxy
Cl-C6 alkyl groups such as a (2-, 3-, 4-, 5-, 6-, 7- or
8-)quinolyloxy)methyl group, a 2-((2-, 3-, 4-, 5-, 6-, 7- or 8-)quinolyloxy)ethyl group, a 1-((2-, 3-, 4-, 5-, 6-, 7- or 8-)quinolyloxy)ethyl group, a 3-((2-, 3-, 4-, 5-, 6-, 7- or 8-)quinolyloxy)propyl group, a 2-((2-, 3-, 4-, 5-, 6-, 7- or 8-)quinolyloxy)propyl group, a 4-((2-, 3-, 4-, 5-, 6-, 7- or 8-)quinolyloxy)butyl group, a 5-
((2-, 3-, 4-, 5-, 6-, 7- or 8-)quinolyloxy)pentyl group,
a 4-(2-, 3-, 4-, 5-, 6-, 7- or 8-)quinolyloxy)pentyl
group, a 6-((2-, 3-, 4-, 5-, 6-, 7- or
8-)quinolyloxy)hexyl group, a 2-methyl-3-((2-, 3-, 4-, 5-, 6-, 7- or 8-)quinolyloxy)propyl group, a 1,1-
dimethyl-2-((2-, 3-, 4-, 5-, 6-, 7- or 8-)quinolyloxy)ethyl group, a 2-methyl-8-
quinoxyloxy)methyl group, a (3-ethyl-7-
quinoxyloxy)methyl group, a (4-n-propyl-6-
quinoxyloxy)methyl group, a (5-n-butyl-4-
quinoxyloxy)methyl group, a (6-n-hexyl-5-
quinoxyloxy)methyl group, a (2-methyl-7-
quinoxyloxy)methyl group, a (7-n-pentyl-6-
quinoxyloxy)methyl group, a (8-methyl-2-
quinoxyloxy)methyl) group, a (2,4-dimethyl-8-
quinoxyloxy)methyl group, and a (3,6,7-trimethyl-2-
quinoxyloxy)methyl group, provided that, on the
quinoline ring, the above described 1 to 3 C1-C6 alkyl
groups may be substituted.

Examples of the 2,3-dihydrobenzofuryloxy C1-
C6 alkyl group (wherein, or the 2,3-dihydrobenzofuran
ring, at least one selected from the group consisting
of a C1-C6 alkyl group and an oxo group may be
substituted) may include 2,3-dihydrobenzofuryloxy C1-C6
alkyl groups such as a (2-, 3-, 4-, 5-, 6- or 7-)2,3-
dihydrobenzofuryloxy)methyl group, a 2-((2-, 3-, 4-, 5-, 6- or 7-)2,3-dihydrobenzofuryloxy)ethyl group, a 1-((2-, 3-, 4-, 5-, 6- or 7-)2,3-dihydrobenzofuryloxy)ethyl group, a 3-((2-, 3-, 4-, 5-, 6- or 7-)2,3-
dihydrobenzofuryloxy)propyl group, a 2-((2-, 3-, 4-, 5-, 6- or 7-)2,3-
dihydrobenzofuryloxy)propyl group, a 4-
(2-, 3-, 4-, 5-, 6- or 7-)2,3-dihydrobenzofuryloxy)butyl group, a 5-(2-, 3-, 4-, 5-, 6- or 7-)2,3-dihydrobenzofuryloxy)pentyl group, a 4-(2-, 3-, 4-, 5-, 6- or 7-)2,3-dihydrobenzofuryloxy)pentyl group, a 6-(2-, 3-, 4-, 5-, 6- or 7-)2,3-dihydrobenzofuryloxy)hexyl group, a 2-methyl-3-(2-, 3-, 4-, 5-, 6- or 7-)2,3-dihydrobenzofuryloxy)propyl group, a 1,1-dimethyl-2-(2-, 3-, 4-, 5-, 6- or 7-)2,3-dihydrobenzofuryloxy)ethyl group, a 2-(2,2-dimethyl-7-2,3-dihydrobenzofuryloxy)ethyl group, a (2,2-dimethyl-7-2,3-dihydrobenzofuryloxy)methyl group, a 2-(3-ethyl-6-2,3-dihydrobenzofuryloxy)ethyl group, a (4-n-propyl-5-2,3-dihydrobenzofuryloxy)methyl group, a (5-tert-butyl-6-2,3-dihydrobenzofuryloxy)methyl group, a (6-n-pentyl-7-2,3-dihydrobenzofuryloxy)methyl group, a (7-n-hexyl-5-2,3-dihydrobenzofuryloxy)methyl group, a 2-(2,4-dimethyl-5-2,3-dihydrobenzofuryloxy)ethyl group, a 2-(2,2,3-trimethyl-7-2,3-dihydrobenzofuryloxy)ethyl group, a (2-oxo-5-2,3-dihydrobenzofuryloxy)methyl group, a (3-oxo-6-2,3-dihydrobenzofuryloxy)methyl group, and a (2-oxo-3-methyl-5-2,3-dihydrobenzofuryloxy)methyl group, provided that, on the 2,3-dihydrobenzofuran ring, 1 to 3 groups selected from the group consisting of the above described Cl-C6 alkyl group and oxo group may be substituted.

Examples of the 1,2,3,4-tetrahydropronaphthoxy Cl-C6 alkyl group (wherein, on the 1,2,3,4-
tetrahydrophenanthrene ring, at least one oxo group may be substituted) may include 1,2,3,4-
tetrahydrophenanthryloxy C1-C6 alkyl groups such as a (1-, 2-, 5- or 6-)-1,2,3,4-tetrahydrophenanthryloxy methyl group,
a 2-((1-, 2-, 5- or 6-)-1,2,3,4-
tetrahydrophenanthryloxy)ethyl group, a 1-((1-, 2-, 5- or 6-)-1,2,3,4-tetrahydrophenanthryloxy)ethyl group, a 3-((1-, 2-, 5- or 6-)-1,2,3,4-tetrahydrophenanthryloxy)propyl group,
a 2-((1-, 2-, 5- or 6-)-1,2,3,4-
tetrahydrophenanthryloxy)propyl group, a 4-((1-, 2-, 5- or 6-)-1,2,3,4-tetrahydrophenanthryloxy)butyl group, a 5-((1-, 2-, 5- or 6-)-1,2,3,4-tetrahydrophenanthryloxy)pentyl group,
a 4-((1- or 2-)-1,2,3,4-tetrahydrophenanthryloxy)pentyl group, a 6-((1- or 2-)-1,2,3,4-
tetrahydrophenanthryloxy)hexyl group, a 2-methyl-3-((1-, 2-, 5- or 6-)-1,2,3,4-tetrahydrophenanthryloxy)propyl group,
a 1,1-dimethyl-2-((1-, 2-, 5- or 6-)-1,2,3,4-
tetrahydrophenanthryloxy)ethyl group, a (1-oxo-(2-, 5- or 6-)-1,2,3,4-tetrahydrophenanthryloxy)methyl group, a (1,4-
dioxo-(2-, 5- or 6-)-1,2,3,4-
tetrahydrophenanthryloxy)methyl group, and a 1,2,4-trioxo-
(3-, 5-, 6-, 7- or 8-)-1,2,3,4-
tetrahydrophenanthryloxy)methyl group, provided that, on the 1,2,3,4-tetrahydrophenanthrene ring, 1 to 3 oxo
groups may be substituted.

Examples of the 2,3-dihydro-1H-indenyloxy C1-C6 alkyl group (wherein, on the 2,3-dihydro-1H-indene ring, at least one oxo group may be substituted) may
include 2,3-dihydro-1H-indenyloxy C1-C6 alkyl groups such as a (1-, 2-, 4- or 5-)2,3-dihydro-1H-indenyloxy methyl group, a 2-((1-, 2-, 4- or 5-)2,3-dihydro-1H-indenyloxy)ethyl group, a 1-((1-, 2-, 4- or 5-)2,3-dihydro-1H-indenyloxy)ethyl group, a 3-((1-, 2-, 4- or 5-)2,3-dihydro-1H-indenyloxy)propyl group, a 2-((1-, 2-, 4- or 5-)2,3-dihydro-1H-indenyloxy)propyl group, a 4-((1-, 2-, 4- or 5-)2,3-dihydro-1H-indenyloxy)butyl group, a 5-((1-, 2-, 4- or 5-)2,3-dihydro-1H-indenyloxy)pentyl group, a 4-((1-, 2-, 4- or 5-)2,3-dihydro-1H-indenyloxy)pentyl group, a 6-((1-, 2-, 4- or 5-)2,3-dihydro-1H-indenyloxy)hexyl group, a 2-methyl-3-((1-, 2-, 4- or 5-)2,3-dihydro-1H-indenyloxy)propyl group, a 1,1-dimethyl-2-((1-, 2-, 4- or 5-)2,3-dihydro-1H-indenyloxy)ethyl group, a (1-oxo-(2-, 3-, 4-, 5-, 6- or 7-)2,3-dihydro-1H-indenyloxy)methyl group, and a (1,3-dioxo-(2-, 4- or 5-)2,3-dihydro-1H-indenyloxy)methyl group, provided that, on the 2,3-dihydro-1H-indene ring, 1 or 2 oxo groups may be substituted.

Examples of the benzoaxathiolanyloxy C1-C6 alkyl group (wherein, on the benzoaxathiolane ring, at least one oxo group may be substituted) may include benzoaxathiolanyloxy C1-C6 alkyl groups such as a (2-, 4-, 5-, 6- or 7-)benzoaxathiolanyloxyethyl group, a 2-((2-, 4-, 5-, 6- or 7-)benzoaxathiolanyloxy)ethyl group, a 1-((2-, 4-, 5-, 6- or 7-)benzoaxathiolanyloxy)ethyl group, a 3-((2-, 4-, 5-, 6- or 7-)benzoaxathiolanyloxy)-
propyl group, a 2-(2-, 4-, 5-, 6- or 7-)benzoxathiolanyloxy)propyl group, a 4-(2-, 4-, 5-, 6- or 7-)benzoxathiolanyloxy)butyl group, a 5-(2-, 4-, 5-, 6- or 7-)benzoxathiolanyloxy)pentyl group, a 6-(2-, 4-, 5-, 6- or 7-)benzoxathiolanyloxy)hexyl group, a 2-methyl-3-(2-, 4-, 5-, 6- or 7-)benzoxathiolanyloxy)propyl group, a 1,1-dimethyl-2-(2-, 4-, 5-, 6- or 7-)benzoxathiolanyloxy)ethyl group, and a (2-oxo-(4-, 5-, 6- or 7-)benzoxathiolanyloxy)ethyl group, provided that, on the benzoxathiolane ring, one oxo group may be substituted.

Examples of the isoquinolyloxy C1-C6 alkyl group may include a (1-, 3-, 4-, 5-, 6-, 7- or 8-)isoquinolyloxy)methyl group, a 2-(1-, 3-, 4-, 5-, 6-, 7- or 8-)isoquinolyloxy)ethyl group, a 1-(1-, 3-, 4-, 5-, 6-, 7- or 8-)isoquinolyloxy)pentyl group, a 3-(1-, 3-, 4-, 5-, 6-, 7- or 8-)isoquinolyloxy)propyl group, a 2-(1-, 3-, 4-, 5-, 6-, 7- or 8-)isoquinolyloxy)propyl group, a 4-(1-, 3-, 4-, 5-, 6-, 7- or 8-)isoquinolyloxy)butyl group, a 5-(1-, 3-, 4-, 5-, 6-, 7- or 8-)isoquinolyloxy)pentyl group, a 4-(1-, 3-, 4-, 5-, 6-, 7- or 8-)isoquinolyloxy)pentyl group, a 6-(1-, 3-, 4-, 5-, 6-, 7- or 8-)isoquinolyloxy)hexyl group, a 2-methyl-3-(1-, 3-, 4-, 5-, 6-, 7- or 8-)isoquinolyloxy)propyl group, and a 1,1-dimethyl-2-(1-, 3-, 4-, 5-, 6-, 7- or 8-)isoquinolyloxy)ethyl group.
Examples of the pyridyloxy C1-C6 alkyl group may include a (2-, 3- or 4-)pyridyloxyethyl group, a 1-((2-, 3- or 4-)pyridyloxy)ethyl group, a 3-((2-, 3- or 4-)pyridyloxy)ethyl group, a 5-((2-, 3- or 4-)pyridyloxy)propyl group, a 2-((2-, 3- or 4-)pyridyloxy)propyl group, a 4-((2-, 3- or 4-)pyridyloxy)butyl group, a 6-((2-, 3- or 4-)pyridyloxy)pentyl group, a 7-((2-, 3- or 4-)pyridyloxy)pentyl group, a 8-((2-, 3- or 4-)pyridyloxy)hexyl group, a 2-methyl-3-((2-, 3- or 4-)pyridyloxy)propyl group, and a 1,1-dimethyl-2-((2-, 3- or 4-)pyridyloxy)ethyl group.

Examples of the dibenzofuryloxy C1-C6 alkyl group may include a (1-, 2-, 3- or 4-)dibenzofuryloxyethyl group, a 2-((1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-)dibenzofuryloxy)ethyl group, a 1-((1-, 2-, 3- or 4-)dibenzofuryloxy)ethyl group, a 3-((1-, 2-, 3- or 4-)dibenzofuryloxy)propyl group, a 2-((1-, 2-, 3- or 4-)dibenzofuryloxy)propyl group, a 4-((1-, 2-, 3- or 4-)dibenzofuryloxy)propyl group, a 2-((1-, 2-, 3- or 4-)dibenzofuryloxy)propyl group, a 6-((1-, 2-, 3- or 4-)dibenzofuryloxy)hexyl group, a 2-methyl-3-((1-, 2-, 3- or 4-)dibenzofuryloxy)propyl group, and a 1,1-dimethyl-2-((1-, 2-, 3- or 4-)dibenzofuryloxy)ethyl group.

Examples of the 2H-1-benzopyranyloxy C1-C6 alkyl group (wherein, on the 2H-1-benzopyran ring, at
least one oxo group may be substituted) may include 2H-1-benzopyranoloxy Cl-C6 alkyl groups such as a (2-, 3-, 4-, 5-, 6-, 7- or 8-)2H-1-benzopyranoloxy methyl group, a 2-((2-, 3-, 4-, 5-, 6-, 7- or 8-)2H-1-benzopyranoloxy)ethyl group, a 1-((2-, 3-, 4-, 5-, 6-, 7- or 8-)2H-1-benzopyranoloxy)ethyl group, a 3-((2-, 3-, 4-, 5-, 6-, 7- or 8-)2H-1-benzopyranoloxy)propyl group, a 2-((2-, 3-, 4-, 5-, 6-, 7- or 8-)2H-1-benzopyranoloxy)propyl group, a 4-((2-, 3-, 4-, 5-, 6-, 7- or 8-)2H-1-benzopyranoloxy)butyl group, a 5-((2-, 3-, 4-, 5-, 6-, 7- or 8-)2H-1-benzopyranoloxy)pentyl group, a 4-((2-, 3-, 4-, 5-, 6-, 7- or 8-)2H-1-benzopyranoloxy)pentyl group, a 6-((2-, 3-, 4-, 5-, 6-, 7- or 8-)2H-1-benzopyranoloxy)hexyl group, a 2-methyl-3-((2-, 3-, 4-, 5-, 6-, 7- or 8-)2H-1-benzopyranoloxy)propyl group, a 1,1-dimethyl-2-((2-, 3-, 4-, 5-, 6-, 7- or 8-)2H-1-benzopyranoloxy)ethyl group, and a (2-oxo-3-, 4-, 5-, 6-, 7- or 8-)2H-1-benzopyranoloxy)methyl group, provided that, on the 2H-1-benzopyran ring, one oxo group may be substituted.

Examples of the benzoisoaxolidyloxy Cl-C6 alkyl group may include a (3-, 4-, 5-, 6- or 7-)benzoisoaxolidyloxy methyl group, a 2-((3-, 4-, 5-, 6- or 7-)benzoisoaxolidyloxy)ethyl group, a 1-((3-, 4-, 5-, 6- or 7-)benzoisoaxolidyloxy)ethyl group, a 3-((3-, 4-, 5-, 6- or 7-)benzoisoaxolidyloxy)propyl group, a 2-((3-, 4-, 5-, 6- or 7-)benzoisoaxolidyloxy)propyl group, a 4-((3-, 4-, 5-, 6- or 7-)benzoisoaxolidyloxy)butyl group,
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a 5-((3-, 4-, 5-, 6- or 7-)-benzoisoxazolyl)pentyl group, a 4-((3-, 4-, 5-, 6- or 7-)-benzoisoxazolyl)pentyl group, a 6-((3-, 4-, 5-, 6- or 7-)benzoisoxazolyl)hexyl group, a 2-methyl-3-((3-, 4-, 5-, 6- or 7-)benzoisoxazolyl)propyl group, and a 1,1-dimethyl-2-((3-, 4-, 5-, 6- or 7-)benzoisoxazolyl)ethyl group.

Examples of the benzofurazanyloxy C1-C6 alkyl group may include a (4- or 5-)benzofurazanyloxymethyl group, a 2-((4- or 5-)benzofurazanyloxy)ethyl group, a 1-((4- or 5-)benzofurazanyloxy)ethyl group, a 3-((4- or 5-)benzofurazanyloxy)propyl group, a 2-((4- or 5-)benzofurazanyloxy)propyl group, a 4-((4- or 5-)benzofurazanyloxy)butyl group, a 5-((4- or 5-)benzofurazanyloxy)pentyl group, a 4-((4- or 5-)benzofurazanyloxy)pentyl group, a 6-((4- or 5-)benzofurazanyloxy)hexyl group, a 2-methyl-3-((4- or 5-)benzofurazanyloxy)propyl group, and a 1,1-dimethyl-2-((4- or 5-)benzofurazanyloxy)ethyl group.

Examples of the quinoxalyloxy C1-C6 alkyl group may include a (2-, 5- or 6-)quinoxalylcxyethyl group, a 2-(2-, 5- or 6-)quinoxalyloxy)ethyl group, a 1-(2-, 5- or 6-)quinoxalyloxy)ethyl group, a 3-((2-, 5- or 6-)quinoxalyloxy)propyl group, a 2-((2-, 5- or 6-)quinoxalyloxy)propyl group, a 4-((2-, 5- or 6-)quinoxalyloxy)pentyl group, a 5-((2-, 5- or 6-)quinoxalyloxy)pentyl group, a 6-((2-, 5- or 6-)quinoxalyloxy)pentyl group, a 6-((2-, 5- or 6-)quinoxalyloxy)pentyl group, a 6-((2-, 5- or 6-)quinoxalyloxy)pentyl group, a 6-((2-, 5- or 6-)quinoxalyloxy)pentyl group.
6-quinoxalyl oxy)hexyl group, a 2-methyl-3-{(2-, 5- or 6-)quinoxalyl oxy}propyl group, and a 1,1-dimethyl-2-
{(2-, 5- or 6-)quinoxalyl oxy}ethyl group.

Examples of the phenyl C2-C10 alkenyl group

(wherein, on the phenyl ring, at least one selected
from the following groups may be substituted: a halogen
atom, a C1-C4 alkenylenedioxy group, a C1-C6 alkylthio
group, a benzoyl group, a cyano group, a nitro group, a
C2-C6 alkanoyloxy group, an amino group which may have
C1-C6 alkyl group(s) as substituent, a hydroxyl group,
a phenyl C1-C6 alkoxy group, a phenoxy group, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a
halogen substituted or unsubstituted C1-C6 alkoxy
group), may include the above described phenyl C2-C6
alkenyl group (wherein, on the phenyl ring, at least
one selected from the group consisting of a halogen
atom, a halogen substituted or unsubstituted C1-C6
alkyl group, and a halogen substituted or unsubstituted
C1-C6 alkoxy group may be substituted), as well as
alkenyl groups containing 2 to 10 carbon atoms and
having 1 to 3 double bonds, wherein, on the C2-C10
alkenyl group, 1 or 2 phenyl groups may be substituted,
such as a 2-n-pentyl-3-phenyl-2-propenyl group, a 9-
phenyl-2-nonényl group, a 10-phenyl-2-decenyln group, a
8-phenyl-1,3-octadienyl group, a 9-phenyl-1,3,5-
onatrienyl group, a 10-2,4,6-decatrienyln group, a 3-
(4-methylthiophenyl)-2-propenyl group, a 3-(3-
methylthiophenyl)-2-propenyl group, a 3-(2-
methylthiophenyl)-2-propenyl group, a 3-(3,4-
dimethylthiophenyl)-2-propenyl group, a 3-(3,4,5-
trimethylthiophenyl)-2-propenyl group, a 3-(4-benzoyl)-
2-propenyl group, a 3-(3-benzoyl)-2-propenyl group, a
5 3-(2-benzoyl)-2-propenyl group, a 3-(3,4-dibenzoyl)-2-
propenyl group, a 3-(2,4,6-tribenzoyl)-2-propenyl group,
a 3-(4-cyanophenyl)-2-propenyl group, a 3-(3-
cyanophenyl)-2-propenyl group, a 3-(2-cyanophenyl)-2-
propenyl group, a 3-(3,4-dicyanophenyl)-2-propenyl
group, a 3-(2,4,6-tricyanophenyl)-2-propenyl group, a
10 3-(4-acetyloxyphenyl)-2-propenyl group, a 3-(4-
acetyloxy-3-methoxyphenyl)-2-propenyl group, a 3-(3-
acetyloxyphenyl)-2-propenyl group, a 3-(2-
acetyloxyphenyl)-2-propenyl group, a 3-(3,4-
diacetyloxyphenyl)-2-propenyl group, a 3-(2,4,6-
triacetyloxyphenyl)-2-propenyl group, a 3-(4-
dimethyaminophenyl)-2-propenyl group, a 3-(4-
dimethylaminophenyl)-2-propenyl group, a 3-(3-
methylaminophenyl)-2-propenyl group, a 3-(2-(N-methyl-
20 N-ethylaminophenyl))-2-propenyl group, a 3-(2,4-
dimethylaminophenyl)-2-propenyl group, a 3-(2,4,6-
tri(dimethylaminophenyl)-2-propenyl group, a 3-(2-
hydroxyphenyl)-2-propenyl group, a 3-(3-hydroxyphenyl)-
2-propenyl group, a 3-(4-hydroxyphenyl)-2-propenyl
25 group, a 3-(3,5-dimethyl-4-hydroxyphenyl)-2-propenyl
group, a 3-(3-methoxy-4-hydroxyphenyl)-2-propenyl group,
a 3-(2-hydroxyphenyl)-2-propenyl group, a 3-(4-
benzyloxyphenyl)-2-propenyl group, a 3-(4-
benzyloxyphenyl)-2-propenyl group, a 3-(2-
benzyloxyphenyl)-2-propenyl group, a 3-(2,4,6-
tribenzyloxyphenyl)-2-propenyl group, a 3-(3,4-
dibenzyloxyphenyl)-2-propenyl group, a 3-(4-
phenoxyphenyl)-2-propenyl group, a 3-(3-phenoxyphenyl)-
2-propenyl group, a 3-(2-phenoxyphenyl)-2-propenyl
group, a 3-(2,4-diphenoxyphenyl)-2-propenyl group, a 3-
(2,4,6-triphenoxyphenyl)-2-propenyl group, a 3-(3,4-
methylenedioxyphenyl)-2-propenyl group, a 3-(2,3-
ethylenedioxyphenyl)-2-propenyl group, and a 3-(3,4-
ethylenedioxyphenyl)-2-propenyl group. The above
phenyl C2-C10 alkenyl group includes both a trans form
and a cis form. On the phenyl ring, 1 to 5 groups, and
preferably 1 to 3 groups selected from the following
groups may be substituted: a halogen atom, the above
described Cl-C4 alkylenedioxy group, the above
described Cl-C6 alkylthio group, benzoyl group, cyano
group, nitro group, the above described C2-C6
alkanoyloxy group, the above described amino group
which may have a Cl-C6 alkyl group as a substituent,
hydroxyl group, the above described phenyl Cl-C6 alkoxy
group, phenoxy group, the above described halogen
substituted or unsubstituted Cl-C6 alkyl group, and the
above described halogen substituted or unsubstituted
Cl-C6 alkoxy group. In a case where the substituent is
a Cl-C4 alkylenedioxy group, 1 or 2 groups are
preferably substituted on the phenyl ring.

Examples of the naphthyl C2-C6 alkenyl group
may include alkenyl groups containing 2 to 6 carbon atoms and having 1 to 3 double bonds, wherein a naphthyl group is substituted, such as a 2-(1- or 2-)naphthylvinyl group, a 3-(1- or 2-)naphthyl-2-propenyl group, a 3-(1- or 2-)naphthyl-2-methyl-2-propenyl group, a 4-(1- or 2-)naphthyl-2-butenyl group, a 4-(1- or 2-)naphthyl-3-butenyl group, a 4-(1- or 2-)naphthyl-1,3-butadienyl group, a 5-(1- or 2-)naphthyl-1,3-pentadienyl group, a 6-(1- or 2-)naphthyl-3-hexadienyl group, a 6-(1- or 2-)naphthyl-2-hexenyl group, a 5-(1- or 2-)naphthyl-2-pentenyl group, and a 6-(1- or 2-)naphthyl-1,3,5-hexadienyl group. The above naphthyl C2-C6 alkenyl group includes both a trans form and a cis form.

Examples of the benzothienyl C2-C6 alkenyl group may include alkenyl groups containing 2 to 6 carbon atoms and having 1 to 3 double bonds, wherein a benzothienyl group is substituted, such as a 2-(2-, 3-, 4-, 5-, 6- or 7-)benzothienylvinyl group, a 3-(2-, 3-, 4-, 5-, 6- or 7-)benzothienyl-2-propenyl group, a 3-(2-, 3-, 4-, 5-, 6- or 7-)benzothienyl-2-methyl-2-propenyl group, a 4-(2-, 3-, 4-, 5-, 6- or 7-)benzothieryl-2-butenyl group, a 4-(2-, 3-, 4-, 5-, 6- or 7-)benzothienyl-3-butenyl group, a 4-(2-, 3-, 4-, 5-, 6- or 7-)benzothienyl-1,3-butadienyl group, a 5-(2-, 3-, 4-, 5-, 6- or 7-)benzothienyl-1,3-pentadienyl group, a 6-(2-, 3-, 4-, 5-, 6- or 7-)benzothienyl-1,3-hexadienyl group, a 6-(2-, 3-, 4-, 5-, 6- or 7-)benzothienyl-2-
hexenyl group, a 5-(2-, 3-, 4-, 5-, 6- or 7-)benzothienyl-2-pentenyl group, and a 6-(2-, 3-, 4-, 5-, 6- or 7-)benzothienyl-1,3,5-hexatrienyl group. The above benzothienyl C2-C6 alkenyl group includes both a trans form and a cis form.

Examples of the benzothiazolyl C2-C6 alkenyl group [wherein, on the benzothiazole ring, at least one C1-C6 alkyl group may be substituted] may include alkenyl groups containing 2 to 6 carbon atoms and having 1 to 3 double bonds, wherein a benzothiazolyl group is substituted, such as a 2-(2-, 4-, 5-, 6- or 7-)benzothiazolylvinyl group, a 3-(2-, 4-, 5-, 6- or 7-)benzothiazolyl-2-propenyl group, a 3-(2-, 4-, 5-, 6- or 7-)benzothiazolyl-2-methyl-2-propenyl group, a 4-(2-, 4-, 5-, 6- or 7-)benzothiazolyl-2-butenyl group, a 4-(2-, 4-, 5-, 6- or 7-)benzothiazolyl-3-butenyl group, a 4-(2-, 4-, 5-, 6- or 7-)benzothiazolyl-1,3-butadienyl group, a 5-(2-, 4-, 5-, 6- or 7-)benzothiazolyl-1,3-pentadienyl group, a 6-(2-, 4-, 5-, 6- or 7-)benzothiazolyl-1,3-hexadienyl group, a 6-(2-, 4-, 5-, 6- or 7-)benzothiazolyl-2-hexenyl group, a 5-(2-, 4-, 5-, 6- or 7-)benzothiazolyl-2-pentenyl group, a 6-(2-, 4-, 5-, 6- or 7-)benzothiazolyl-1,3,5-hexadienyl group, a 3-(2-methyl-5-benzothiazolyl)-2-propenyl group, a 3-(2-ethyl-4-benzothiazolyl)-2-propenyl group, a 3-(2-n-propyl-6-benzothiazolyl)-2-propenyl group, a 3-(2-n-butyl-7-benzothiazolyl)-2-propenyl group, a 3-(4-n-pentyl-5-benzothiazolyl)-2-propenyl group, a 3-(5-n-
hexyl-2-benzothiazolyl)-2-propenyl group, a 3-(12,4-
dimethyl-5-benzothiazolyl)-2-propenyl group, and a 3-(2,4,5-trimethyl-7-benzothiazolyl)-2-propenyl group.
The above benzothiazolyl C2-C6 alkenyl group includes both a trans form and a cis form.

Examples of the phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a piperidinyl group (wherein, on the piperidine ring, at least one phenoxy group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted)) and a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) is substituted), may include phenyl C1-C6 alkyl groups such as a 4-(1-piperidyl)benzyl group, a 2,4-di(4-piperidyl)benzyl group, a 2,4,6-tri(2-piperidyl)benzyl group, a 4-(4-(4-trifluoromethoxyphenoxy)-1-piperidyl)benzyl group, a 4-(4-(4-
trifluoromethylphenoxy)-1-piperidyl)benzyl group, a 4-(4-(4-chlorophenoxy)-1-piperidyl)benzyl group, a 4-(4-(3,4-di(trifluoromethoxy)phenoxy)-1-piperidyl)benzyl group, a 4-(4-(2,4,6-tri(trifluoromethyl)phenoxy)-1-
piperidyl)benzyl group, a 4-(4-12,4-dichlorophenoxy)-1-
piperidyl)benzyl group, a 4-(4-(2,4,6-
trifluorophenoxy)-1-piperidyl)benzyl group, a 3-(2,4-
diphenoxy-3-piperidyl)benzyl group, a 2-(1,2,3-
triphenoxy-4-piperidyl)benzyl group, a 4-(4-
trifluoromethoxyphenoxy)benzyl group, a 4-(4-
trifluoromethylphenoxy)benzyl group, a 4-(4-
chlorophenoxy)benzyl group, a 4-(2,4-
dichlorophenoxy)benzyl group, a 4-(3,4,5-
trifluorophenoxy)benzyl group, a 4-(3-
methylphenoxy)benzyl group, a 4-(2-
methoxyphenoxy)benzyl group, a 4-(2,4-
dimethylphenoxy)benzyl group, a 4-(3,4-
dimethoxyphenoxy)benzyl group, a 4-(2,4,6-
trimethylphenoxy)benzyl group, a 4-(3,4,5-
trimethoxyphenoxy)benzyl group, a 2,4-diphenoxybenzyl
group, a 2,4,6-triphenoxybenzyl group, and a 2-phenoxy-
4-(1-piperidyl)benzyl group [wherein, on the phenyl
ring, 1 to 3 groups selected from the group consisting
of the above described piperidinyl group (wherein, on
the piperidine ring, 1 to 3 phenoxy groups may be
substituted [wherein, on the phenyl ring, 1 to 5 groups,
and preferably 1 to 3 groups selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted (C1-C6 alkoxyl group may be
substituted)]) and the above described phenoxy group
(wherein, on the phenyl ring, 1 to 5 groups, and
preferably 1 to 5 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted].

Examples of the diphenyl C1-C6 alkyl group wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] may include C1-C6 alkyl groups wherein 2 phenyl groups is substituted [wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], such as a diphenylmethyl group, a 2,2-diphenylethyl group, a 1,1-diphenylethyl group, a 3,3-diphenylpropyl group, a 2,3-diphenylpropyl group, a 4,4-diphenylbutyl group, a 5,5-diphenylpentyl group, a 4,5-diphenylpentyl group, a 6,6-diphenylhexyl group, a 2-methyl-3,3-diphenylpropyl group, a 1,1-dimethyl-2,2-diphenylethyl group, a di(4-chlorophenyl)methyl group, a di(4-

trifluoromethoxyphenyl)methyl group, a di(4-

trifluoromethylphenyl)methyl group, a di(3-
methoxyphenyl)methyl group, a di(2,4-
dichlorophenyl)methyl group, a di(2-methylphenyl)methyl
group, a di(2,4,6-trifluorophenyl) methyl group, a di(3,4-dimethoxyphenyl) methyl group, a di(2,4,6-
trimethoxyphenyl) methyl group, a di(3,4-di-
trimethylphenyl) methyl group, and a 1-(4-
trifluoromethoxyphenyl)-1-(4-chlorophenyl) methyl group.

Examples of the phenyl group (wherein, on the
phenyl ring, at least one selected from the group
consisting of a Cl-C4 alkylenedioxy group, a phenyl
group, a Cl-C6 alkoxy carbonyl group, a hydroxyl group,
and a phenoxy group (wherein, on the phenyl ring, at
least one selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted
Cl-C6 alkyl group, and a halogen substituted or
unsubstituted Cl-C6 alkoxy group may be substituted),
is substituted) may include phenyl groups such as a 4-
biphenyl group, a 4-tert-butoxycarbonylphenyl group, a
4-ethoxycarbonylphenyl group, a 2-biphenyl group, a 4-
hydroxyphenyl group, a 4-(4-chlorophenoxy)phenyl group,
a 2,3-ethylenedioxyphenyl group, a 3-biphenyl group, a
3-tert-butoxycarbonylphenyl group, a 3-
methoxycarbonylphenyl group, a 2,4-diphenylphenyl group,
a 3-hydroxyphenyl group, a 4-(4-
trifluoromethoxyphenoxy)phenyl group, a 2,3-
methylenedioxyphenyl group, a 2,4,6-triphenyl group, a
2-tert-butoxycarbonylphenyl group, a 2-
propoxycarbonylphenyl group, a 2-n-pentyloxyphenyl
group, a 2-hydroxyphenyl group, a 4-(4-

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trifluoromethylphenoxy)phenyl group, a 3,4-
ethylenedioxyphenyl group, a 2,4,6-trihydroxyphenyl
group, a 4-n-hexyloxy carbonylphenyl group, a 2,4-
diethoxy carbonylphenyl group, a 2-biphenyl group, a
3,4-dihydroxyphenyl group, a 4-(2,4-
dichlorophenoxy)phenyl group, a 3-(2,4,6-
trifluorophenoxy)phenyl group, a 2,4,6-
triethoxy carbonylphenyl group, a 3-(2-
methylphenoxy)phenyl group, a 4-(3-methylphenoxy)phenyl
group, a 2-(4-methylphenoxy)phenyl group, a 3-(2,3-
dimethylphenoxy)phenyl group, a 4-(2,4,5-
trimethylphenoxy)phenyl group, a 3-(2-
methoxyphenoxy)phenyl group, a 4-(3-
methoxyphenoxy)phenyl group, a 2-(4-
methoxyphenoxy)phenyl group, a 3-(3,4-
dimethoxyphenoxy)phenyl group, a 4-(2,4,6-
trimethoxyphenoxy)phenyl group, a 2-phenoxy-4-
ethoxy carbonylphenyl group, and a 2-phenyl-3-
phenoxyphenyl group (wherein, on the phenyl ring, 1 to
3 groups selected from the group consisting of the
above described C1-C6 alkylenedioxy group, the above
described phenyl group, the above described C1-C6
alkoxycarbonyl group, hydroxyl group, and the above
described phenoxy group (wherein, on the phenyl ring, 1
to 5 groups, and preferably 1 to 3 groups selected from
the group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a
halogen substituted or unsubstituted C1-C6 alkoxy group
may be substituted, is substituted).

Examples of the benzofuryl group [wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom and a Cl-C6 alkyl group may be substituted] may include benzofuryl groups such as a (2-, 3-, 4-, 5-, 6- or 7-)benzofuryl group, a 5-chloro-7-benzofuryl group, a 5-methyl-7-benzofuryl group, a 4-iodo-6-benzofuryl group, a 6-ethyl-7-benzofuryl group, a 6-bromo-5-benzofuryl group, a 7-n-propyl-4-benzofuryl group, a 7-fluoro-2-benzofuryl group, a 4-n-butyl-2-benzofuryl group, a 2,5-dichloro-7-benzofuryl group, a 3,6-dimethyl-7-benzofuryl group, a 3,5,6-trifluoro-2-benzofuryl group, a 3,4,5-trimethyl-3-benzofuryl group, a 5-chloro-4-methyl-7-benzofuryl group, and a 5-methyl-3-fluoro-8-benzofuryl group, provided that, on the benzofuran ring, 1 to 3 groups selected from the group consisting of the above described halogen atom and the above described Cl-C6 alkyl group may be substituted.

Examples of the benzothiazolinyl group [wherein, on the benzothiazoline ring, at least one oxo group may be substituted] may include benzothiazolinyl groups such as a (2-, 4-, 5-, 6-, or 7-)benzothiazolyl group and a 2-oxo-6-benzothiazolyl group, provided that, on the benzothiazoline ring, one oxo group may be substituted.

Examples of the benzothienyl group [wherein, on the benzothiophene ring, at least one halogen atom
may be substituted] may include benzothienyl groups such as a (2-, 3-, 4-, 5-, 6- or 7-)benzothienyl group, a 5-fluoro-4-benzothienyl group, a 6-fluoro-2-benzothienyl group, a 2-chloro-3-benzothienyl group, a 3-bromo-6-benzothienyl group, a 4-iodo-5-benzothienyl group, a 2,4,6-trichloro-7-benzothienyl group, and a 4,5-difluoro-2-benzothienyl group, provided that, on the benzothiophene ring, 1 to 3 halogen atoms may be substituted.

Examples of the 1,2,3,4-tetrahydroquinolyl group (wherein, on the 1,2,3,4-tetrahydroquinoline ring, at least one selected from the group consisting of an oxo group and a C1-C6 alkyl group may be substituted) may include 1,2,3,4-tetrahydroquinolyl groups such as a (1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-)1,2,3,4-tetrahydroquinolyl group, a 2-oxo-(1-, 3-, 4-, 5-, 6-, 7- or 8-)1,2,3,4-tetrahydroquinolyl group, a 2,4-dioxo-(1-, 3-, 5-, 6-, 7- or 8-)1,2,3,4-tetrahydroquinolyl group, a 3-oxo-(1-, 2-, 4-, 5-, 6-, 7- or 8-)1,2,3,4-tetrahydroquinolyl group, a 1-methyl-2-oxo-5-1,2,3,4-tetrahydroquinolyl group, a 2-methyl-1-1,2,3,4-tetrahydroquinolyl group, a 3-ethyl-2-1,2,3,4-tetrahydroquirololyl group, a 4-n-propyl-3-1,2,3,4-tetrahydroquinolyl group, a 5-n-butyl-4-1,2,3,4-tetrahydroquinolyl group, a 6-n-penty-1-1,2,3,4-tetrahydroquinolyl group, a 7-n-hexyl-6-1,2,3,4-tetrahydroquinolyl group, a 8-methyl-7-1,2,3,4-tetrahydroquinolyl group, a 4,6-dimethyl-5-1,2,3,4-tetrahydroquinolyl group.
tetrahydroquinolyl group, and a 5,6,7-trimethyl-4-
1,2,3,4-tetrahydroquinolyl group, provided that, on the
1,2,3,4-tetrahydroquinoline ring, 1 to 3 groups
selected from the group consisting of an oxo group and
the above described C1-C6 alkyl group may be
substituted.

Examples of the 1,2-dihydrohydroquinolyl
group (wherein, on the 1,2-dihydrohydroquinoline ring,
at least one oxo group may be substituted) may include
1,2-dihydrohydroquinolyl groups such as a (1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-)1,2-dihydrohydroquinolyl group and
a 2-oxo-(1-, 3-, 4-, 5-, 6-, 7- or 8-)1,2-
dihydrohydroquinolyl group, provided that, on the 1,2-
dihydrohydroquinoline ring, one oxo group may be
substituted.

Examples of the 1,2,3,4-tetrahydro-
quinoxazolinyll group (wherein, on the 1,2,3,4-
tetrahydroquinazoline ring, at least one selected from
the group consisting of an oxo group and a C1-C6 alkyl
group may be substituted) may include 1,2,3,4-
tetrahydroquinazolinyll groups such as a (1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-)1,2,3,4-tetrahydroquinazolinyll group,
a 2-oxo-(1-, 3-, 4-, 5-, 6-, 7- or 8-)1,2,3,4-
tetrahydroquinazolinyll group, a 4-oxo-(1-, 2-, 3-, 5-
25 6-, 7- or 8-)1,2,3,4-tetrahydroquinazolinyll group, a
2,4-dioxo-(1-, 3-, 5-, 6-, 7- or 8-)1,2,3,4-
tetrahydroquinazolinyll group, a 1-methyl-2,4-dioxo-(3-, 5-
6-, 7- or 8-)1,2,3,4-tetrahydroquinazolinyll group,
a 3-ethyl-2,4-dioxo-(1-, 5-, 6-, 7- or 8-)1,2,3,4-tetrahydroquinazolinyl group, a 1,3-dimethyl-2,4-dioxo-(5-, 6-, 7- or 8-)1,2,3,4-tetrahydroquinazolinyl group, a 1-n-propyl-5-methyl-2-oxo-(3-, 4-, 6-, 7- or 8-)1,2,3,4-tetrahydroquinazolinyl group, a 1-n-butyl-6-methyl-4-oxo-(2-, 3-, 5-, 7- or 8-)1,2,3,4-tetrahydroquinazolinyl group, a 1-n-pentyl-7-methyl-2-oxo-(3-, 4-, 5-, 6- or 8-)1,2,3,4-tetrahydroquinazolinyl group, and a 1-n-hexyl-8-methyl-2,4-dioxo-(3-, 5-, 6- or 7-)1,2,3,4-tetrahydroquinazolinyl group, provided that, on the 1,2,3,4-tetrahydroquinazoline ring, 1 to 4 groups selected from the group consisting of an oxo group and the above described C1-C6 alkyl group may be substituted.

Examples of the benzothienyl substituted C1-C6 alkyl group [wherein, on the benzothiophene ring, at least one halogen atom may be substituted] may include benzothienyl substituted C1-C6 alkyl groups such as a 2-benzothienylmethyl group, a 3-benzothienylmethyl group, a 4-benzothienylmethyl group, a 5-benzothienylmethyl group, a 6-benzothienylmethyl group, a 7-benzothienylmethyl group, a 2-(2-benzothienyl)ethyl group, a 3-(2-benzothienyl)propyl group, a 4-(2-benzothienyl)butyl group, a 5-(2-benzothienyl)pentyl group, a 6-(2-benzothienyl)hexyl group, a 5-chloro-3-benzothienylmethyl group, a 3,4-dibromo-2-benzothienylmethyl group, and a 4,5,6-trichloro-2-
benzothienylmethyl group, provided that, on the benzothiophene ring, 1 to 3 halogen atoms may be substituted.

Examples of the naphthyl substituted C1-C6 alkyl group may include a 1-naphthylmethyl group, a 2-naphthylmethyl group, a 2-(1-naphthyl)ethyl group, a 1-(2-naphthyl)ethyl group, a 3-(1-naphthyl)propyl group, a 3-(2-naphthyl)propyl group, a 4-(1-naphthyl)butyl group, a 4-(2-naphthyl)butyl group, a 5-(1-naphthyl)pentyl group, a 5-(2-naphthyl)pentyl group, a 6-(1-naphthyl)hexyl group, and a 6-(2-naphthyl)hexyl group.

Examples of the pyridyl substituted C1-C6 alkyl group (wherein, on the pyridine ring, at least one halogen atom may be substituted) may include pyridyl substituted C1-C6 alkyl groups such as a 2-pyridylmethyl group, a 3-pyridylmethyl group, a 4-pyridylmethyl group, a 2-(2-pyridyl)ethyl group, a 2-(3-pyridyl)ethyl group, a 2-(4-pyridyl)ethyl group, a 3-(2-pyridyl)propyl group, a 3-(3-pyridyl)propyl group, a 3-(4-pyridyl)propyl group, a 4-(2-pyridyl)butyl group, a 4-(3-pyridyl)butyl group, a 4-(4-pyridyl)butyl group, a 5-(2-pyridyl)pentyl group, a 5-(3-pyridyl)pentyl group, a 5-(4-pyridyl)pentyl group, a 6-(2-pyridyl)hexyl group, a 6-(3-pyridyl)hexyl group, a 6-(4-pyridyl)hexyl group, a 2-chloro-3-pyridylmethyl group, a 3-bromo-2-pyridylmethyl group, a 4-fluoro-2-pyridylmethyl group, a 2-(2-chloro-4-pyridyl)ethyl
group, a 2-(3-chloro-5-pyridyl)ethyl group, a 2-(4-iodo-3-pyridyl)ethyl group, a 3-(2-bromo-5-pyridyl)propyl group, a 3-(3-fluoro-4-pyridyl)propyl group, a 3-(4-chloro-2-pyridyl)propyl group, a 4-(2-iodo-5-pyridyl)butyl group, a 4-(3-bromo-5-pyridyl)butyl group, a 4-(4-chloro-3-pyridyl)butyl group, a 5-(2-chloro-5-pyridyl)pentyl group, a 5-(3-fluoro-2-pyridyl)pentyl group, a 5-(4-bromo-2-pyridyl)pentyl group, a 6-(2-chloro-5-pyridyl)hexyl group, a 6-(3-fluoro-4-pyridyl)hexyl group, a 6-(4-bromo-2-pyridyl)hexyl group, a (2,6-dichloro-4-pyridyl)methyl group, and a (2,3,4-trichloro-6-pyridyl)methyl group, provided that, on the pyridine ring, 1 to 3 halogen atoms may be substituted as substituents.

Examples of the furyl substituted Cl-C6 alkyl group [wherein, on the furan ring, at least one nitro group may be substituted] may include furyl substituted Cl-C6 alkyl groups such as a 2-furylmethyl group, a 3-furylmethyl group, a 2-(2-furyl)ethyl group, a 3-(2-furyl)propyl group, a 3-(3-furyl)propyl group, a 4-(2-furyl)butyl group, a 4-(3-furyl)butyl group, a 5-(2-furyl)pentyl group, a 5-(3-furyl)pentyl group, a 6-(2-furyl)hexyl group, a 6-(3-furyl)hexyl group, a 5-nitro-2-furylmethyl group, a 5-nitro-3-furylmethyl group, a 2-(5-nitro-2-furyl)ethyl group, a 3-(5-nitro-2-furyl)propyl group, a 4-(5-nitro-2-furyl)butyl group, a 4-(5-nitro-3-furyl)butyl group, a 5-(5-nitro-2-
furyl)pentyl group, a 5-(5-nitro-3-furyl)pentyl group, a 6-(5-nitro-2-furyl)hexyl group, a 6-(5-nitro-3-furyl)hexyl group, a (4,5-dinitro-2-furyl)methyl group, and a (2,4,5-trinitro-3-furyl)methyl group, provided that, on the furan ring, 1 to 3 nitro groups may be substituted as substituents.

Examples of the thiienyl substituted C1-C6 alkyl group (wherein, on the thiophene ring, at least one halogen atom may be substituted) may include thiienyl substituted C1-C6 alkyl groups such as a 2-thienylmethyl group, a 3-thienylmethyl group, a 2-(2-thienyl)ethyl group, a 3-(2-thienyl)propyl group; a 3-(3-thienyl)propyl group, a 4-(2-thienyl)butyl group, a 4-(3-thienyl)butyl group, a 5-(2-thienyl)pentyl group, a 5-(3-thienyl)pentyl group, a 6-(2-thienyl)hexyl group, a 6-(3-thienyl)hexyl group, a 5-chloro-2-thienylmethyl group, a 5-chloro-3-thienylmethyl group, a 2-(4-bromo-2-thienyl)ethyl group, a 3-(3-fluoro-2-thienyl)propyl group, a 4-(5-iodo-2-thienyl)butyl group, a 4-(4-chloro-3-thienyl)butyl group, a 5-(3-chloro-2-thienyl)pentyl group, a 5-(2-chloro-3-thienyl)pentyl group, a 6-(3-chloro-2-thienyl)hexyl group, a 6-(5-chloro-3-thienyl)hexyl group, a (4,5-dichloro-2-thienyl)methyl group, and a (2,4,5-trichloro-3-thienyl)methyl group, provided that, on the thiophene ring, 1 to 3 halogen atoms may be substituted as substituents.

Examples of the phenyl group (wherein, on the
phenyl ring, at least one selected from the group consisting of a halogen atom and a halogen substituted or unsubstituted C1-C6 alkyl group may be substituted) may include a phenyl group, a 2-fluorophenyl group, a 3-fluorophenyl group, a 4-fluorophenyl group, a 2-chlorophenyl group, a 3-chlorophenyl group, a 4-chlorophenyl group, a 2-bromophenyl group, a 3-bromophenyl group, a 4-bromophenyl group, a 2-iodophenyl group, a 3-iodophenyl group, a 4-iodophenyl group, a 2,3-difluorophenyl group, a 3,4-difluorophenyl group, a 3,5-difluorophenyl group, a 2,4-difluorophenyl group, a 2,6-difluorophenyl group, a 2,3-dichlorophenyl group, a 3,4-dichlorophenyl group, a 3,5-dichlorophenyl group, a 2,4-dichlorophenyl group, a 2,6-dichlorophenyl group, a 3,4,5-trifluorophenyl group, a 3,4,5-trichlorophenyl group, a 2,4,6-trifluorophenyl group, a 2,4,6-trichlorophenyl group, a 2-fluoro-4-bromophenyl group, a 4-chloro-3-fluorophenyl group, a 2,3,4-trichlorophenyl group, a 3,4,5-trifluorophenyl group, a 2,3,4,5,6-pentafluorophenyl group, a 2,4,6-trimethylphenyl group, a 4-n-butylphenyl group, a 2,4-dimethylphenyl group, a 2,3-dimethylphenyl group, a 2,6-dimethylphenyl group, a 3,5-dimethylphenyl group, a 2,5-dimethylphenyl group, a 3,5-ditri fluoromethylphenyl group, a 3-methyl-4-fluorophenyl group, a 4-bromo-3-trifluoromethylphenyl group, a 2-methylphenyl group, a 3-methylphenyl group, a 4-methylphenyl group, a 2-methyl-3-chlorophenyl group, a 3-methyl-4-chlorophenyl group...
group, a 2-chloro-4-methylphenyl group, a 2-methyl-3-fluorophenyl group, a 2-trifluoromethylphenyl group, a 3-trifluoromethylphenyl group, a 4-trifluoromethylphenyl group, a 2-pentafluoroethylphenyl group, a 3-pentafluoroethylphenyl group, a 4-pentafluoroethylphenyl group, a 2-isopropylphenyl group, a 3-isopropylphenyl group, a 4-isopropylphenyl group, a 2-tert-butylphenyl group, a 3-tert-butylphenyl group, a 4-tert-butylphenyl group, a 2-sec-butylphenyl group, a 3-sec-butylphenyl group, a 4-sec-butylphenyl group, a 2-n-heptafluoropropylphenyl group, a 3-n-heptafluoropropylphenyl group, a 4-n-heptafluoropropylphenyl group, a 4-n-pentylphenyl group, a 4-n-hexylphenyl group, a 2,3,4-trifluorophenyl group, and a 2,4,6-trifluorophenyl group.

Examples of the thiazolyl substituted C1-C6 alkyl group [wherein, on the thiazole ring, at least one selected from the group consisting of a C1-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom and a halogen substituted or unsubstituted C1-C6 alkyl group may be substituted) may be substituted] may include thiazolyl substituted C1-C6 alkyl groups such as a 4-thiazolylmethyl group, a 5-thiazolylmethyl group, a 2-methyl-4-thiazolylmethyl group, a 2-methyl-5-thiazolylmethyl group, a 2,5-dimethyl-4-thiazolylmethyl group, a 2,4-dimethyl-5-thiazolylmethyl group, a 2-methyl-5-phenyl-4-
thiazolylmethyl group, a 2-methyl-4-phenyl-5-
thiazolylmethyl group, a 2-phenyl-4-thiazolylmethyl
group, a 2-phenyl-5-thiazolylmethyl group, a 2-phenyl-
5-methyl-4-thiazolylmethyl group, a 2-phenyl-4-methyl-
5-thiazolylmethyl group, a 2-methyl-5-(2-fluorophenyl)-
4-thiazolylmethyl group, a 2-methyl-4-(2-fluorophenyl)-
5-thiazolylmethyl group, a 2-(2-chlorophenyl)-6-
thiazolylmethyl group, a 2-(2-bromophenyl)-5-
thiazolylmethyl group, a 2-(2-fluorophenyl)-5-methyl-4-
thiazolylmethyl group, a 2-(2-fluorophenyl)-4-methyl-5-
3-thiazolylmethyl group, a 2-methyl-5-(3-iodophenyl)-4-
thiazolylmethyl group, a 2-methyl-4-(3-fluorophenyl)-5-
thiazolylmethyl group, a 2-(2,3-difluorophenyl)-4-
thiazolylmethyl group, a 2-(3-fluorophenyl)-5-
thiazolylmethyl group, a 2-(3-fluorophenyl)-5-methyl-4-
thiazolylmethyl group, a 2-(3-fluorophenyl)-4-methyl-5-
thiazolylmethyl group, a 2-methyl-5-(3,4,5,6-
trichlorophenyl)-4-thiazolylmethyl group, a 2-methyl-4-
(2,3,4,5,6-pentafluorophenyl)-5-thiazolylmethyl group,
a 2-(4-fluorophenyl)-4-thiazolylmethyl group, a 4-(2-
fluorophenyl)-5-thiazolylmethyl group, a 2-(4-
fluorophenyl)-5-methyl-4-thiazolylmethyl group, a 2-(4-
fluorophenyl)-4-methyl-5-thiazolylmethyl group, a 2-
methyl-5-(2-chlorophenyl)-4-thiazolylmethyl group, a 2-
methyl-4-(2-chlorophenyl)-5-thiazolylmethyl group, a 2-
(2-chlorophenyl)-4-thiazolylmethyl group, a 2-(2-
chlorophenyl)-5-thiazolylmethyl group, a 2-(2-
chlorophenyl)-5-methyl-4-thiazolylmethyl group, a 2-(2-
chlorophenyl)-4-methyl-5-thiazolylmethyl group, a 2-methyl-5-(3-chlorophenyl)-4-thiazolylmethyl group, a 2-methyl-4-(3-chlorophenyl)-5-thiazolylmethyl group, a 2-(3-chlorophenyl)-4-thiazolylmethyl group, a 2-(2-fluorophenyl)-5-thiazolylmethyl group, a 2-(3-chlorophenyl)-5-methyl-4-thiazolylmethyl group, a 2-(3-chlorophenyl)-4-methyl-5-thiazolylmethyl group, a 2-methyl-5-(4-chlorophenyl)-4-thiazolylmethyl group, a 2-methyl-4-(4-chlorophenyl)-5-thiazolylmethyl group, a 2-(4-chlorophenyl)-4-thiazolylmethyl group, a 2-(4-chlorophenyl)-5-thiazolylmethyl group, a 2-(4-chlorophenyl)-5-methyl-4-thiazolylmethyl group, a 2-(4-chlorophenyl)-4-methyl-5-thiazolylmethyl group, a 2-(2-thiazolyl)ethyl group, a 2-(4-thiazolyl)ethyl group, a 2-(5-thiazolyl)ethyl group, a 2-(2-methyl-4-thiazolyl)ethyl group, a 2-(2-methyl-5-thiazolyl)ethyl group, a 2-(2,5-dimethyl-4-thiazolyl)ethyl group, a 2-(2,4-dimethyl-5-thiazolyl)ethyl group, a 2-(2-methyl-5-phenyl-4-thiazolyl)ethyl group, a 2-(2-methyl-4-thiazolyl)ethyl group, a 2-(2-phenyl-5-thiazolyl)ethyl group, a 2-(2-phenyl-5-methyl-4-thiazolyl)ethyl group, a 3-(2-thiazolyl)propyl group, a 2-(4-thiazolyl)propyl group, a 3-(5-thiazolyl)propyl group, a 3-(2-methyl-4-thiazolyl)propyl group, a 2-(2-methyl-5-thiazolyl)propyl group, a 3-(2,5-dimethyl-4-thiazolyl)propyl group, a 3-(2,4-dimethyl-5-thiazolyl)propyl group, a 3-(2-methyl-5-phenyl-4-thiazolyl)propyl group, a 3-(2-methyl-5-phenyl-4-
thiazolyl)propyl group, a 3-(2-methyl-4-phenyl-5-thiazolyl)propyl group, a 2-(2-phenyl-4-thiazolyl)propyl group, a 3-(3-phenyl-5-thiazolyl)propyl group, a 3-(2-phenyl-5-methyl-4-thiazolyl)propyl group, a 4-(2-thiazolyl)butyl group, a 4-(4-thiazolyl)butyl group, a 3-(5-thiazolyl)butyl group, a 4-(2-methyl-4-thiazolyl)butyl group, a 4-(2-methyl-5-thiazolyl)butyl group, a 4-(2,5-dimethyl-4-thiazolyl)butyl group, a 4-(2,4-dimethyl-5-thiazolyl)butyl group, a 4-(2-methyl-5-phenyl-4-thiazolyl)butyl group, a 4-(2-methyl-5-phenyl-5-thiazolyl)butyl group, a 4-(2-phenyl-4-thiazolyl)butyl group, a 4-(2-phenyl-5-methyl-4-thiazolyl)butyl group, a 5-(2-thiazolyl)pentyl group, a 5-(4-thiazolyl)pentyl group, a 5-(5-thiazolyl)pentyl group, a 5-(2-methyl-4-thiazolyl)pentyl group, a 5-(2-methyl-5-thiazolyl)pentyl group, a 5-(2,5-dimethyl-4-thiazolyl)pentyl group, a 5-(2,4-dimethyl-5-thiazolyl)pentyl group, a 5-(2-methyl-5-phenyl-4-thiazolyl)pentyl group, a 5-(2-methyl-5-phenyl-5-thiazolyl)pentyl group, a 5-(2-phenyl-4-thiazolyl)pentyl group, a 5-(4-phenyl-5-thiazolyl)pentyl group, a 5-(2-phenyl-5-methyl-4-thiazolyl)pentyl group, a 6-(2-thiazolyl)hexyl group, a 6-(4-thiazolyl)hexyl group, a 6-(5-thiazolyl)hexyl group, a 6-(2-methyl-4-thiazolyl)hexyl group, a 6-(2-methyl-5-thiazolyl)hexyl group, a 6-(2,5-dimethyl-4-thiazolyl)hexyl group, a 6-(2,4-dimethyl-5-thiazolyl)hexyl group, a 6-(2,5-dimethyl-4-thiazolyl)hexyl group.
thiazolyl)hexyl group, a 6-(2,4-dimethyl-5-thiazolyl)hexyl group, a 6-(2-methyl-5-phenyl-4-thiazolyl)hexyl group, a 6-(2-methyl-4-phenyl-5-thiazolyl)hexyl group, a 6-(2-phenyl-4-thiazolyl)hexyl group, a 6-(4-phenyl-5-thiazolyl)hexyl group, a 6-(2-phenyl-5-methyl-4-thiazolyl)hexyl group, a 2-(2,3-dimethylphenyl)-4-thiazolylmethyl group, a 2-(3-methylphenyl)-5-thiazolylmethyl group, a 2-(3-trifluoromethylphenyl)-5-methyl-4-thiazolylmethyl group, a 2-(3-ethylphenyl)-4-methyl-5-thiazolylmethyl group, a 2-(2-trifluoroethylphenyl)-4-methyl-5-thiazolylmethyl group, and a 2-methyl-5-(2,4,6-trimethylphenyl)-4-thiazolylmethyl group, provided that, on the thiazole ring, 1 or 2 groups selected from the group consisting of a Cl-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom and a halogen substituted or unsubstituted Cl-C6 alkyl group may be substituted) may be substituted:

Examples of the tetrazolyl substituted Cl-C6 alkyl group (wherein, on the tetrazole ring, at least one Cl-C6 alkyl group may be substituted) may include tetrazolyl substituted Cl-C6 alkyl groups such as a 5-(1H)-tetrazolylmethyl group, a 2-(5-(1H)-tetrazolyl)ethyl group, a 1-(5-(1H)-tetrazolyl)ethyl group, a 3-(5-(1H)-tetrazolyl)propyl group, a 4-(5-(1H)-tetrazolyl)butyl group, a 5-(5-(1H)-tetrazolyl)pentyl group, a 6-(5-(1H)-tetrazolyl)hexyl
group, a 2-methyl-3-(5-(1H)-tetrazolyl)propyl group, a
1,1-dimethyl-2-(5-(1H)-tetrazolyl)ethyl group, a 1-
methyl-5-(1H)-tetrazolylmethyl group, a 1-ethyl-5-(1H)-
tetrazolylmethyl group, a 1-n-propyl-5-(1H)-
tetrazolylmethyl group, a 1-n-butyl-5-(1H)-
tetrazolylmethyl group, a 1-n-pentyl-5-(1H)-
tetrazolylmethyl group, a 1-n-hexyl-5-(1H)-
tetrazolylmethyl group, a 2-(1-methyl-5-(1H)-
tetrazolyl)ethyl group, a 2-(1-ethyl-5-(1H)-
tetrazolyl)ethyl group, a 2-(1-n-propyl-5-(1H)-
tetrazolyl)ethyl group, a 2-(1-n-butyl-5-(1H)-
tetrazolyl)ethyl group, a 2-(1-n-pentyl-5-(1H)-
tetrazolyl)ethyl group, and a 2-(1-n-hexyl-5-(1H)-
tetrazolyl)ethyl group; provided that, on the tetrazole
ring, one Cl-C6 alkyl group may be substituted.

Examples of the isoxazolyl substituted Cl-C6
alkyl group [wherein, on the isoxazole ring, at least
one Cl-C6 alkyl group may be substituted] may include
isoxazolyl substituted Cl-C6 alkyl groups such as a (3-,
4- or 5-isoxazolyl)methyl group, a 2-(3-, 4- or 5-
isoxazolyl)ethyl group, a 1-(3-, 4- or 5-
isoxazolyl)ethyl group, a 3-(3-, 4- or 5-
isoxazolyl)propyl group, a 4-(3-, 4- or 5-
isoxazolyl)butyl group, a 5-(3-, 4- or 5-
isoxazolyl)pentyl group, a 6-(3-, 4- or 5-
isoxazolyl)hexyl group, a 3-methyl-2-(3-, 4- or 5-
isoxazolyl)propyl group, a 1,1-dimethyl-2-(3-, 4- or 5-
isoxazolyl)ethyl group, a (3-methyl-4-isoxazolyl)methyl
group, a (4-ethyl-3-isoxazolyl)methyl group, a (5-n-propyl-3-isoxazolyl)methyl group, a (4-n-butyl-5-isoxazolyl)methyl group, a (5-n-pentyl-3-isoxazolyl)methyl group, a (3-n-hexyl-4-isoxazolyl)methyl group, a (3,4-dimethyl-5-isoxazolyl)methyl group, a 2-(3-methyl-4-isoxazolyl)ethyl group, a 1-(4-ethyl-3-isoxazolyl)ethyl group, a 3-(5-n-propyl-3-isoxazolyl)propyl group, a 4-(4-n-butyl-5-isoxazolyl)butyl group, a 5-(5-n-pentyl-3-isoxazolyl)pentyl group, a 6-(3-n-hexyl-4-isoxazolyl)hexyl group, and a 2-(3,4-dimethyl-5-isoxazolyl)ethyl group, provided that, on the isoxazole ring, 1 or 2 Cl-C6 alkyl groups may be substituted.

Examples of the 1,2,4-oxadiazolyl substituted Cl-C6 alkyl group [wherein, on the 1,2,4-oxadiazole ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, a Cl-C6 alkyl group may be substituted)] may include 1,2,4-oxadiazolyl substituted Cl-C6 alkyl groups such as a (3- or 5-)1,2,4-oxadiazolylmethyl group, a 2-((3- or 5-)1,2,4-oxadiazolyl)ethyl group, a 1-((3- or 5-)1,2,4-oxadiazolyl)ethyl group, a 3-((3- or 5-)1,2,4-oxadiazolyl)propyl group, a 4-((3- or 5-)1,2,4-oxadiazolyl)butyl group, a 5-((3- or 5-)1,2,4-oxadiazolyl)pentyl group, a 6-((3- or 5-)1,2,4-oxadiazolyl)hexyl group, a 3-methyl-2-((3- or 5-)1,2,4-oxadiazolyl)propyl group, a 1,1-dimethyl-2-((3- or 5-)1,2,4-oxadiazolyl)ethyl group, a (3-phenyl-5-1,2,4-
oxadiazolyl)methyl group, a (5-phenyl-3-1,2,4-oxadiazolyl)methyl group, a (3-(3-methylphenyl)-5,1,2,4-oxadiazolyl)methyl group, a (5-(3,4-dimethylphenyl)-3-1,2,4-oxadiazolyl)methyl group, a (3-(2,4,6-trimethylphenyl)-5-1,2,4-oxadiazolyl)methyl group, a (5-(2-ethylphenyl)-3-1,2,4-oxadiazolyl)methyl group, a 2-(3-n-propylphenyl)-5-1,2,4-oxadiazolyl)ethyl group, a 1-(5-(4-n-butylphenyl)-3-1,2,4-oxadiazolyl)ethyl group, a 3-(3-(3-n-pentylphenyl)-5-1,2,4-oxadiazolyl)propyl group, a 4-(5-(5-n-hexylphenyl)-3-1,2,4-oxadiazolyl)butyl group, a 5-(3-(3-ethyl-4-methylphenyl)-5-1,2,4-oxadiazolyl)pentyl group, and a 6-(5-(2-methylphenyl)-3-1,2,4-oxadiazolyl)hexyl group, provided that, on the 1,2,4-oxadiazole ring, one phenyl group may be substituted, provided that (wherein, on the phenyl ring, 1 to 3 C1-C6 alkyl groups may be substituted).

Examples of the benzofurazanyl substituted C1-C6 alkyl group may include 4-benzofurazanylmethyl, 5-benzofurazanylmethyl, 6-benzofurazanylmethyl, 7-benzofurazanylmethyl, 1-(4-benzofurazanyl)ethyl, 2-(5-benzofurazanyl)ethyl, 3-(6-benzofurazanyl)propyl, 4-(7-benzofurazanyl)butyl, 5-(4-benzofurazanyl)pentyl, 6-(5-benzofurazanyl)hexyl, 2-methyl-3-(5-benzofurazanyl)propyl, and 1,1-dimethyl-2-(7-benzofurazanyl)ethyl.

The phenylamino group (wherein a C1-C6 alkyl group may be substituted on position N of the
phenylamino group, and wherein, on the phenyl ring of the phenylamino group, at least one halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted; may be an unsubstituted phenylamino group (alias: anilino group), or a phenylamino group wherein the above defined 1 to 3 halogen substituted or unsubstituted C1-C6 alkoxy groups are substituted. Examples of the phenylamino group may include a phenylamino group, a 2-methoxyphenylamino group, a 3-methoxyphenylamino group, a 4-methoxyphenylamino group, a 2-ethoxyphenylamino group, a 3-ethoxyphenylamino group, a 4-ethoxyphenylamino group, a 4-n-propoxyphenylamino group, a 4-tert-butoxyphenylamino group, a 4-n-butoxyphenylamino group, a 2-trifluoromethoxyphenylamino group, a 3-trifluoromethoxyphenylamino group, a 4-trifluoromethoxyphenylamino group, a 2-pentafluoroethoxyphenylamino group, a 3-pentafluoroethoxyphenylamino group, a 2,3-dimethoxyphenylamino group, a 3,4,5-trimethoxyphenylamino group, a 4-n-pentyloxyphenylamino group, a 4-n-hexyloxyphenylamino group, a 3,5-ditrifluoromethoxyphenylamino group, an N-phenyl-N-methylamino group, an N-(2-methoxyphenyl)-N-ethylamino group, an N-(3-methoxyphenyl)-N-n-propylamino group, an N-(4-methoxyphenyl)-N-n-butylamino group, an N-(2-ethoxyphenyl)-N-n-pentylamino group, an N-(3-ethoxyphenyl)-N-n-hexylamino group, an N-(4-
ethoxyphenyl)-N-methylamino group, an N-(4-n-propoxyphenyl)-N-ethylamino group, an N-(4-n-butoxyphenyl)-N-n-propylamino group, an N-(4-n-butoxyphenyl)-N-n-butylamino group, an N-(2-trifluoromethoxyphenyl)-N-n-pentylamino group, an N-(3-trifluoromethoxyphenyl)-N-n-hexylamino group, an N-(4-trifluoromethoxyphenyl)-N-methylamino group, an N-(2-pentafluoroethoxyphenyl)-N-ethylamino group, an N-(3-pentafluoroethoxyphenyl)-N-n-propylamino group, an N-(2,3-dimethoxyphenyl)-N-methylamino group, an N-(3,4,5-trimethoxyphenyl)-N-methylamino group, an N-(4-n-pentyluxoxyphenyl)-N-methylamino group, an N-(4-n-hexyloxoxyphenyl)-N-methylamino group, and an N-(3,5-dinitrifluoromethoxyphenyl)-N-methylamino group.

Examples of the phenoxy group (wherein, on the phenyl ring, a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may include phenoxy groups such as a phenoxy group, a 2-methoxyphenoxy group, a 3-methoxyphenoxy group, a 4-methoxyphenoxy group, a 4-isopropoxyphenoxy group, a 4-n-butoxyphenoxy group, a 2,4-dimethoxyphenoxy group, a 2,3-dimethoxyphenoxy group, a 2,3,4,5,6-pentamethoxyphenoxy group, a 3,5-dimethoxyphenoxy group, a 2,5-dimethoxyphenoxy group, a 2,4,6-trimethoxyphenoxy group, a 3,5-di(trifluoromethoxy)phenoxy group, a 4-methoxy-3-trifluoromethoxyphenoxy group, a 2,6-dimethoxyphenoxy group, a 2-trifluoromethoxyphenoxy group, a 3-trifluoromethoxyphenoxy group, a 4-
trifluromethoxyphenoxy group, a 2,3-
di(trifluoromethoxy)phenoxy group, a 2,4-
di(trifluoromethoxy)phenoxy group, a 2-
pentafluoroethoxyphenoxy group, a 3-
pentafluoroethoxyphenoxy group, a 4-
pentafluoroethoxyphenoxy group, a 2-isopropoxyphenoxy
group, a 3-isopropoxyphenoxy group, a 4-
isopropoxyphenoxy group, a 2-tert-butoxyphenoxy group,
a 3-tert-butoxyphenoxy group, a 4-tert-butoxyphenoxy
group, a 2-sec-butoxyphenoxy group, a 3-sec-
butoxyphenoxy group, a 4-sec-butoxyphenoxy group, a 4-
-n-hexyloxyphenoxy group, a 2-n-
heptafluoropropoxyphenoxy group, a 3-n-
heptafluoropropoxyphenoxy group, and a 4-n-
heptafluoropropoxyphenoxy group, provided that, on the
phenyl ring, 1 to 5 groups, and preferably 1 to 3
groups selected from the group consisting of halogen
substituted or unsubstituted C1-C6 alkoxy groups may be
substituted.

Examples of the amino group (wherein, on the
amino group, at least one selected from the group
consisting of a C1-C6 alkyl group and a phenyl group
[wherein, on the phenyl ring, at least one selected
from the group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a
halogen substituted or unsubstituted C1-C6 alkoxy group
may be substituted] may be substituted as a
substituent: may include amino groups such as an amino
group, a methylamino group, a dimethylamino group, an ethylamino group, a diethylamino group, an n-propylamino group, an n-butylamino group, an n-pentylamino group, a 3-n-hexylamino group, a phenylamino group, a (4-chlorophenyl)amino group, a (4-bromophenyl)amino group, a (2,4-dichlorophenyl)amino group, a (2,4,6-trichlorophenyl)amino group, a (2,3,4,5,6-pentafluorophenyl)amino group, a (4-fluorophenyl)amino group, a (4-iodophenyl)amino group, a (4-chlorophenyl)amino group, a (3-methylphenyl)amino group, a (4-trifluoromethylphenyl)amino group, a (4-trifluoromethylphenyl)amino group, a 2-(4-trifluoromethylphenyl)amino group, a 3-(4-trifluoromethylphenyl)amino group, a (3,4-dimethylphenyl)amino group, a (3,4,5-trimethylphenyl)amino group, a (2-methoxyphenyl)amino group, a (4-trifluoromethoxyphenyl)amino group, a 3-(4-trifluoromethoxyphenyl)amino group, a (3,5-dimethoxyphenyl)amino group, a (2,5-dimethoxyphenyl)amino group, a (2,4,6-trimethoxyphenyl)amino group, an N-methyl-N-(4-trifluoromethylphenyl)amino group, and an N-ethyl-N-(4-trifluoromethoxyphenyl)amino group, provided that, on the amino group, 1 or 2 groups selected from the group consisting of a Cl-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted as substituents.

Examples of the piperidyl group (wherein, on the piperidine ring, at least one selected from the group consisting of a phenoxy group (wherein, on the phenyl ring, a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted as a substituent) and an amino group (wherein, on the amino group, at least one selected from the group consisting of a C1-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted as a substituent) may include piperidyl groups such as a 2-piperidyl group, a 3-piperidyl group, a 4-piperidyl group, a 2,4-diamino-1-piperidyl group, a 2,4,6-triamino-1-piperidyl group, a 4-amino-3-phenoxy-1-piperidyl group, a 4-phenoxy-2-amino-1-piperidyl group, a 2-amino-1-piperidyl group, a 3-amino-1-piperidyl group; a 4-amino-1-piperidyl group, a 4-methylamino-1-piperidyl group, a 4-ethylamino-1-piperidyl group, a 4-n-propylamino-1-piperidyl group, a 4-dimethylamino-1-piperidyl group, a 4-diethylamino-1-piperidyl group, a 4-di-n-propylamino-1-piperidyl group, a 4-phenylamino-1-piperidyl group, a 4-(N-phenyl-N-methylamino)-1-piperidyl group, a 4-(2-fluorophenylamino)-1-piperidyl
group, a 4-(3-fluorophenylamino)-1-piperidyl group, a 4-
(4-fluorophenylamino)-1-piperidyl group, a 4-(2-
chlorophenylamino)-1-piperidyl group, a 4-(2,3-
chlorophenylamino)-1-piperidyl group, a 4-(4-
chlorophenylamino)-1-piperidyl group, a 4-(2,3-
dichlorophenylamino)-1-piperidyl group, a 4-(2,4,6-
trifluorophenylamino)-1-piperidyl group, a 4-(2,4-
dichlorophenylamino)-1-piperidyl group, a 4-(3,4-
dichlorophenylamino)-1-piperidyl group, a 4-(3,5-
dichlorophenylamino)-1-piperidyl group, a 4-(2,3,4,5,6-
pentafluorophenylamino)-1-piperidyl group, a 4-(2-
trifluoromethylphenylamino)-1-piperidyl group, a 4-(2-
methylphenylamino)-1-piperidyl group, a 4-(2,3-
dimethylphenylamino)-1-piperidyl group, a 4-(2-
trifluoromethylphenylamino)-1-piperidyl group, a 4-
(2,4,6-trimethylphenylamino)-1-piperidyl group, a 4-(4-
trifluoromethylphenylamino)-1-piperidyl group, a 4-(2-
pentafluoroethylphenylamino)-1-piperidyl group, a 4-(3-
pentafluoroethylphenylamino)-1-piperidyl group, a 4-(4-
pentafluoroethylphenylamino)-1-piperidyl group, a 4-(2-
trifluoromethoxyphenylamino)-1-piperidyl group, a 4-(2-
methoxyphenylamino)-1-piperidyl group, a 4-(2,3-
dimethoxyphenylamino)-1-piperidyl group, a 4-(2,4,6-
trimethoxyphenylamino)-1-piperidyl group, a 4-(N-
methyl-N-(2,4,6-trimethoxyphenylamino))-1-piperidyl
group, a 4-(N-methyl-N-(3,4-dimethylphenylamino))-1-
piperidyl group, a 4-(3-trifluoromethoxyphenylamino)-1-
piperidyl group, a 4-(4-trifluoromethoxyphenylamino)-1-
piperidyl group, a 4-(2-pentafluorooxyphenoxy)-1-piperidyl group, a 4-(3-
pentafluoroethoxyphenylamino)-1-piperidyl group, a 4-(4-
pentafluorooxyphenoxy)-1-piperidyl group, a 4-
(2-fluorophenylamino)-1-piperidyl group, a 4-(3-
fluorophenylamino)-1-piperidyl group, a 4-(4-
fluorophenylamino)-1-piperidyl group, a 4-phenoxo-1-
piperidyl group, a 2,4-diphenoxo-1-piperidyl group, a
2,4,6-triphenoxo-1-piperidyl group, a 4-(2-
methoxyphenoxy)-1-piperidyl group, a 1-(3-
methoxyphenoxy)-4-piperidyl group, a 1-(4-
methoxyphenoxy)-4-piperidyl group, a 2-(2-
ethoxyphenoxy)-3-piperidyl group, a 3-(3-
ethoxyphenoxy)-4-piperidyl group, a 4-(4-
ethoxyphenoxy)-5-piperidyl group, a 3-(4-n-
propoxyphenoxy)-2-piperidyl group, a 2-(4-tert-
butoxyphenoxy)-1-piperidyl group, a 1-(4-n-
butoxyphenoxy)-2-piperidyl group, a 2-(2-
trifluoromethoxyphenoxy)-3-piperidyl group, a 3-(3-
trifluoromethoxyphenoxy)-4-piperidyl group, a 4-(4-
trifluoromethoxyphenoxy)-3-piperidyl group, a 3-(2-
pentafluorooxyphenoxy)-2-piperidyl group, a 6-(3-
pentafluorooxyphenoxy)-1-piperidyl group, a 1-(2,3-
dimethoxyphenoxy)-4-piperidyl group, a 4-(3,4,5-
trimethoxyphenoxy)-1-piperidyl group, a 4-(4-n-
pentyloxyphenoxy) group, and a 4-(4-n-hexyloxyphenoxy)-
1-piperidyl group, provided that, on the piperidine
ring, 1 to 3 groups selected from the group consisting
of a phenoxy group (wherein, on the phenyl ring, 1 to 5, and preferably 1 to 3 halogen substituted or unsubstituted Cl-C₆ alkoxy groups may be substituted as substituents) and an amino group (wherein, on the amino group, 1 or 2 groups selected from the group consisting of a Cl-C₆ alkyl group and a phenyl group [wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C₆ alkyl group, and a halogen substituted or unsubstituted Cl-C₆ alkoxy group may be substituted] may be substituted as substituents) may be substituted.

Examples of the piperazinyl group (wherein, on the piperazine ring, at least one selected from the following groups may be substituted: a Cl-C₆ alkoxy carbonyl group, a phenyl Cl-C₆ alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C₆ alkyl group, and a halogen substituted or unsubstituted Cl-C₆ alkoxy group may be substituted), a phenyl C₂-C₆ alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C₆ alkyl group, and a halogen substituted or unsubstituted Cl-C₆ alkoxy group may be substituted), and a benzoyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted)), may include piperazinyl groups such as a
(1-, 2- or 3-)-piperazinyl group, a 4-tert-
butyloxy carbonyl-1-piperazinyl group, a 4-ethoxy carbonyl-
1-piperazinyl group, a 4-methoxy carbonyl-1-piperazinyl
group, a 2,4-dimethoxy carbonyl-1-piperazinyl group, a
2,6,4-triethoxy carbonyl-1-piperazinyl group, a 4-(4-
trifluoromethoxy benzyl)-1-piperazinyl group, a 4-(4-
chlorobenzyl)-1-piperazinyl group, a 4-(4-
methoxy benzyl)-1-piperazinyl group, a 4-(4-
bromobenzyl)-1-piperazinyl group, a 4-(4-methyl benzyl)-
1-piperazinyl group, a 4-(2,4-dichlorobenzyl)-1-
piperazinyl group, a 4-(3,4-dimethoxy benzyl)-1-
piperazinyl group, a 4-(2,4,6-trifluorobenzyl)-1-
piperazinyl group, a 4-(3,4-dimethyl benzyl)-1-
piperazinyl group, a 4-(2,4,6-trimethoxy benzyl)-1-
piperazinyl group, a 4-(2,4,6-trimethyl benzyl)-1-
piperazinyl group, a 4-(4-iodobenzyl)-1-piperazinyl
group, a 4-(4-trifluoromethyl benzyl)-1-piperazinyl
group, a 4-(3,4-dichlorobenzyl)-1-piperazinyl group, a
4-(3-(4-trifluoromethyl phenyl)-2-propenyl)-1-
piperazinyl group, a 4-(3-(4-trifluoromethyl phenyl)-2-
propenyl)-1-piperazinyl group, a 4-(4-
trifluoromethyl benzoyl)-1-piperazinyl group, a 4-(3-(4-
chlorophenyl)-2-propenyl)-1-piperazinyl group, a 4-(3-
(4-methyl phenyl)-2-propenyl)-1-piperazinyl group, a 4-
(3-(4-methoxy phenyl)-2-propenyl)-1-piperazinyl group, a
4-(3-(3,4-dimethylphenyl)-2-propenyl)-1-piperazinyl group, a 4-(3-(3,4-dimethoxyphenyl)-2-propenyl)-1-piperazinyl group, a 4-(2-(3,4,5-trimethylphenyl)-2-propenyl)-1-piperazinyl group, a 4-(3-(3,4,5-trimethoxyphenyl)-2-propenyl)-1-piperazinyl group, a 4-(3-(3,4-dichlorophenyl)-2-propenyl)-1-piperazinyl group, a 4-(3-(2,4,6-trifluorophenyl)-2-propenyl)-1-piperazinyl group, a 4-(3-(4-iodophenyl)-2-propenyl)-1-piperazinyl group, a 4-(3-(3-bromophenyl)-2-propenyl)-1-piperazinyl group, a 4-(4-fluorobenzyl)-1-piperazinyl group, a 4-(4-methylbenzoyl)-1-piperazinyl group, a 4-(4-methoxybenzoyl)-1-piperazinyl group, a 4-(3,4-dimethylbenzoyl)-1-piperazinyl group, a 4-(2,4-dimethylbenzoyl)-1-piperazinyl group, a 4-(3,4,5-trimethylbenzoyl)-1-piperazinyl group, a 4-(2,4,6-trimethoxybenzoyl)-1-piperazinyl group, a 4-(4-chlorobenzoyl)-1-piperazinyl group, a 4-(2,4,6-trifluorobenzoyl)-1-piperazinyl group, a 4-(4-bromobenzoyl)-1-piperazinyl group, a 4-(4-iodobenzoyl)-1-piperazinyl group, a 4-(3,4-dichlorobenzoyl)-1-piperazinyl group, a 4-(4-fluorobenzoyl)-1-piperazinyl group, a 4-benzyl-3-(3-phenyl-2-propenyl)-1-piperazinyl group, and a 4-benzoyl-3,5-dibenzyl-1-piperazinyl group, provided that, on the piperazine ring, 1 to 3 groups selected from the following groups may be substituted: the above described C1-C6 alkoxy carbonyl group, the above described phenyl C1-C6 alkyl group (wherein, on the phenyl ring, 1 to 5 groups, and
preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), the above described phenyl C2-C6 alkenyl group (which is unsubstituted, or which is composed of 1 or 2 phenyl groups, wherein 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted, and alkenyl groups containing 2 to 6 carbon atoms and having 1 to 3 double bonds), and the above described benzoyl group (wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted).
homopiperazinyl groups such as a (1-, 2-, 3-, 4-, 5-, 6- or 7-)homopiperazinyl group, a 3,4-dibenzyl-1-homopiperazinyl group, a 2,7-dibenzyl-1-homopiperazinyl group, a 2,3,4-tribenzyl-1-homopiperazinyl group, a 2,4,6-tribenzyl-1-homopiperazinyl group, a 4-benzyl-1-homopiperazinyl group, a 4-(2-phenethyl)-1-homopiperazinyl group, a 4-(3-phenylpropyl)-1-homopiperazinyl group, a 4-(4-phenylbutyl)-1-homopiperazinyl group, a 4-(5-phenylpentyl)-1-homopiperazinyl group, a 4-(6-phenylhexyl)-1-homopiperazinyl group, a 4-(2-fluorobenzyl)-1-homopiperazinyl group, a 4-(3-fluorobenzyl)-1-homopiperazinyl group, a 4-(4-fluorobenzyl)-1-homopiperazinyl group, a 4-(2-chlorobenzyl)-1-homopiperazinyl group, a 4-(3-chlorobenzyl)-1-homopiperazinyl group, a 4-(4-chlorobenzyl)-1-homopiperazinyl group, a 4-(2,3-dichlorobenzyl)-1-homopiperazinyl group, a 4-(2,4-dichlorobenzyl)-1-homopiperazinyl group, a 4-(3,4-dichlorobenzyl)-1-homopiperazinyl group, a 4-(3,5-dichlorobenzyl)-1-homopiperazinyl group, a 4-(3,4,5-trichlorobenzyl)-1-homopiperazinyl group, a 4-(2,3,4,5,6-pentafluorobenzyl)-1-homopiperazinyl group, a 4-(2-trifluoromethylbenzyl)-1-homopiperazinyl group, a 4-(3-trifluoromethylbenzyl)-1-homopiperazinyl group, a 4-(4-trifluoromethylbenzyl)-1-homopiperazinyl group, a 4-(4-methylbenzyl)-1-homopiperazinyl group, a 4-(3,4-dimethylbenzyl)-1-homopiperazinyl group, a 4-(2,4,6-
trimethylbenzyl)-1-homopiperazinyl group, a 4-(2-
pentafluorostyryl)-1-homopiperazinyl group, a 4-
(3-pentafluorostyryl)-1-homopiperazinyl group, a
4-(4-pentafluorostyryl)-1-homopiperazinyl group, a

4-(2-trifluoromethoxybenzyl)-1-homopiperazinyl group, a
4-(3-trifluoromethoxybenzyl)-1-homopiperazinyl group, a
4-(4-trifluoromethoxybenzyl)-1-homopiperazinyl group, a
4-(4-methoxybenzyl)-1-homopiperazinyl group, a 4-(3,4-
dimethoxybenzyl)-1-homopiperazinyl group, a 4-(2,4,6-
trimethoxybenzyl)-1-homopiperazinyl group, a 4-(2-
pentafluoroethoxybenzyl)-1-homopiperazinyl group, a 4-
(3-pentafluoroethoxybenzyl)-1-homopiperazinyl group, a
4-(4-pentafluoroethoxybenzyl)-1-homopiperazinyl group, a
4-(2-(4-trifluoromethoxyphenyl)ethyl)-1-
homopiperazinyl group, a 4-(3-(4-
trifluoromethoxyphenyl)propyl)-1-homopiperazinyl group,
a 4-(4-(4-trifluoromethoxyphenyl)butyl)-1-
homopiperazinyl group, a 4-(5-(4-
trifluoromethoxyphenyl)pentyl)-1-homopiperazinyl group,
a 4-(6-(4-trifluoromethoxyphenyl)hexyl)-1-
homopiperazinyl group, a 4-(2-(4-
trifluoromethylphenyl)ethyl)-1-homopiperazinyl group, a
4-(3-(4-trifluoromethylphenyl)propyl)-1-homopiperazinyl
group, a 4-(4-(4-trifluoromethylphenyl)butyl)-1-
homopiperazinyl group, a 4-(5-(4-
trifluoromethylphenyl)pentyl)-1-homopiperazinyl group,
3-, 5-, 6- or 7-) homopiperazinyl group, a 4-
methoxycarbonyl(1-, 2-, 3-, 5-, 6- or
7-) homopiperazinyl group, and a 4-
ethoxycarbonylcarbonyl(1-, 2-, 3-, 5-, 6- or
7-) homopiperazinyl group, provided that, on the
homopiperazine ring, 1 to 3 groups selected from the
group consisting of the above described C1-C6
alkoxycarbonyl group and a phenyl C1-C6 alkyl group
(wherein, on the phenyl ring, 1 to 5 groups, and
preferably 1 to 3 groups selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted) may be substituted.

Examples of the phenoxy substituted phenyl
group (wherein, on the phenyl ring, at least one
halogen substituted or unsubstituted C1-C6 alkoxy group
may be substituted) may include phenoxy substituted
phenyl groups such as a 2-phenoxyphenyl group, a 2,3-
diphenoxyphenyl group, a 2,4,6-triphenoxyphenyl group,
a 3-(2-methoxyphenoxy)phenyl group, a 4-(3-
methoxyphenoxy)phenyl group, a 2-(4-
methoxyphenoxy)phenyl group, a 3-(4-
isopropoxyphenoxy)phenyl group, a 4-(4-n-
butoxyphenoxy)phenyl group, a 2-(2,4-
dimethoxyphenoxy)phenyl group, a 3-(2,3-
dimethoxyphenoxy)phenyl group, a 4-(2,3,4,5,6-
pentamethoxyphenoxy)phenyl group, a 2-(3,5-
dimethoxyphenoxy)phenyl group, a 3-(2,5-
dimethoxyphenoxy)phenyl group, a 4-(2,4,6-
trimethoxyphenoxy)phenyl group, a 2-(3,5-
di(trifluoromethoxy)phenoxy)phenyl group, a 3-(4-
5 methoxy-3-trifluoromethoxyphenoxy)phenyl group, a 4-
(2,6-dimethoxyphenoxy)phenyl group, a 2-(2-
trifluoromethoxyphenoxy)phenyl group, a 3-(3-
trifluoromethoxyphenoxy)phenyl group, a 4-(4-
trifluoromethoxyphenoxy)phenyl group, a 2-(2,3-
10 di(trifluoromethoxy)phenoxy)phenyl group, a 3-(2,4-
di(trifluoromethoxy)phenoxy)phenyl group, a 4-(2-
pentafluoroethoxyphenoxy)phenyl group, a 2-(3-
pentafluoroethoxyphenoxy)phenyl group, a 3-(4-
pentafluoroethoxyphenoxy)phenyl group, a 4-(2-
15 isopropoxyphenoxy)phenyl group, a 2-(3-
isopropoxyphenoxy)phenyl group, a 3-(4-
isopropoxyphenoxy)phenyl group, a 4-(2-tert-
butoxyphenoxy)phenyl group, a 2-(3-tert-
butoxyphenoxy)phenyl group, a 3-(4-tert-
20 butoxyphenoxy)phenyl group, a 4-(2-sec-
butoxyphenoxy)phenyl group, a 3-(3-sec-
butoxyphenoxy)phenyl group, a 4-(4-sec-
butoxyphenoxy)phenyl group, a 2-(4-n-
25 hexyloxyphenoxy)phenyl group, a 3-(2-n-
heptafluoropropoxyphenoxy)phenyl group, a 4-(3-n-
heptafluoropropoxyphenoxy)phenyl group, and a 2-(4-n-
heptafluoropropoxyphenoxy)phenyl group, provided that,
on the phenyl ring, 1 to 5, and preferably 1 to 3
halogen substituted or unsubstituted Cl-C6 alkoxy
groups may be substituted.

Examples of the phenoxy group [wherein, on
the phenyl ring, at least one selected from the group
consisting of a halogen substituted or unsubstituted
Cl-C6 alkoxy group and a phenoxy substituted phenyl
group (wherein, on the phenyl ring, at least one
halogen substituted or unsubstituted Cl-C6 alkoxy group
may be substituted) may include

phenoxy groups such as a phenoxy group, a 2-
methoxyphenoxy group, a 3-methoxyphenoxy group, a 4-
methoxyphenoxy group, a 4-isopropoxyphenoxy group, a 4-
n-butoxyphenoxy group, a 2,4-dimethoxyphenoxy group, a
2,3-dimethoxyphenoxy group, a 2,3,4,5,6-
pentamethoxyphenoxy group, a 3,5-dimethoxyphenoxy
group, a 2,5-dimethoxyphenoxy group, a 2,4,6-
trimethoxyphenoxy group, a 3,5-
di(trifluoromethoxy)phenoxy group, a 4-methoxy-3-
trifluoromethoxyphenoxy group, a 2,6-dimethoxyphenoxy
group, a 2-trifluoromethoxyphenoxy group, a 3-
trifluoromethoxyphenoxy group, a 4-
trifluoromethoxyphenoxy group, a 2,3-
di(trifluoromethoxy)phenoxy group, a 2,4-
di(trifluoromethoxy)phenoxy group, a 2-
pentafluoroethoxyphenoxy group, a 3-
pentafluoroethoxyphenoxy group, a 4-
pentafluoroethoxyphenoxy group, a 2-isopropoxyphenoxy
group, a 3-isopropoxyphenoxy group, a 4-
isoproxyphenoxy group, a 2-tert-butoxyphenoxy group, a 3-tert-butoxyphenoxy group, a 4-tert-butoxyphenoxy group, a 2-sec-butoxyphenoxy group, a 3-sec-butoxyphenoxy group, a 4-sec-butoxyphenoxy group, a 4-n-hexyloxyphenoxy group, a 2-n-heptafluoropropoxyphenoxy group, a 3-n-heptafluoropropoxyphenoxy group, a 4-n-heptafluoropropoxyphenoxy group, a 2-(2-phenoxyphenyl)phenoxy group, a 2,3-di(2-phenoxyphenyl)phenoxy group, a 2,3-di(2-phenoxyphenyl)-4-methoxyphenoxy group, a 2,4-dimethoxy-3-(3-phenoxyphenyl)phenoxy group, a 3-(2,3-diphenoxypheynyl)phenoxy group, a 4-(2,4,6-triphenoxyphenyl)phenoxy group, a 2-(3-(2-methoxyphenoxy)phenyl)phenoxy group, a 3-(4-(3-methoxyphenoxy)phenyl)phenoxy group, a 4-(2-(4-methoxyphenoxy)phenyl)phenoxy group, a 2-(3-(4-isoproxyphenoxy)phenyl)phenoxy group, a 3-(4-(4-n-butoxyphenoxy)phenyl)phenoxy group, a 4-(2-(2,4-dimethoxyphenoxy)phenyl)phenoxy group, a 2-(3-(2,3-dimethoxyphenoxy)phenyl)phenoxy group, a 3-(4-(2,3,4,5,6-pentamethoxyphenoxy)phenyl)phenoxy group, a 4-(2-(3,5-dimethoxyphenoxy)phenyl)phenoxy group, a 2-(3,2,5-dimethoxyphenoxy)phenyl)phenoxy group, a 3-(4-(2,4,6-trimethoxyphenoxy)phenyl)phenoxy group, a 4-(2-(3,5-di(trifluoromethoxy)phenoxy)phenyl)phenoxy group, a 2-(3-(4-methoxy-3-trifluoromethoxyphenoxy)phenyl)phenoxy group, a 3-(4-
(2,5-dimethoxyphenoxyl)phenyl)phenoxy group, a 4-(2-(2-
trifluoromethoxyphenoxy)phenyl)phenoxy group, a 2-(3-
(3-trifluoromethoxyphenoxyl)phenyl)phenoxy group, a 3-
(4-(4-trifluoromethoxyphenoxy)phenyl)phenoxy group, a
4-(2-(2,3-di(trifluoromethoxy)phenoxy)phenyl)phenoxy
group, a 2-(3-(2,4-
di(trifluoromethoxy)phenoxy)phenyl)phenoxy group, a 3-
(4-(2-pentafluoroethoxyphenoxy)phenyl)phenoxy group, a
4-(2-(3-pentafluoroethoxyphenoxy)phenyl)phenoxy group,
a 2-(3-(4-pentafluoroethoxyphenoxy)phenyl)phenoxy
group, a 3-(4-(2-isopropoxyphenoxy)phenyl)phenoxy

group, a 4-(2-(3-isopropoxyphenoxy)phenyl)phenoxy

group, a 2-(3-(4-isopropoxyphenoxy)phenyl)phenoxy
group, a 3-(2-(2-tert-butoxyphenoxy)phenyl)phenoxy
group, a 4-(2-(3-tert-butoxyphenoxy)phenyl)phenoxy
group, a 2-(3-(4-tert-butoxyphenoxy)phenyl)phenoxy

group, a 3-(4-(2-sec-butoxyphenoxy)phenyl)phenoxy

group, a 2-(2-(3-sec-butoxyphenoxy)phenyl)phenoxy

group, a 2-(3-(4-sec-butoxyphenoxy)phenyl)phenoxy

group, a 4-(2-(4-n-hexyloxyphenoxy)phenyl)phenoxy
group, a 2-(3-(2-n-heptafluoropropoxyphenoxy)phenyl)phenoxy group, a 3-(4-
(3-n-heptafluoropropoxyphenoxy)phenyl)phenoxy group,
and a 4-(2-(4-n-
heptafluoropropoxyphenoxy)phenyl)phenoxy group,
provided that, on the phenyl ring, 1 to 5 groups, and
preferably 1 to 3 groups selected from the group
consisting of a halogen substituted or unsubstituted
C1-C6 alkoxy group and a phenoxy substituted phenyl group (wherein, on the phenyl ring, 1 to 5, and preferably 1 to 3 halogen substituted or unsubstituted C1-C6 alkoxy groups may be substituted) may be substituted.

Examples of the homopiperazinyl group (wherein, on the homopiperazine ring, at least one selected from the following groups may be substituted: a C1-C6 alkoxy carbonyl group, a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a phenyl C1-C6 alkoxy carbonyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], a phenyl carbamoyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted).
may be substituted), a phenyl C2-C6 alkenyl group
(wherein, on the phenyl ring, at least one selected
from the group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a
halogen substituted or unsubstituted C1-C6 alkoxy group
may be substituted), and a benzoyl group (wherein, on
the phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted), may include homopiperazinyl groups such
as a (1-, 2-, 3-, 4-, 5-, 6- or 7-)homopiperazinyl
group, a 4-tetrt-butoxycarbonyl-1-homopiperazinyl group,
a 4-ethoxycarbonyl-1-homopiperazinyl group, a 4-
methoxycarbonyl-1-homopiperazinyl group, a 2,4-
dimethoxycarbonyl-1-homopiperazinyl group, a 2,4,6-
triethoxycarbonyl-1-homopiperazinyl group, a 4-(4-
trifluoromethoxybenzyl)-1-homopiperazinyl group, a 4-
(4-chlorobenzyl)-1-homopiperazinyl group, a 4-(4-
methoxybenzyl)-1-homopiperazinyl group, a 4-(4-
bromobenzyl)-1-homopiperazinyl group, a 4-(4-
methylbenzyl)-1-homopiperazinyl group, a 4-(2,4-
dichlorobenzyl)-1-homopiperazinyl group, a 4-(3,4-
dimethoxybenzyl)-1-homopiperazinyl group, a 4-(2,4,6-
trifluorobenzyl)-1-homopiperazinyl group, a 4-(3,4-
dimethylbenzyl)-1-homopiperazinyl group, a 4-(2,4,6-
trimethoxybenzyl)-1-homopiperazinyl group, a 4-(2,4,6-
trimethylbenzyl)-1-homopiperazinyl group, a 4-(4-

iodobenzyl)-1-homopiperazinyl group, a 4-(4-
trifluoromethylbenzyl)-1-homopiperazinyl group, a 4-
(3,4-dichlorobenzyl)-1-homopiperazinyl group, a 4-(3-
(4-trifluoromethylphenyl)-2-propenyl)-1-homopiperazinyl
5 group, a 4-(3-(4-trifluoromethylphenyl)-2-propenyl)-1-
homopiperazinyl group, a 4-(4-trifluoromethylbenzoyl)-1-
homopiperazinyl group, a 4-(3-(4-chlorophenyl)-2-
propenyl)-1-homopiperazinyl group, a 4-(3-(4-
methylphenyl)-2-propenyl)-1-homopiperazinyl group, a 4-
10 (3-(4-methoxyphenyl)-2-propenyl)-1-homopiperazinyl
group, a 4-(3-(3,4-dimethylphenyl)-2-propenyl)-1-
homopiperazinyl group, a 4-(3-(3,4-dimethoxyphenyl)-2-
propenyl)-1-homopiperazinyl group, a 4-(3-(3,4,5-
trimethylphenyl)-2-propenyl)-1-homopiperazinyl group, a
15 4-(3-(3,4,5-trimethoxyphenyl)-2-propenyl)-1-
homopiperazinyl group, a 4-(3-(3,4-dichlorophenyl)-2-
propenyl)-1-homopiperazinyl group, a 4-(3-(2,4,6-
trifluorophenyl)-2-propenyl)-1-homopiperazinyl group, a
20 4-(3-(4-iodophenyl)-2-propenyl)-1-homopiperazinyl
group, a 4-(3-(3-bromophenyl)-2-propenyl)-1-
homopiperazinyl group, a 4-(4-fluorobenzyl)-1-
homopiperazinyl group, a 4-(4-methylbenzoyl)-1-
homopiperazinyl group, a 4-(4-methoxybenzoyl)-1-
homopiperazinyl group, a 4-(3,4-dimethylbenzoyl)-1-
25 homopiperazinyl group, a 4-(2,4-dimethoxybenzoyl)-1-
homopiperazinyl group, a 4-(3,4,5-trimethylbenzoyl)-1-
homopiperazinyl group, a 4-(2,4,6-trimethoxybenzoyl)-1-
homopiperazinyl group, a 4-(4-chlorobenzoyl)-1-
homopiperazinyl group, a 4-(2,4,6-trifluorobenzoyl)-1-
homopiperazinyl group, a 4-(4-bromobenzoyl)-1-
homopiperazinyl group, a 4-(4-iodobenzoyl)-1-
homopiperazinyl group, a 4-(3,4-dichlorobenzoyl)-1-
homopiperazinyl group, a 4-(4-fluorobenzoyl)-1-
homopiperazinyl group, a 4-benzyl-3-(3-phenyl-2-
propenyl)-1-homopiperazinyl group, a 4-benzyl-3,5-
dibenzyl-1-homopiperazinyl group, a 2,7-dibenzyl-4-
phenyl-homopiperazinyl group, a 4-(4-
trifluoromethylphenyl)-1-homopiperazinyl group, a 4-(4-
trifluoromethoxyphenyl)-1-homopiperazinyl group, a 4-
(4-chlorophenyl)-1-homopiperazinyl group, a 4-(4-
methoxyphenyl)-1-homopiperazinyl group, a 4-(4-
methylphenyl)-1-homopiperazinyl group, a 4-(2,4-
dimethoxyphenyl)-1-homopiperazinyl group, a 4-(2,4-
dimethylphenyl)-1-homopiperazinyl group, a 4-(2,4,6-
trimethoxyphenyl)-1-homopiperazinyl group, a 4-(2,4,6-
trimethylphenyl)-1-homopiperazinyl group, a 4-(3,4-
dichlorophenyl)-1-homopiperazinyl group, a 4-(2,4,6-
trifluorophenyl)-1-homopiperazinyl group, a 4-(4-
bromophenyl)-1-homopiperazinyl group, a 4-(4-
iodophenyl)-1-homopiperazinyl group, a 4-(4-
fluorophenyl)-1-homopiperazinyl group, a 4-(4-
trifluoromethoxybenzylloxycarbonyl)-1-homopiperazinyl-
group, a 4-(4-chlorobenzylloxycarbonyl)-1-
homopiperazinyl group, a 4-(4-
methoxybenzylloxycarbonyl)-1-homopiperazinyl group, a 4-
(4-bromobenzylloxycarbonyl)-1-homopiperazinyl group, a
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4-(4-methylbenzyloxy carbonyl)-1-homopiperazinyl group, a
4-(2,4-dichlorobenzyloxy carbonyl)-1-homopiperazinyl
group, a 4-(3,4-dimethoxybenzyloxy carbonyl)-1-
homopiperazinyl group, a 4-(2,4,6-
trifluorobenzyloxy carbonyl)-1-homopiperazinyl group, a
4-(3,4-dimethylbenzyloxy carbonyl)-1-homopiperazinyl
group, a 4-(2,4,6-trimethoxybenzyloxy carbonyl)-1-
homopiperazinyl group, a 4-(2,4,6-
trimethylbenzyloxy carbonyl)-1-homopiperazinyl group, a

10 4-(4-iodobenzyloxy carbonyl)-1-homopiperazinyl group, a
4-(4-trifluoromethylbenzyloxy carbonyl)-1-
homopiperazinyl group, a 4-(3,4-
dichlorobenzyloxy carbonyl)-1-homopiperazinyl group, a
4-(4-trifluoromethoxyphenylcarbamoyl)-1-homopiperazinyl
group, a 4-(4-chlorophenylcarbamoyl)-1-homopiperazinyl
group, a 4-(4-methoxyphenylcarbamoyl)-1-homopiperazinyl
group, a 4-(4-bromophenylcarbamoyl)-1-homopiperazinyl
group, a 4-(4-methylphenylcarbamoyl)-1-homopiperazinyl
group, a 4-(2,4-dichlorophenylcarbamoyl)-1-

15 homopiperazinyl group, a 4-(3,4-
dimethoxyphenylcarbamoyl)-1-homopiperazinyl group, a 4-
(2,4,6-trifluorophenylcarbamoyl) -1-homopiperazinyl
group, a 4-(3,4-dimethylphenylcarbamoyl) -1-
homopiperazinyl group, a 4-(2,4,6-
trimethoxyphenylcarbamoyl)-1-homopiperazinyl group, a
4-(2,4,6-trimethylphenylcarbamoyl)-1-homopiperazinyl
group, a 4-(4-iodophenylcarbamoyl)-1-homopiperazinyl
group, a 4-(4-trifluoromethylphenylcarbamoyl)-1-

20
homopiperazinyl group, a 3,4-dilphenylcarbamoyl)-1-
homopiperazinyl group, a 4-(2-(4-
trifluoromethylphenyl)ethyl)-1-homopiperazinyl group,
and a 4-(3-(4-trifluoromethylphenyl)propyl)-1-
homopiperazinyl group, provided that, on the
homopiperazine ring, 1 to 3 groups selected from the
following groups may be substituted: the above
described C1-C6 alkoxy carbonyl group, the above
described phenyl C1-C6 alkyl group [wherein, on the
phenyl ring, 1 to 5 groups, and preferably 1 to 3
groups selected from the group consisting of a halogen
atom, a halogen substituted or unsubstituted C1-C6
alkyl group, and a halogen substituted or unsubstituted
C1-C6 alkoxy group may be substituted], the above
described phenyl group [wherein, on the phenyl ring, 1
to 5 groups, and preferably 1 to 3 groups selected from
the group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a
halogen substituted or unsubstituted C1-C6 alkoxy group
may be substituted], the above described phenyl C1-C6
alkoxy carbonyl group [wherein, on the phenyl ring, 1 to
5 groups, and preferably 1 to 3 groups selected from
the group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a
halogen substituted or unsubstituted C1-C6 alkoxy group
may be substituted], the above described
phenylcarbamoyl group [wherein, on the phenyl ring, 1
to 5 groups, and preferably 1 to 3 groups selected from
the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), the above described phenyl C2-C6 alkenyl group (which is unsubstituted, or which is composed of 1 or 2 phenyl groups, wherein 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted, and alkenyl groups containing 2 to 6 carbon atoms and having 1 to 3 double bonds), and the above described benzoyl group (wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted).

Examples of the 1,2,3,4-tetrahydroisoquinolyl group (wherein, on the 1,2,3,4-tetrahydroisoquinoline ring, at least one amino group may be substituted (wherein, on the amino group, at least one selected from the group consisting of a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) and a Cl-C6 alkyl group may be
substituted], may include 1,2,3,4-tetrahydroisoquinolyl groups such as a 1,2,3,4-tetrahydro(1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-)isoquinolyl group, a 4,6-diamino-1,2,3,4-tetrahydro-2-isoquinolyl group, a 4,6,7-triamino-1,2,3,4-tetrahydro-2-isoquinolyl group, a 7-(N-methyl-N-(4-trifluoromethoxybenzyl)amino)-1,2,3,4-tetrahydro-2-isoquinolyl group, a 6-(4-trifluoromethoxyphenoxy)-1,2,3,4-tetrahydro-2-isoquinolyl group, a 7-(N-methyl-N-(4-trifluoromethylbenzyl)amino)-1,2,3,4-tetrahydro-2-isoquinolyl group, a 7-(N-methyl-N-(4-chlorobenzyl)amino)-1,2,3,4-tetrahydro-2-isoquinolyl group, a 7-(N-(4-chlorobenzyl)amino)-1,2,3,4-tetrahydro-2-isoquinolyl group, a 7-(N-methyl-N-(2,4,6-tri(trifluoromethoxy)benzyl)amino)-1,2,3,4-tetrahydro-2-isoquinolyl group, a 7-(N-methyl-N-(2,4-di(trifluoromethyl)benzyl)amino)-1,2,3,4-tetrahydro-2-isoquinolyl group, and a 7-(N-methyl-N-(2,3-diiodobenzyl)amino)-1,2,3,4-tetrahydro-2-isoquinolyl group, provided that, on the 1,2,3,4-tetrahydroisoquinoline ring, 1 to 3 amino groups may be substituted (wherein, on the amino group, 1 or 2 groups selected from the group consisting of the above described phenyl C1-C6 alkyl group (wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted
C1-C6 alkoxy group may be substituted) and the above described C1-C6 alkyl group may be substituted).

Examples of the oxazolyl group (wherein, on the oxazole ring, at least one selected from the following groups may be substituted: a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a C1-C6 alkyl group, and a piperidyl group (wherein, on the piperidine ring, at least one phenoxy group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted)), may include oxazolyl groups such as a (2-, 4- or 5-)oxazolyl group, a 4-(4-chlorophenyl)-2-oxazolyl group, a 4-(4-trifluoromethoxyphenyl)-2-oxazolyl group, a 2-(4-trifluoromethylphenyl)-4-oxazolyl group, a 4-(4-trifluoromethylphenyl)-2-oxazolyl group, a 2-(4-trifluoromethoxyphenyl)-4-oxazolyl group, a 4-(3,4-dichlorophenyl)-2-oxazolyl group, a 5-(4-bromophenyl)-2-oxazolyl group, a 4-(4-fluorophenyl)-2-oxazolyl group, a 5-(4-iodophenyl)-2-oxazolyl group, a 2-(2,4,6-trifluorophenyl)-4-oxazolyl group, a 4-(4-methylphenyl)-2-oxazolyl group, a 4-(3-methoxyphenyl)-2-oxazolyl group, a 2-(3,4-
dimethylphenyl)-5-oxazolyl group, a 4-(2,4-
dimethoxyphenyl)-2-oxazolyl group, a 4-(2,4,6-
trimethylphenyl)-2-oxazolyl group, a 4-(3,4,5-
trimethoxyphenyl)-2-oxazolyl group, a 4,5-diphenyl-2-
oxazolyl group, a 2,4-diphenyl-5-oxazolyl group, and a
4-methyl-5-(4-(4-trifluoromethoxyphenoxy)-(1-, 2- or
3-))piperidyl)-2-oxazolyl group, provided that, on the
oxazole ring, 1 or 2 groups selected from the following
groups may be substituted: a phenyl group (wherein, on
the phenyl ring, 1 to 5 groups, and preferably 1 to 3
groups selected from the group consisting of a halogen
atom, a halogen substituted or unsubstituted C1-C6
alkyl group, and a halogen substituted or unsubstituted
C1-C6 alkoxy group may be substituted], the above
described C1-C6 alkyl group, and the below described
piperidyl group (wherein, on the piperidine ring, 1 to
3 phenoxy groups may be substituted (wherein, on the
phenyl ring, 1 to 5 groups, and preferably 1 to 3
groups selected from the group consisting of a halogen
atom, a halogen substituted or unsubstituted C1-C6
alkyl group, and a halogen substituted or unsubstituted
C1-C6 alkoxy group may be substituted]).

Examples of the isoindoliny1 group (wherein,
on the isoindoline ring, at least one selected from the
group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a
halogen substituted or unsubstituted C1-C6 alkoxy group
may be substituted) may include isoindoliny1 groups
such as a (1-, 2-, 4- or 5-)isoindoliny1 group, a 4-
chloro-(1-, 2-, 3-, 5-, 6- or 7-)isoindoliny1 group, a
4-trifluoromethyl-(1-, 2-, 3-, 5-, 6- or 7-)isoindoliny1 group, a 4-trifluoromethoxy-(1-, 2-, 3-, 5-,
6- or 7-)isoindoliny1 group, a 5-methyl-(1-, 2-, 3-, 4-, 6- or 7-)isoindoliny1 group, a 4-methoxy-(1-, 2-, 3-, 5-, 6- or 7-)isoindoliny1 group, a 3,4-
difluoro-(1-, 2-, 5-, 6- or 7-)isoindoliny1 group, a
4,5,6-trichloro(1-, 2-, 3- or 7-)isoindoliny1 group, a
4,5-dimethyl(1-, 2-, 3-, 6- or 7-)isoindoliny1 group, a
4,5,6-trimethyl(1-, 2-, 3- or 7-)isoindoliny1 group, a
4,5-dimethoxy(1-, 2-, 3-, 6- or 7-)isoindoliny1 group,
a 4,5,6-trimethoxy(1-, 2-, 3- or 7-)isoindoliny1 group,
and a 1,1-dimethyl-5-bromo-(2-, 3-, 4-, 6- or
7-)isoindoliny1 group, provided that, on the
isoindoline ring, 1 to 3 groups selected from the group
consisting of the above described halogen atom, the
above described halogen substituted or unsubstituted
Cl-C6 alkyl group, and the above described halogen
substituted or unsubstituted Cl-C6 alkoxy group may be
substituted.

Examples of the piperaziny1 group (wherein,
on the piperazine ring, at least one phenyl group may
be substituted (wherein, on the phenyl ring, at least
one selected from the group consisting of a halogen
atom, a halogen substituted or unsubstituted Cl-C6
alkyl group, and a halogen substituted or unsubstituted
Cl-C6 alkoxy group may be substituted)) may include
piperazinyl groups such as a (1-, 2- or 3-)piperazinyl group, a 4-phenyl-1-piperazinyl group, a 2,4-diphenyl-1-piperazinyl group, a 2,4,5-triphenyl-1-piperazinyl group, a 4-(4-trifluoromethoxyphenyl)-1-piperazinyl group, a 4-(4-trifluoromethylphenyl)-1-piperazinyl group, a (4-chlorophenyl-1-piperazinyl)methyl group, a 4-(2,4-dichlorophenyl)-1-piperazinyl group, a 4-(2,4,5-trifluorophenyl)-1-piperazinyl group, a 2,4-di(trifluoromethyl)phenyl-1-piperazinyl group, and a 2,4,6-tri(trifluoromethoxy)phenyl-1-piperazinyl group, provided that, on the piperazine ring, the above described 1 to 3 phenyl groups may be substituted (wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted).

Examples of the thiazolyl group (wherein, on the thiazole ring, at least one selected from the following groups may be substituted: a phenoxy C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted); a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted); a phenyl C1-C6 alkyl group [wherein, on
the phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted]; a group -(W₁)ONR²⁻R³⁻ [wherein W₁ and o are
the same as described above, and R² and R³, which may
be identical or different, each represent a hydrogen
atom, C1-C6 alkyl group, phenyl group (wherein, on the
phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted), or phenyl C1-C6 alkyl group (wherein, on
the phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted)]; a piperazinyl group [wherein, on the
piperazine ring, at least one phenyl group may be
substituted (wherein, on the phenyl ring, at least one
selected from the group consisting of a halogen atom, a
halogen substituted or unsubstituted C1-C6 alkyl group,
and a halogen substituted or unsubstituted C1-C6 alkoxy
group may be substituted)]; a piperidyl group [wherein,
on the piperidine ring, at least one selected from the
group consisting of a phenoxy group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] and a phenyl C1-C6 alkyl group may be substituted]; and a phenoxy group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted]), may include thiazolyl groups such as a (2-, 4- or 5-)thiazolyl group, a 2-((4-fluoromethoxyphenoxy)methyl)-4-thiazolyl group, a 4-((4-fluoromethoxyphenoxy)methyl)-2-thiazolyl group, a 2-((4-fluoromethylphenoxy)methyl)-4-thiazolyl group, a 2-((4-chlorophenoxy)methyl)-4-thiazolyl group, a 2-((3-methoxyphenoxy)methyl)-4-thiazolyl group, a 2-((2-methylphenoxy)methyl)-5-thiazolyl group, a 2-((2,4-dimethoxyphenoxy)methyl)-5-thiazolyl group, a 2-((3,4-dimethylphenoxy)methyl)-4-thiazolyl group, a 5-((2,4,6-trimethoxyphenoxy)methyl)-2-thiazolyl group, a 2-((3,4,5-trimethylphenoxy)methyl)-4-thiazolyl group, a 2-((2,4,6-trifluorophenoxy)methyl)-4-thiazolyl group, a 4-((3,4-dichlorophenoxy)methyl)-2-thiazolyl group, a 2-((4-bromophenoxy)methyl)-4-thiazolyl group, a 2-((4-iodophenoxy)methyl)-4-thiazolyl group, a 4-((4-fluorophenoxy)methyl)-2-thiazolyl group, a 2,5-
diphenoxymethyl-4-thiazolyl group, a 4,5-
diphenoxymethyl-2-thiazolyl group, a 2-(4-
fluorophenyl)-4-thiazolyl group, a 4-(4-fluorophenyl)-
2-thiazolyl group, a 2-(4-chlorophenyl)-4-thiazolyl
group, a 4-(4-chlorophenyl)-2-thiazolyl group, a 2-(4-
trifluoromethylphenyl)-4-thiazolyl group, a 2-(4-
trifluoromethoxyphenyl)-4-thiazolyl group, a 4-(4-
trifluoromethylphenyl)-2-thiazolyl group, a 4-(4-
trifluoromethoxyphenyl)-2-thiazolyl group, a 2-(3,4-
dichlorophenyl)-4-thiazolyl group, a 4-(3,4-
dichlorophenyl)-2-thiazolyl group, a 4-(2,4,6-
trifluorophenyl)-2-thiazolyl group, a 5-(4-
bromophenyl)-2-thiazolyl group, a 5-(4-fluorophenyl)-4-
thiazolyl group, a 2-(4-iodophenyl)-5-thiazolyl group,
a 2-(4-methylphenyl)-4-thiazolyl group, a 2-(4-
methoxyphenyl)-4-thiazolyl group, a 2-(2,4-
dimethylphenyl)-5-thiazolyl group, a 4-(3,4-
dimethoxyphenyl)-2-thiazolyl group, a 4-(2,4,6-
trimethylphenyl)-5-thiazolyl group; a 5-(3,4,5-
trimethoxyphenyl)-4-thiazolyl group, a 2,4-diphenyl-5-
thiazolyl group, a 4,5-diphenyl-2-thiazolyl group, a 2-
phenyl-5-phenoxyethyl-4-thiazolyl group, a 2-(4-
fluorobenzyl)-4-thiazolyl group, a 2-(4-chlorobenzyl)-
4-thiazolyl group, a 2-(4-trifluoromethylbenzyl)-4-
thiazolyl group, a 2-(4-trifluoromethoxybenzyl)-4-
thiazolyl group, a 2-(3,4-dichlorobenzyl)-4-thiazolyl
group, a 4-(2,4,6-trifluorobenzyl)-2-thiazolyl group, a
5-(4-bromobenzyl)-2-thiazolyl group, a 5-(4-
fluorobenzyl)-4-thiazolyl group, a 2-(4-iodobenzyl)-5-thiazolyl group, a 2-(4-methylbenzyl)-4-thiazolyl group, a 2-(4-methoxybenzyl)-4-thiazolyl group, a 2-(2,4-dimethylbenzyl)-5-thiazolyl group, a 4-(3,4-dimethoxybenzyl)-2-thiazolyl group, a 4-(2,4,6-trimethylbenzyl)-5-thiazolyl group, a 5-(3,4,5-trimethoxybenzyl)-4-thiazolyl group, a 2,4-dibenzy1-5-thiazolyl group, a 4,5-dibenzyl-2-thiazolyl group, a 2-benzyl-5-phenoxymethyl-4-thiazolyl group, a 4-(4-chlorobenzyl)amino-2-thiazolyl group, a 4-(4-trifluoromethoxybenzyl)amino-2-thiazolyl group, a 4-(4-trifluoromethylbenzyl)amino-2-thiazolyl group, a 4-(N-methyl-N-(4-chlorobenzyl)amino)-2-thiazolyl group, a 4-(N-methyl-N-(4-trifluoromethoxybenzyl)amino)-2-thiazolyl group, a 4-(N-methyl-N-(4-trifluoromethylbenzyl)amino)-2-thiazolyl group, a 4-(4-chlorophenyl)amino-2-thiazolyl group, a 4-(4-trifluoromethoxyphenyl)amino-2-thiazolyl group, a 4-(4-trifluoromethylphenyl)amino-2-thiazolyl group, a 4-(N-methyl-N-(4-chlorophenyl)amino)-2-thiazolyl group, a 4-(N-methyl-N-(4-trifluoromethoxyphenyl)amino)-2-thiazolyl group, a 4-(N-methyl-N-(4-trifluoromethylphenyl)amino)-2-thiazolyl group, a 4-(4-chlorobenzyl)aminomethyl-2-thiazolyl group, a 4-(4-trifluoromethylbenzyl)aminomethyl-2-thiazolyl group, a 4-(N-methyl-N-(4-chlorobenzyl)aminomethyl)-2-thiazolyl group, a 4-(N-methyl-N-(4-
trifluoromethoxybenzyl)aminomethyl)-2-thiazolyl group, a 4-(N-methyl-N-(4-trifluoromethylbenzyl)aminomethyl)-2-thiazolyl group, a 4-(4-chlorophenyl)aminomethyl-2-thiazolyl group, a 4-(4-
trifluoromethoxyphenyl)aminomethyl-2-thiazolyl group, a 4-(4-trifluoromethylphenyl)aminomethyl-2-thiazolyl group, a 4-(N-methyl-N-(4-chlorophenyl)aminomethyl)-2-thiazolyl group, a 4-(N-methyl-N-(4-
trifluoromethoxyphenyl)aminomethyl)-2-thiazolyl group,
a 4-(N-methyl-N-(4-trifluoromethylphenyl)aminomethyl)-2-
thiazolyl group, a 4-(4-bromobenzyl)amino-2-thiazolyl
group, a 4-(4-methoxybenzyl)amino-2-thiazolyl group, a
4-(4-methylbenzyl)amino-2-thiazolyl group, a 4-(N-
methyl-N-(3,4-dichlorobenzyl)amino)-2-thiazolyl group,
a 4-(N-methyl-N-(2,4-dimethoxybenzyl)amino)-2-thiazolyl
group, a 4-(N-methyl-N-(3,4-dimethylbenzyl)amino)-2-
thiazolyl group, a 4-(4-bromophenyl)amino-2-thiazolyl
group, a 4-(4-methoxyphenyl)amino-2-thiazolyl group, a
4-(4-methylphenyl)amino-2-thiazolyl group, a 4-(N-
methyl-N-(3,4-dichlorophenyl)amino)-2-thiazolyl group,
a 4-(N-methyl-N-(3,4-dimethoxyphenyl)amino)-2-thiazolyl
group, a 4-(N-methyl-N-(2,4-dimethylphenyl)amino)-2-
thiazolyl group, a 4-(4-bromobenzyl)aminomethyl-2-
thiazolyl group, a 4-(4-methoxybenzyl)aminomethyl-2-
thiazolyl group, a 4-(4-methylbenzyl)aminomethyl-2-
thiazolyl group, a 4-(N-methyl-N-(3,4-
dichlorobenzyl)aminomethyl)-2-thiazolyl group, a 4-(N-
methyl-N-(4-methoxybenzyl)aminomethyl)-2-thiazolyl
group, a 4-(N-methyl-N-(3,4-dimethylbenzyl)aminomethyl)-2-thiazolyl group, a 4-(4-bromophenyl)aminomethyl-2-thiazolyl group, a 4-(4-methoxyphenyl)aminomethyl-2-thiazolyl group, a 4-(4-methylphenyl)aminomethyl-2-thiazolyl group, a 4-(N-methyl-N-(3,4-dichlorophenyl)aminomethyl)-2-thiazolyl group, a 4-(N-methyl-N-(2,4-dimethoxyphenyl)aminomethyl)-2-thiazolyl group, a 4-(N-methyl-N-(3,4-dimethylphenyl)aminomethyl)-2-thiazolyl group, a 4-(4-fluorobenzyl)amino-2-thiazolyl group, a 4-(2,4,6-trimethoxybenzyl)amino-2-thiazolyl group, a 4-(3,4,5-trimethylbenzyl)amino-2-thiazolyl group, a 4-(N-methyl-N-(4-iodobenzyl)amino)-2-thiazolyl group, a 4-(N-methyl-N-(2,4,6-trifluorobenzyl)amino)-2-thiazolyl group, a 4-(N-methyl-N-(4-iodobenzyl)amino)-2-thiazolyl group, a 4-(4-fluorophenyl)amino-2-thiazolyl group, a 4-(2,4,6-trimethoxyphenyl)amino-2-thiazolyl group, a 4-(3,4,5-trimethylphenyl)amino-2-thiazolyl group, a 4-(N-methyl-N-(4-iodophenyl)amino)-2-thiazolyl group, a 4-(N-methyl-N-(2,4,6-trifluorophenyl)amino)-2-thiazolyl group, a 4-(4-fluorobenzyl)aminomethyl-2-thiazolyl group, a 4-(3,4,6-trimethoxybenzyl)aminomethyl-2-thiazolyl group, a 4-(2,4,6-trimethylbenzyl)aminomethyl-2-thiazolyl group, a 4-(N-methyl-N-(4-iodobenzyl)aminomethyl)-2-thiazolyl group, a 4-(N-methyl-N-(2,4,6-trifluorobenzyl)aminomethyl)-2-thiazolyl group, a 4-(4-fluorophenyl)aminomethyl-2-thiazolyl group, a 4-(2,4,6-
trimethoxyphenyl)aminomethyl-2-thiazolyl group, a 4-(3,4,5-trimethylphenyl)aminomethyl-2-thiazolyl group, a 4-(N-methyl-N-(4-iodophenyl)aminomethyl)-2-thiazolyl group, a 4-(N-methyl-N-(2,4,6-trifluorophenyl)aminomethyl)-2-thiazolyl group, a 4-(N-methyl-N-(4-trifluoromethylphenyl)aminomethyl)-2-thiazolyl group, a 4-(4-trifluoromethoxyphenox)-2-thiazolyl group, a 4-(4-trifluoromethylphenoxy)-2-thiazolyl group, a 4-(4-chlorophenoxy)-2-thiazolyl group, a 4-(3,4-dichlorophenoxy)-2-thiazolyl group, a 4-(4-methoxyphenoxy)-2-thiazolyl group, a 4-(4-methylphenoxy)-2-thiazolyl group, a 4-(3,4-dimethoxyphenoxy)-2-thiazolyl group, a 5-(2,4-dimethylphenoxy)-4-thiazolyl group, a 4-(2,4,6-trimethoxyphenoxy)-5-thiazolyl group, a 4-(3,4,5-trimethylphenoxy)-2-thiazolyl group, a 4-(4-fluorophenoxy)-2-thiazolyl group, a 2-(4-bromophenoxy)-5-thiazolyl group, a 2-(4-iodophenoxy)-4-thiazolyl group, a 5-(2,4,6-trifluorophenoxy)-2-thiazolyl group, a 4-(4-(4-trifluoromethylphenyl)-1-piperazinyl)-2-thiazolyl group, a 4-(4-(4-trifluoromethoxyphenyl)-1-piperazinyl)-2-thiazolyl group, a 4-(4-(4-chlorophenyl)-1-piperazinyl)-2-thiazolyl group, a 4-(4-(4-trifluoromethylphenoxy)-1-piperazinyl)-2-thiazolyl group, a 4-(4-(4-trifluoromethoxyphenoxy)-1-piperazinyl)-2-thiazolyl group, a 4-(4-(4-chlorophenoxy)-1-piperazinyl)-2-thiazolyl group, a 5-(3,4-diphenyl-1-piperazinyl)-2-thiazolyl group, a 2-
(3,4,5-triphenyl-1-piperazinyl)-4-thiazolyl group, a 5-
(3,4,5-triphenoxo-1-piperazinyl)-4-thiazolyl group, a
4-(3,4-diphenoxo-1-piperazinyl)-5-thiazolyl group, a 4-
(4-(4-trifluoromethoxyphenyl)-1-piperazinyl)-5-phenoxy-
2-thiazolyl group, a 4-(4-(4-trifluoromethoxyphenoxo)-
1-piperazinyl)-5-phenoxy-2-thiazolyl group, a 4-phenyl-
2-thiazolyl group, a 2-phenyl-4-thiazolyl group, and a
2-(4-benzyl-(1-,2- or 3-)piperidyl)-(4- or
5-)thiazolyl group, provided that, on the thiazole

ring, 1 or 2 groups selected from the following groups
may be substituted: the above described phenoxy Cl-C6
alkyl group [wherein, on the phenyl ring, 1 to 5
groups, and preferably 1 to 3 groups selected from the
group consisting of a halogen atom, a halogen

substituted or unsubstituted Cl-C6 alkyl group, and a
halogen substituted or unsubstituted Cl-C6 alkoxy group
may be substituted]; the above described phenyl group
[wherein, on the phenyl ring, 1 to 5 groups, and
preferably 1 to 3 groups selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted Cl-C6 alkyl group, and a halogen
substituted or unsubstituted Cl-C6 alkoxy group may be
substituted]; the above described phenyl Cl-C6 alkyl
group [wherein, on the phenyl ring, 1 to 5 groups, and
preferably 1 to 3 groups selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted Cl-C6 alkyl group, and a halogen
substituted or unsubstituted Cl-C6 alkoxy group may be
substituted); a group \( (W_o) \circ NR^1 R^2 \) (wherein \( W_o \) and \( o \) are the same as described above, and \( R^1 \) and \( R^2 \), which may be identical or different, each represent a hydrogen atom, the above described Cl-C6 alkyl group, the above described phenyl group (wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), or the above described phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted)); the above described piperazinyl group (wherein, on the piperazine ring, at least 1 to 3 phenyl groups may be substituted; wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted)); the above described piperidyl group (wherein, on the piperidine ring, 1 to 3 groups selected from the group consisting of a phenoxyl group (wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) and the above described phenyl C1-C6 alkyl group may be substituted); and a phenoxy group wherein, on the phenyl ring, 1 to 5 groups, and preferably 1 to 3 groups selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted].

A naphthyl substituted C1-C6 alkyl group wherein, on the naphthalene ring, at least one C1-C6 alkoxy group may be substituted) includes, in addition to naphthyl substituted C1-C6 alkyl group as described above, a naphthyl C1-C6 alkyl group wherein, on the naphthalene ring, 1 to 4 C1-C6 alkoxy groups may be substituted), for example, a 2-(6-methoxy-2-naphthyl) methyl group, (4-methoxy-1-naphthyl) metnyl group, 2-(4-methoxy-1-naphthyl) ethyl group, (4-methoxy-1-naphthyl) methyl group, 2-(3-ethoxy-1-naphthyl) ethyl group, 2-n-propoxy-1-naphthylmethyl group, 5-tert-butoxy-2-naphthyl methyl group, 6-n-pentyloxy-3-naphthylmethyl group, 7-n-hexyloxy-4-naphthylmethyl group, 2-(2,4-dimethoxy-1-naphthyloxy)ethyl group, 2-(1,1,4,4-tetramethoxy-5-naphthioloxy)ethyl group or the like.

An imidazolyl group wherein, on the imidazole ring, at least one selected from the group
consisting of a halogen atom and a nitro group may be substituted) includes an imidazolyl group (wherein, on the imidazole ring, 1 to 3 substituents selected from the group consisting of a halogen atom and a nitro group may be substituted), for example, a \((1-, 2-, 4-\) or \(5-\))imidazolyl group, \(2\)-chloro-\(4\)-nitro-\((1-\) or \(5-\))imidazolyl group, \(2\)-bromo-\((1-, 4-\) or \(5-\))imidazolyl group, \(4\)-fluoro-\((1-, 2-\) or \(5-\))imidazolyl group, \(2, 5\)-dichloro-\((1-\) or \(4-\))imidazolyl group, \(2, 4, 5\)-trichloro-\(1\)-imidazolyl group, \(2\)-nitro-\((1-, 4-\) or \(5-\))imidazolyl group, \(4\)-nitro-\((1-, 2-\) or \(5-\))imidazolyl group, \(2, 5\) dinitro-\((1-\) or \(4-\))imidazolyl group, \(2, 4, 5\)-trinitro-\(1\)-imidazolyl group or the like.

A phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a benzofuryl group, a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) includes, in addition to a phenyl Cl-C6 alkyl group as described above (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), a phenyl Cl-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety (wherein on the phenyl ring, 1 to 5 preferably 1 to 3 substituents selected
from the group consisting of a benzofuryl group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), for example, a 4-{(2-, 3-, 4-, 5-, 6- or 7-)benzofuryl}benzyl group, 2-{(2-, 3-, 4-, 5-, 6- or 7-)benzofuryl}benzyl group, 3-{(2-, 3-, 4-, 5-, 6- or 7-)benzofuryl}benzyl group, 2,4-di{(2-, 3-, 4-, 5-, 6- or 7-)benzofuryl}benzyl group, 2,4,6-tri{(2-, 3-, 4-, 5-, 6- or 7-)benzofuryl}benzyl group, 2-trifluoromethyl-4-{(2-, 3-, 4-, 5-, 6- or 7-)benzofuryl}benzyl group, 3-trifluoromethoxy-4- (2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)benzyl group, 4-chloro-3-{(2-, 3-, 4-, 5-, 6- or 7-)benzofuryl}benzyl group or the like.

A furyl C1-C6 alkyl group (wherein, on the furan ring, at least one phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted) includes a furyl C1-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety (wherein, on the furan ring, 1 to 3 phenyl groups as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted) may be substituted), for example, a (2- or
3-)furylmethyl group, 1-{(2- or 3-)furyl}ethyl group,
2-{(2- or 3-)furyl}ethyl group, 3-{(2- or
3-)furyl}propyl group, 2-{(2- or 3-)furyl}propyl group,
4-{(2- or 3-)furyl}butyl group, 5-{(2- or
3-)furyl}pentyl group, 4-{(2- or 3-)furyl}pentyl group,
6-{(2- or 3-)furyl}hexyl group, 1,1-dimethyl-2-{(2- or
3-)furyl}ethyl group, 2-methyl-3-{(2- or
3-)furyl}propyl group, 2-{(4-chlorophenyl)-(3-, 4- or
5-)furylmethyl group, 2-{(2-chloro-5-
trifluoromethylphenyl)-(3-, 4- or 5-)furylmethyl group,
2-{(4-trifluoromethoxyphenyl)-(3-, 4- or
5-)furylmethyl group, 2-{(2,4-dichlorophenyl)-(3-, 4- or
5-)furylmethyl group, 2-{(2,4,6-trifluorophenyl)-(3-, 4- or
5-)furylmethyl group, 2-{(4-methylphenyl)-(3-, 4- or
5-)furylmethyl group, 2-{(4-methoxyphenyl)-(3-, 4- or
5-)furylmethyl group, 2-{(2,4-dimethylphenyl)-(3-, 4- or
5-)furylmethyl group, 2-{(3,4-dimethoxyphenyl)-(3-, 4- or
5-)furylmethyl group, 2-{(2,4,6-trimethylphenyl)-(3-, 4- or
5-)furylmethyl group, 2-{(3,4,5-trimethoxyphenyl)-
(3-, 4- or 5-)furylmethyl group, 2,4-diphenyl(3- or
5-)furylmethyl group, 2,4,5-triphenyl-3-furylmethyl
group or the like.

A pyridyl C1-C6 alkyl group [wherein, on the
pyridine ring, at least one selected from the group
consisting of a furyl group and a phenyl group
(wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted; may be substituted) includes, in addition to a pyridyl Cl-C6 alkyl group as described above, a pyridyl Cl-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety (wherein, on the pyridine ring, 1 to 3 substituents selected from the group consisting of a furyl group and a phenyl group as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 5 substituents selected from the group consisting of a benzofuryl group, a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted; may be substituted), for example, a 3-(2- or 3-)furyl-(2-, 4-, 5- or 6-)pyridylmethyl group, 2-(4-trifluoromethoxyphenyl)-(3-, 4-, 5- or 6-)pyridylmethyl group, 2-(4-trifluoromethylphenyl)-(3-, 4-, 5- or 6-)pyridylmethyl group, 2-(4-methoxyphenyl)-(3-, 4-, 5- or 6-)pyridylmethyl group, 2-(4-methylphenyl)-(3-, 4-, 5- or 6-)pyridylmethyl group, 2-(3-chloro-4-fluorophenyl)-(3-, 4-, 5- or 6-)pyridylmethyl group, 2-(2-4-dimethoxyphenyl)-(3-, 4-, 5- or 6-)pyridylmethyl group, 2-(3,4,5-trimethoxyphenyl)-(3-, 4-, 5- or 6-)pyridylmethyl group, 2-(2,4-dimethylphenyl)-(3-, 4-, 5- or 6-)pyridyl
methyl group, 2-(2,4,6-trimethylphenyl)-(3-, 4-, 5- or 6-)pyridylmethyl group, 2-(2,4,6-trichlorophenyl)-(3-, 4-, 5- or 6-)pyridylmethyl group, 2-(3-chloro-4-trifluoromethoxyphenyl)-(3-, 4-, 5- or 6-)pyridylmethyl group, 2,4-di(2- or 3-)furyl(5- or 6-)pyridylmethyl group, 2,4,6-triphenyl(3- or 5-)pyridylmethyl group, 2-furyl-5-phenyl(3-, 4- or 6-)pyridylmethyl group or the like.

A benzothienyl C1-C6 alkyl group (wherein, on the benzothiophene ring, at least one halogen atom may be substituted) includes a benzothienyl substituted C1-C6 alkyl group which may be substituted by 1 to 3 halogen atoms on the benzofuran ring, for example, a 2-benzothienylmethyl group, 1-(2-benzothienyl)ethyl group, 2-(4-benzothienyl) ethyl group, 3-(5-benzothienyl)propyl group, 4-(6-benzothienyl) butyl group, 5-(7-benzothieryl)pentyl group, 6-(2-benzothienyl) hexyl group, 4-fluoro-2-benzothienylmethyl group, 5-fluoro-2-benzothienylmethyl group, 6-fluoro-2-benzothienylmethyl group, 7-fluoro-2-benzothienylmethyl group, 4-chloro-2-benzothienylmethyl group, 5-chloro-2-benzothienylmethyl group, 6-chloro-2-benzothienylmethyl group, 7-chloro-2-benzothienylmethyl group, 4-bromo-2-benzothienylmethyl group, 5-bromo-2-benzothienylmethyl group, 6-bromo-2-benzothienylmethyl group, 7-bromo-2-benzothienylmethyl group, 4-iodo-2-benzothienylmethyl group, 5-iodo-2-benzothienylmethyl group, 6-iodo-2-
benzothienylmethyl group, 7-iodo-2-benzothienylmethyl group, 4-fluoro-3-benzothienylmethyl group, 5-fluoro-3-benzothienylmethyl group, 6-fluoro-3-benzothienylmethyl group, 7-fluoro-3-benzothienylmethyl group, 4-chloro-3-benzothienylmethyl group, 5-chloro-3-benzothienylmethyl group, 6-chloro-3-benzothienylmethyl group, 7-chloro-3-benzothienylmethyl group, 4-bromo-3-benzothienylmethyl group, 5-bromo-3-benzothienylmethyl group, 6-bromo-3-benzothienylmethyl group, 7-bromo-3-benzothienylmethyl group, 4-iodo-3-benzothienylmethyl group, 5-iodo-3-benzothienylmethyl group, 6-iodo-3-benzothienylmethyl group, 7-iodo-3-benzothienylmethyl group, 2-(4-fluoro-2-benzothienyl)ethyl group, 2-(5-fluoro-2-benzothienyl)ethyl group, 2-(6-fluoro-2-benzothienyl)ethyl group, 2-(7-fluoro-2-benzothienyl)ethyl group, 2-(4-chloro-2-benzothienyl)ethyl group, 2-(5-chloro-2-benzothienyl)ethyl group, 2-(6-chloro-2-benzothienyl)ethyl group, 2-(7-chloro-2-benzothienyl)ethyl group, 2-(4-fluoro-3-benzothienyl)methyl group, 2-(5-fluoro-3-benzothienyl)methyl group, 2-(6-fluoro-3-benzothienyl)methyl group, 2-(7-fluoro-3-benzothienyl)methyl group, 2-(4-chloro-3-benzothienyl)ethyl group, 2-(5-chloro-3-benzothienyl)ethyl group, 2-(6-chloro-3-benzothienyl)ethyl group, 2-(7-chloro-3-benzothienyl)ethyl group, 2-(4-fluoro-2-
benzothienyl)ethyl group, 6-(5-fluoro-2-benzothienyl)hexyl group, 6-(6-fluoro-2-benzothienyl)hexyl group,
6-(7-fluoro-2-benzothienyl)hexyl group,
6-(4-chloro-2-benzothienyl)hexyl group, 6-(5-chloro-2-benzothienyl)hexyl group, 6-(6-chloro-2-benzothienyl)hexyl group,
6-(7-chloro-2-benzothienyl)hexyl group,
6-(4-fluoro-3-benzothienyl)methyl group, 6-(5-fluoro-3-benzothienyl)hexyl group,
6-(6-fluoro-3-benzothienyl)hexyl group, 6-(7-fluoro-3-benzothienyl)hexyl group, 6-(4-chloro-3-benzothienyl)hexyl group, 6-(5-chloro-3-benzothienyl)hexyl group, 6-(6-chloro-3-benzothienyl)hexyl group, 6-(7-chloro-3-benzothienyl)hexyl group,
(2,4-dibromo-3-benzothienyl)methyl group, (4,5,6-trichloro-3-benzothienyl)methyl group or the like,

A benzofuryl C2-C6 alkenyl group (wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) includes a benzofuryl group, which is a group consisting of a benzofuryl group unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group.
and a halogen substituted or unsubstituted C1-C6 alkoxy group, and a linear or branched alkenyl group
containing 2 to 6 carbon atoms and having 1 to 3 double bonds. The benzofuranyl C2-C6 alkenyl group includes
both trans and cis forms. The benzofuranyl C2-C6 alkenyl group includes 2-((2-, 3-, 4-, 5-, 6- or
7-)benzofuranyl)vinyl group, 3-((2-, 3-, 4-, 5-, 6- or
7-)benzofuranyl)-2-propenyl group, 3-((2-, 3-, 4-, 5-, 6-
or 7-)benzofuranyl)-2-methyl-2-propenyl group, 4-((2-, 3-, 4-, 5-, 6- or 7-)benzofuranyl)-2-buteny1 group, 4-
((2-, 3-, 4-, 5-, 6- or 7-)benzofuranyl)-3-buteny1 group,
4-((2-, 3-, 4-, 5-, 6- or 7-)benzofuranyl)-1,3-butadienyl
group, 5-((2-, 3-, 4-, 5-, 6- or 7-)benzofuranyl)-1,3,5-
hexatrienyl group, 6-((2-, 3-, 4-, 5-, 6- or
7-)benzofuranyl)-1,3-hexadienyl group, 3-((5-
trifluoromethyl(2-(2-, 3-, 4-, 5- or 7-)benzofuranyl)-2-
propenyl group, 3-(5-trifluoromethoxy(2-, 3-, 4-, 5- or
7-)benzofuranyl)-2-propenyl group, 3-(7-chloro-(2-, 3-, 4-, 5- or 7-)benzofuranyl)-2-propenyl group, 3-((2,6-
dimethyl-(3-, 4-, 5- or 7-)benzofuranyl)-2-propenyl
group, 3-((3,6-dimethoxy(2-, 3-, 4-, 5- or
7-)benzofuranyl)-2-propenyl group, 3-(4,5,6-trimethyl(2-
3- or 7-)benzofuranyl)-2-propenyl group, 3-(3, 5, 6-
trimethoxy (2-,4- or 7-)benzofuranyl)-2-propenyl group,
3-(3-chloro-6-trifluoromethyl(2-, 3-, 4-, 5- or
7-)benzofuranyl)-2-propenyl group or the like.

A thiazolyl group (wherein, on the thiazole ring, at least one phenyl group (wherein, on the phenyl
ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] may be substituted, including a thiazolyl group (wherein, on the thiazole ring, 1 to 2 phenyl groups as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), for example, a (2-, 4- or 5-)thiazolyl group, 4-phenyl-(2- or 5-)thiazolyl group, 2-phenyl-(4- or 5-)thiazolyl group, 5-phenyl-(2- or 4-)thiazolyl group, 2,5-diphenyl-4-thiazolyl group, 2,4-diphenyl-5-thiazolyl group, 2-(4-trifluoromethylphenyl)-(4- or 5-)thiazolyl group, 2-(4-trifluoromethoxyphenyl)-(4- or 5-)thiazolyl group, 2-(4-chlorophenyl)-(4- or 5-)thiazolyl group, 2-(3-chloro-4-trifluoromethylphenyl)-(4- or 5-)thiazolyl group, 2-(4-methylphenyl)-(4- or 5-)thiazolyl group, 2-(2,4-dimethylphenyl)-(4- or 5-)thiazolyl group, 2-(3, 4, 6-trimethylphenyl)-(4- or 5-)thiazolyl group, 2-(4-methoxyphenyl)-(4- or 5-)thiazolyl group, 2-(2,4-dimethoxyphenyl)-(4- or 5-)thiazolyl group, 2-(3, 4, 6-trimethoxyphenyl)-(4- or 5-)thiazolyl group, 2-(2,4-dichlorophenyl)-(4- or 5-)thiazolyl group, 2-(3, 4, 6-trifluorophenyl)-(4- or 5-)thiazolyl group or the like.
An isoindolinonyloxy group [wherein, on the isoindoline ring, at least one selected from the group consisting of a C1-C6 alkoxyalkyl group, phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a benzo furyl group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a furyl C1-C6 alkyl group (wherein, on the furan ring, at least one phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted), a pyridyl C1-C6 alkyl group (wherein, on the pyridine ring, at least one selected from the group consisting of a furyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a benzo furyl group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted), a benzofuryl C1-C6
alkyl group (wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a benzothienyl C1-C6 alkyl group (wherein, on the benzothiophene ring, at least one halogen atom may be substituted), a benzofuryl C2-C6 alkenyl group (wherein, on the benzofuryl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a thiazolyl group (wherein, on the thiazole ring, at least one phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted) and a phenoxy C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted) includes an isoindolinyloxy group (wherein, on the isoindoline ring, 1 to 3 substituents selected from the group consisting of a linear or branched C1-C6 alkoxy carbonyl group containing 1 to 6 carbon atoms as described
above, a phenyl C1-C6 alkyl group having a linear or branched alkyl group on the alkyl moiety as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a benzofuryl group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a phenyl C2-C6 alkenyl group having a linear or branched alkenyl group containing 2 to 6 carbon atoms on the alkenyl moiety and having 1 to 3 double bonds as described above, and including both trans and cis forms (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a furyl C1-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety as described above (wherein, on the furan ring, 1 to 3 phenyl groups (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a pyridyl C1-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety as described above (wherein, on the pyridine
ring, 1 to 3 substituents selected from the group consisting of a furyl group and a phenyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a benzofuryl group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted], a benzofuryl C1-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety as described above (wherein, on the benzofuran ring, 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], a benzothienyl C1-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety as described above (wherein, on the benzothiophene ring, 1 to 3 halogen atoms may be substituted), a benzofuryl C2-C6 alkenyl group having a linear or branched alkenyl group containing 2 to 6 carbon atoms on the alkenyl moiety and having 1 to 3 double bonds as described above, and including both trans and cis forms (wherein, on the benzofuran ring, 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1 to C6 alkoxy group may be
substituted), a thiazolyl group as described above
[wherein, on the thiazole ring, 1 to 2 phenyl groups
(wherein, on the phenyl ring, 1 to 5, preferably 1 to 3
substituents selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted
Cl-C6 alkyl group and a halogen substituted or
unsubstituted Cl-C6 alkoxy group may be substituted
may be substituted] and a phenoxy Cl-C6 alkyl group
having a linear or branched alkyl group containing 1 to
6 carbon atoms on the alkyl moiety as described above
(wherein, on the phenyl ring, 1 to 5, preferably 1 to 2
substituents selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted
Cl-C6 alkyl group and a halogen substituted or
unsubstituted Cl-C6 alkoxy group may be substituted
may be substituted], for example, a (1-, 2-, 3- or
4-)isoindolinyloxy group, 1-tert-butoxycarbonyl-(2-, 3-
or 4-)isoindolinyloxy group, 1-(2-(4-chlorophenyl)-(3-, 4-
or 5-)furylmethyl)-(2-, 3- or 4-)isoindolinyloxy
group, 1-(2-(2-chloro-5-trifluoromethylphenyl)-(3-, 4-
or 5-)furylmethyl)-(2-, 3- or 4-)isoindolinyloxy
group, 1-(3-trifluoromethyl-4-chlorobenzyl)-(2-, 3- or
4-)isoindolinyloxy group, 1-(4-(2-, 3-, 4-, 5-, 6- or
7-)benzofuryl)benzyl)-(2-, 3- or 4-)isoindolinyloxy
group, 1-(3-(2- or 3-)furyl)-(2-, 4-, 5- or
6-)pyridylmethyl)-(2-, 3- or 4-)isoindolinyloxy group,
1-(2-(4-trifluoromethoxyphenyl)-(3-, 4-, 5- or
6-)pyridylmethyl)-(2-, 3- or 4-)isoindolinyloxy group,
1-(2-(3-chloro-4-fluorophenyl)-(3-, 4-, 5- or 8-)pyridylmethyl)-(2-, 3- or 4-)isoindolinyloxy group, 1-(6-trifluoromethyl (2-, 3-, 4-, 5- or 7-)benzofurymethyl)-(2-, 3- or 4-)isoindolinyloxy group, 1-(5-chloro-(2-, 3-, 4-, 6- or 7-)benzothienylmethyl)-(2-, 3- or 4-)isoindolinyloxy group, 1-(6-chloro-(2-, 3-, 4-, 5- or 7-)benzofurymethyl)-(2-, 3- or 4-)isoindolinyloxy group, 1-(5-trifluoromethoxy (2-, 3-, 4-, 6- or 7-)benzofurymethyl)-(2-, 3- or 4-)isoindolinyloxy group, 1-(3-(6-trifluoromethyl(2-, 3-, 4-, 5- or 7-)benzofuryl)-2-propenyl)-(2-, 3- or 4-)isoindolinyloxy group, 1-(5-chloro-(2-, 3-, 4-, 6- or 7-)benzofurymethyl)-(2-, 3- or 4-)isoindolinyloxy group, 1-(2-(4-trifluoromethylphenyl)-(4- or 5-)thiazolylmethyl)-(2-, 3- or 4-)isoindolinyloxy group, 1-(2-(4-trifluoromethoxyphenoxo)ethyli)-(2-, 3- or 4-)isoindolinyloxy group, 1,3-diethoxycarbonyl-(2- or 4-)isoindolinyloxy group, 2-phenoxymethyl-4-(2-, 3-, 4-, 5-, 6- or 7-)benzofurymethyl)-(1-, 3-, 5-, 6- or 7-)isoindolinyloxy group, 2-(2- or 3-)furylmethyl)-4,5-dimethoxycarbonyl-(1-, 3-, 6- or 7-)isoindolinyloxy group or the like.

A benzothiazolodinyloxy group [wherein, on the benzothiazolodine ring, at least one selected from the group consisting of an oxo group and a phenyl Cl-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a
halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted] includes a benzothiazolidinyloxy group [wherein, on the
benzothiazolidine ring, 1 to 3 substituents selected
from the group consisting of an oxo group and a phenyl
C1-C6 alkyl group having a linear or branched alkyl
group containing 1 to 6 carbon atoms on the alkyl
molety as described above [wherein, on the phenyl ring,
1 to 5, preferably 1 to 3 substituents selected from
the group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group and a
halogen substituted or unsubstituted C1-C6 alkoxy group
may be substituted), for example, a
(2-, 3-, 4-, 5-, 6- or 7-)benzothiazoldinyloxy group,
3(4-trifluoromethoxybenzyl)-2-oxo-(4-, 5-, 6- or
7-)benzothiazoldinyloxy group, 3-(4-
trifluoromethylbenzyl)-(2-, 4-, 5-, 6- or
7-)benzothiazoldinyloxy group, 3-(4-chlorobenzyl)-(2-,
4-, 5-, 6- or 7-)benzothiazoldinyloxy group, 3-(4-
methylbenzyl)-(2-, 4-, 5-, 6- or
7-)benzothiazoldinyloxy group, 3-(3,4-dimethylbenzyl)-(2-, 4-, 5-, 6- or 7-)benzothiazoldinyloxy group, 3-
(2,4,6-trimethylbenzyl)-(2-, 4-, 5-, 6- or
7-)benzothiazoldinyloxy group, 3-(4-methoxybenzyl)-(2-, 4-, 5-, 6- or 7-)benzothiazoldinyloxy group, 3-
(3,4-dimethoxybenzyl)-(2-, 4-, 5-, 6- or
7-)benzothiazoldinyloxy group, 3-(3,4,5-
trimethoxybenzyl)-(2-, 4-, 5-, 6- or
7-)benzothiazolyldinyloxy group, 3-(4-fluorobenzyl)-(2-, 4-, 5- 6- or 7-)benzothiazolyldinyloxy group, 3-(3,4-
dichlorobenzyl)-(2-, 4-, 5-, 6- or
7-)benzothiazolyldinyloxy group, 3-(2,4,6-
trifluorobenzyl)-(2-, 4-, 5-, 6- or
7-)benzothiazolyldinyloxy group, 2-oxo-(2-, 4-, 5-, 6-
or 7-)benzothiazolyldinyloxy group, 2,3-dibenzyl(4-, 5-, 6- or 7-)benzothiazolyldinyloxy group, 2,3,5-
tribenzyl(4-, 5-, 6- or 7-)benzothiazolyldinyloxy group
or the like.

An indolyloxy group (wherein, on the indole ring, at least one phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the
15 group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkyl group may be substituted) may be substituted) includes an indolyloxy group (wherein, on the indole ring, 1 to 3
20 phenyl Cl-C6 alkyl groups having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen
25 substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) may be substituted), for example, a (1-, 2-, 3-, 4-, 5-, 6- or 7-)indolyloxy group, 1-(4-
trifluromethoxybenzyl)- (2-, 3-, 4-, 5-, 6- or
indolyl group, 1-(4-trifluoromethylbenzyl)-(2-, 3-, 4-, 5-, 6- or 7-)indolyl group, 1-(4-
chlorobenzyl)-(2-, 3-, 4-, 5-, 6- or 7-)indolyl group, 5-(4-methylbenzyl)-(1-, 3-, 4-, 5-, 6- or
7-)indolyl group, 3-(3,4-dimethylbenzyl)-(1-, 2-, 3-, 4-, 5-, 6- or 7-)indolyl group, 4-(2,4,6-
trimethylbenzyl)-(1-, 2-, 3-, 5-, 6- or 7-)indolyl group, 5-(4-methoxybenzyl)-(1-, 2-, 3-, 4-, 6- or
7-)indolyl group, 6-(3,4-dimethoxybenzyl)-(1-, 2-, 3-, 4-, 5- or 7-)indolyl group, 7-(3,4,5-
trimethoxybenzyl)-(1-, 2-, 3-, 4-, 5- or 6-)indolyl group, 1-(4-fluorobenzyl)-(2-, 3-, 4-, 5-, 6- or
7-)indolyl group, 1-(3,4-dichlorobenzyl)-(2-, 3-, 4-, 5-, 6- or 7-)indolyl group, 1-(2,4,6-
trifluorobenzyl)-(2-, 3-, 4-, 5-, 6- or 7-)indolyl group, 1,3-dibenzyl(2-, 4-, 5-, 6- or 7-)indolyl group, 1,3,5-tri benzyl(2-, 4-, 6- or 7-)indolyl group or the like.

A pyrrolidinyl group (wherein, on the
pyrrolidine ring, at least one amino group (wherein, or
the amino group, at least one selected from the group
consisting of a C1-C6 alkyl group and a phenyl group
(wherein, on the phenyl ring, at least one selected
from the group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group and a
halogen substituted or unsubstituted C1-C6 alkoxy group
may be substituted) may be substituted)
includes a pyrrolidinyl group (wherein, on the pyrrolidine ring, 1 to 3 amino groups (wherein, on the amino group, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a C1-C6 alkyl group as described above and a phenyl group as described above (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted) are substituted), for example, a 3-(N-(methyl)-N-(3,4-dichlorophenyl)amino)-(1-, 2-, 4- or 5-)pyrrolidinyl group, 3-amino-(1-, 2-, 4- or 5-)pyrrolidinyl group, 2, 3-diamino-(1-, 4- or 5-)pyrrolidinyl group, 2,3,5-triamino-(1- or 4-)pyrrolidinyl, 3-(N-methyl-N-(4-methylphenyl)amino)-(1-, 2-, 4- or 5-)pyrrolidinyl group, 3-(N-ethyl-N-(3-methoxyphenyl)amino)-(1-, 2-, 4- or 5-)pyrrolidinyl group, 3-(N-(4-trifluoromethylphenyl)amino)-(1-, 2-, 4- or 5-)pyrrolidinyl group, 3-\(N\)-(4-trifluoromethoxyphenyl)amino)-(1-, 2-, 4- or 5-)pyrrolidinyl group, 3-(N-methyl-N-(3,4,5-trifluorophenyl)amino)-(1-, 2-, 4- or 5-)pyrrolidinyl group, 3-(N-methyl-N-(3-chloro-4-trifluoromethylphenyl)amino)-(1-, 2-, 4- or 5-)pyrrolidinyl group, 3-(N-phenylamino)-(1-, 2-, 4- or 5-)pyrrolidinyl group, 3-methylamino-(1-, 2-, 4- or 5-)pyrrolidinyl group, 3-methylamino-(1-, 2-, 4- or
5-pyrrolidinyl group or the like.

An indolinyI group (wherein, on the indoline ring, at least one halogen atom may be substituted) includes an indolinyI group (wherein, on the indoline ring, 1 to 3 halogen atoms may be substituted), for example, a (1-, 2-, 3-, 4-, 5-, 6- or 7-)indolinyI group, 5-bromo-(1-, 2-, 3-, 4-, 6- or 7-)indolinyI group, 4-chloro-(1-, 2-, 3-, 5-, 6- or 7-)indolinyI group, 6-fluoro-(1-, 2-, 3-, 4-, 5- or 7-)indolinyI group, 5,7-dichloro-(1-, 2-, 3-, 4- or 6-)indolinyI group, 3,5,6-trifluoro-(1-, 2-, 4- or 7-)indolinyI group or the like.

An indolinyloxy group (wherein, on the indoline ring, at least one selected from the group consisting of a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) and an oxo group may be substituted) includes an indolinyloxy group (wherein, on the indoline ring, 1 to 3 substituents selected from the group consisting of a phenyl C1-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted
C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted, and an oxo group may be substituted, for example, a {1-, 2-, 3-, 4-, 5-, 6- or 7-}indolinyloxy group, 1-{4-trifluoromethoxybenzyl}-2, 3-dioxo(1-, 2-, 3-, 4-, 5-, 6- or 7-)indolinyloxy group, 1-{4-trifluoromethoxybenzyl}-2-oxo (3-, 4-, 5-, 6- or 7-)indolinyloxy group, 1-{4-trifluoromethylbenzyl}-2, 3-, 4-, 5-, 6- or 7-)indolinyloxy group, 1-{4-chlorobenzyl}-(2-, 3-, 4-, 5-, 6- or 7-)indolinyloxy group, 3-{4-methylbenzyl}-(1-, 2-, 4-, 5-, 6- or 7-)indolinyloxy group, 4-{3,4-dimethylbenzyl}-(1-, 2-, 3-, 5-, 6- or 7-)indolinyloxy group, 2-{2,4,6-trimethyl benzyl}-(1-, 3-, 4-, 5-, 6- or 7-)indolinyloxy group, 5-{4-methoxybenzyl}-(1-, 2-, 3-, 4-, 6- or 7-)indolinyloxy group, 6-{3,4-dimethoxybenzyl}-(1-, 2-, 3-, 4-, 5- or 7-)indolinyloxy group, 7-{3,4,5-trimethoxybenzyl}-(1-, 2-, 3-, 4-, 5- or 6-)indolinyloxy group, 1-{4-fluorobenzyl}-(2-, 3-, 4-, 5-, 6- or 7-)indolinyloxy group, 1-{3,4-dichlorobenzyl}-(2-, 3-, 4-, 5-, 6- or 7-)indolinyloxy group, 1-{2,4,6-trifluorobenzyl}-(2-, 3-, 4-, 5-, 6- or 7-)indolinyloxy group, 2-oxo-(1-, 3-, 4-, 5-, 6-, or 7-)indolinyloxy group, 1,3-dibenzyl(2-, 4-, 5-, 6- or 7-)indolinyloxy group, 1,5,6-tibenzyl(1-, 2-, 3-, 4- or 7-)indolinyloxy group, 2,3-dioxo(1-, 4-, 5-, 6- or 7-)indolinyloxy group or the like.

A pyrrolyl group [wherein, on the pyrrole
ring, at least one selected from the group consisting of a C1-C6 alkyl group and a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) includes a pyrrolyl group (wherein, on the pyrrole ring, 1 to 3 substituents selected from the group consisting of a C1-C6 alkyl group as described above and a phenyl C1-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted may be substituted), for example, a (1-, 2- or 3-)pyrrolyl group, 1-(4-trifluoromethoxybenzyl)-(2- or 3-)pyrrolyl group, 1-(4-trifluoromethylbenzyl)-(2- or 3-)pyrrolyl group, 1-(4-chlorobenzyl)-(2- or 3-)pyrrolyl group, 1-(4-methoxybenzyl)-(2- or 3-)pyrrolyl group, 1-(4-methylbenzyl)-(2- or 3-)pyrrolyl group, 1-(3,4-dimethoxybenzyl)-(2- or 3-)pyrrolyl group, 1-(2,4,6-trimethoxybenzyl)-(2- or 3-)pyrrolyl group, 1-(3,4-dimethylbenzyl)-(2- or 3-)pyrrolyl group, 1-(2,4,6-trimethylbenzyl)-(2- or 3-)pyrrolyl group, 1-(2,4,6-trifluorobenzyl)-(2- or 3-)pyrrolyl group.
3-pyrrolyl group, 1-(2,6-dichlorobenzyl)-(2- or 3-)pyrrolyl group, 1-benzyl-(2- or 3-)pyrrolyl group, 1,2-dibenzyl-(3- or 4- or 5-)pyrrolyl group, 1,2,4-tribenzyl-(3- or 5-)pyrrolyl group, 2-(3-chloro-4-trifluoromethoxybenzyl)-(1- or 3- or 4- or 5-)pyrrolyl group, 1-methyl-(2- or 3-)pyrrolyl group, 1-ethyl-(2- or 3-)pyrrolyl group, 1-n-propyl-(2- or 3-)pyrrolyl group, 1-n-butyl-(2- or 3-)pyrrolyl group, 1-n-pentyl-(2- or 3-)pyrrolyl group, 1-hexyl-(2- or 3-)pyrrolyl group, 1,3-dimethyl-(2- or 4- or 5-)pyrrolyl group, 1,3,4-trimethyl-(2- or 5-)pyrrolyl group, 1-benzyl-3-methyl-(2-, 4- or 5-)pyrrolyl group or the like.

A phenylthio group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) includes a phenylthio group unsubstituted or having 1 to 5, preferably 1 to 3 substitutes selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group as defined above, examples of which include a phenylthio group, 2-fluorophenylthio group, 3-fluorophenylthio group, 4-fluorophenylthio group, 2-chlorophenylthio group, 3-chlorophenylthio group, 4-chlorophenylthio group, 2-bromophenylthio group, 3-bromophenylthio group, 4-bromophenyl group, 2-
iodophenylthio group, 3-iodophenylthio group, 4-
iodophenylthio group, 2,3-difluorophenylthio group,
3,4-difluorophenyl group, 3,5-difluorophenylthio group,
2,4-difluorophenylthio group, 2,6-difluorophenylthio
5
group, 2,3-dichlorophenylthio group, 3,4-
dichlorophenylthio group, 3,5-dichlorophenylthio group,
2,4-dichlorophenylthio group, 2,6-dichlorophenylthio
group, 3,4,5-trifluorophenylthio group, 3,4,5-
trichlorophenylthio group, 2,4,6-trifluorophenylthio
10
group, 2,4,6-trichlorophenylthio group, 2-fluoro-4-
brocomphenylthio group, 4-chloro-3-fluorophenylthio
group, 2,3,4-trichlorophenylthio group, 2,3,4,5,6-
pentafluorophenylthio group, 2,4,6-trimethylphenylthio
group, 4-n-butylyphenylthio group, 2,4-
dimethylphenylthio group, 2,3-dimethylphenylthio group,
2,6-dimethylphenylthio group, 3,5-dimethylphenylthio
15
group, 2, 5-dimethylphenylthio group, 3,5-
ditrifluoromethylphenylthio group, 4-n-butoxyphenylthio
group, 2,4-dimethoxyphenylthio group, 2,3-
dimethoxyphenylthio group, 2,6-dimethoxyphenylthio
20
group, 3,5-dimethoxyphenylthio group, 2,5-
dimethoxyphenylthio group, 2,4,6-trimethoxyphenylthio
group, 3,5-ditrifluoromethoxyphenylthio group, 3-
chloro-4-methoxyphenylthio group, 2-chloro-4-
25 trifluoromethoxyphenylthio group, 3-methyl-4-
fluorophenylthio group, 4-bromo-3-
trifluoromethylphenylthio group, 2-methylphenylthio
group, 3-methylphenylthio group, 4-methylphenylthio
group, 2-methyl-3-chlorophenylthio group, 3-methyl-4-
chlorophenylthio group, 2-chloro-4-methylphenylthio
group, 2-methyl-3-fluorophenylthio group, 2-
trifluoromethylphenylthio group, 3-
trifluoromethylphenylthio group, 4-
trifluoromethylphenylthio group, 2-
pentafluoroethylphenylthio group, 3-
pentafluoroethylphenylthio group, 4-
pentafluoroethylphenylthio group, 2-isopropylphenylthio
group, 3-isopropylphenylthio group, 4-
isopropylphenylthio group, 2-tert-butylphenylthio
group, 3-tert-butylphenylthio group, 4-tert-
butylphenylthio group, 2-sec-butylphenylthio group, 3-
sec-butylphenylthio group, 4-sec-butylphenylthio group,
2-n-heptafluoropropylphenylthio group, 3-n-
heptafluoropropylphenylthio group, 4-n-
heptafluoropropylphenylthio group, 4-pentylphenylthio
group, 4-hexylphenylthio group, 2-methoxyphenylthio
group, 3-methoxyphenylthio group, 4-methoxyphenylthio
group, 3-chloro-2-methoxyphenylthio group, 2-fluoro-3-
methoxyphenylthio group, 2-fluoro-4-methoxyphenylthio
group, 2,3,4-trifluorophenylthio group, 2-
trifluoromethoxyphenylthio group, 3-
trifluoromethoxyphenylthio group, 4-
trifluoromethoxyphenylthio group, 3-fluoro-2-
trifluoromethoxyphenylthio group, 2-fluoro-3-
trifluoromethoxyphenylthio group, 3-fluoro-4-
trifluoromethoxyphenylthio group, 3-chloro-2-
trifluoromethoxyphenylthio group, 2-chloro-3-
trifluoromethoxyphenylthio group, 3-chloro-4-
trifluoromethoxyphenylthio group, 2-
pentafluoroethoxyphenylthio group, 3-
pentafluoroethoxyphenylthio group, 4-
pentafluoroethoxyphenylthio group, 3-chloro-2-
pentafluoroethoxyphenylthio group, 2-chloro-3-
pentafluoroethoxyphenylthio group, 3-chloro-4-
pentafluoroethoxyphenylthio group, 2-
isopropoxyphenylthio group, 3-isopropoxyphenylthio
group, 4-isopropoxyphenylthio group, 2-tert-
butoxyphenylthio group, 3-tert-butoxyphenylthio group,
4-tert-butoxyphenylthio group, 2-sec-butoxyphenylthio
group, 3-sec-butoxyphenylthio group, 4-sec-
butoxyphenylthio group, 2-n-
heptafluoropropoxyphenylthio group, 3-n-
heptafluoropropoxyphenylthio group, 4-n-
heptafluoropropoxyphenylthio group, 4-n-
pent oxyphenylthio group, 4-n-hexyloxyphenylthio group
or the like.

A piperazinyl group (wherein, on the
piperazine ring, at least one selected from the group
consisting of a phenyl C1-C6 alkyl group (wherein, on
the phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted), a phenyl group (wherein, on the phenyl
ring, at least one selected from the group consisting of a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] and a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) includes, in addition to a piperazinyl group as described above (wherein, on the piperazinyl ring, at least one phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a piperazinyl group [wherein, on the piperazine ring, 1 to 3 substituents selected from the group consisting of a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a
halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), a phenyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a phenoxy group as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) and a phenyl C2-C6 alkenyl group having a linear or branched alkenyl group containing 2 to 6 carbon atoms on the alkenyl moiety as and having 1 to 3 double bonds as described later, and including both trans and cis forms (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), for example, 4-(3-(4-trifluoromethylphenyl)-2-propenyl)-(1-2- or 3-)piperazinyl group, 4-(4-methoxyphenyl)-(1-2- or 3-)piperazinyl group, 4-(3,4-dimethylphenyl)-(1-2- or 3-)piperazinyl group, 4-(4-fluorophenyl)-(1-2- or 3-)piperazinyl group, 4-(4-trifluoromethylphenyl)-(1-2- or 3-)piperazinyl group, 4-(4-methylphenyl)-(1-2- or 3-)piperazinyl group, 4-(4-methylphenyl)-(1-2- or 3-)piperazinyl group, 4-(4-methylphenyl)-(1-2- or 3-)piperazinyl group, 4-(4-methylphenyl)-(1-2- or 3-)piperazinyl group.
or 3-\)piperazinyl group, 4-(3,4-dichlorophenyl)-(1-, 2-
or 3-\)piperazinyl group, 4-(4-trifluoromethoxyphenyl)-(1-, 2- or 3-\)piperazinyl group, 4-(4-(4-
chlorophenoxy)phenyl)-(1-, 2- or 3-\)piperazinyl group or the like.

A naphthyl C1-C6 alkyl group includes a naphthylalkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety, for example, a ((1- or 2-)naphthyl) methyl group, 1-((1- or 2-)naphthyl)ethyl group, 2-((1-or 2-)naphthyl)ethyl group, 3-((1- or 2-)naphthyl)propyl group, 2-((1- or 2-)naphthyl)propyl group, 4-((1- or 2-)naphthyl)butyl group, 5-((1- or 2-)naphthyl)pentyl group, 4-((1- or 2-)naphthyl)pentyl group, 6-((1- or 2-)naphthyl)hexyl group, 2-methyl-3-((1- or 2-)naphthyl)propyl group, 1,1-dimethyl-2-((1- or 2-)naphthyl)ethyl group or the like.

A piperazinyl group [wherein, on the piperazine ring, at least one selected from the group consisting of a C1-C6 alkoxy carbonyl group, a furyl C1-C6 alkyl group [wherein, on the furan ring, at least one phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] may be substituted], a pyridyl C1-C6 alkyl group [wherein, on the pyridine ring, at least one selected from the group...
consisting of a furyl group and a phenyl group
(wherein, on the phenyl ring, at least one selected
from the group consisting of a halogen atom, a halogen
substituted or unsubstituted Cl-C6 alkyl group and a
halogen substituted or unsubstituted Cl-C6 alkoxy group
may be substituted) may be substituted), a benzothiophenyl
Cl-C6 alkyl group (wherein, on the benzothiophene ring,
at least one selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted
Cl-C6 alkyl group and a halogen substituted or
unsubstituted Cl-C6 alkoxy group may be substituted), a
phenyl C2-C6 alkenyl group (wherein, on the phenyl
ring, at least one selected from the group consisting
of a halogen atom, a halogen substituted or
unsubstituted Cl-C6 alkyl group and a halogen
substituted or unsubstituted Cl-C6 alkoxy group may be
substituted), a benzofuryl Cl-C6 alkyl group (wherein,
on the benzofuran ring, at least one selected from the
group consisting of a halogen atom, a halogen
substituted or unsubstituted Cl-C6 alkyl group and a
halogen substituted or unsubstituted Cl-C6 alkoxy group
may be substituted), a benzofuryl C2-C6 alkenyl group
(wherein, on the benzofuran ring, at least one selected
from the group consisting of a halogen atom, a halogen
substituted or unsubstituted Cl-C6 alkyl group and a
halogen substituted or unsubstituted Cl-C6 alkoxy group
may be substituted), a thiazoly1 Cl-C6 alkyl group
(wherein, on the thiazole ring, at least one phenyl
group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), a phenoxy Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), an indolyl Cl-C6 alkyl group (wherein, on the indole ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) and a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of benzofuranyl group, a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) may be substituted]. Includes, in addition to a piperazinyl group as described above [wherein, on the piperazine ring, at least one phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of benzofuranyl group, a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be
substituted) may be substituted), a piperazinyl group which may be substituted on the piperazine ring by 1 to 3 substituents selected from the group consisting of a Cl-C6 alkoxy carbonyl group as described later, a furyl Cl-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety as described later (wherein, on the furyl ring, 1 to 3 phenyl groups (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkyl group may be substituted) may be substituted), a pyridyl Cl-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety as described later (wherein, on the pyridine ring, 1 to 3 substituents selected from the group consisting of a furyl group and a phenyl group (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) may be substituted), a benzothienyl Cl-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety as described later (wherein, on the benzothiophene ring, 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a phenyl C2-C6 alkenyl group having a linear or branched alkenyl group containing 2 to 6 carbon atoms on the alkenyl moiety and having 1 to 3 double bonds as described later, and including both trans and cis forms (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a benzofuryl C1-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety as described later [wherein, on the benzofuran ring, 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], a benzofuryl C2-C6 alkenyl group having a linear or branched alkenyl group having a linear or branched alkenyl group containing 2 to 6 carbon atoms and having 1 to 3 double bonds on the alkenyl moiety as described later, and including both trans and cis forms (wherein, on the benzofuran ring, 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a
thiazolyl C1-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety as described later (wherein, on the thiazole ring, 1 or 2 phenyl groups (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted), a phenoxy C1-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety as described later (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), an indolyl C1-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety as described later (wherein, on the indole ring, 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) and a phenyl C1-C6 alkyl group as described later (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a benzofuryl ring, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group
and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), for example, a 4-tert-butoxycarbonyl-(1-, 2- or 3-)piperazinyl group, 4-((2-, 3-, 4-, 5-, 6- or 7-)benzofuranyl)benzyl)-(1-, 2-
or 3-)piperazinyl group, 4-((2- or 3-)furyl|pyridyl)methyl)-(1-, 2- or 3-)piperazinyl group, 4-(2-(4-trifluoromethoxyphenyl)pyridylmethyl)-
(1-, 2- or 3-)piperazinyl group, 4-(2(3-chloro-4-fluorophenyl)pyridylmethyl)-(1-, 2- or 3-)piperazinyl group, 4-(5-trifluoromethyl(2-, 3-, 4-, 6- or
7-)benzofuranyl)methyl)-(1-, 2- or 3-)piperazinyl group, 4-(6-trifluoromethyl-(2-, 3-, 4-, 5- or
7-)benzofuranyl)methyl)-(1-, 2- or 3-)piperazinyl group, 4-(5-chloro(2-, 3-, 4-, 6- or 7-)benzothienyl)methyl)-
(1-, 2-, or 3-)piperazinyl group, 4-(6-chloro(2-, 3-, 4-, 5- or 7-)benzofuranyl)methyl)-(1-, 2- or
3-)piperazinyl group, 4-(5-trifluoromethoxy(2-, 3-, 4-, 6- or 7-)benzofuranyl)methyl)-(1-, 2- or 3-)piperazinyl group, 4-(3-(4-trifluoromethylphenyl)-2-propenyl)-(1-, 2- or 3-)piperazinyl group, 4-(3-(3,4-dichlorophenyl)-
2-propenyl)-(1-, 2- or 3-)piperazinyl group, 4-(3-(4-chlorophenyl)-2-propenyl)-(1-, 2- or 3-)piperazinyl group, 4-(3-(6-trifluoromethyl(2-, 3-, 4-, 5- or
7-)benzofuranyl)-2-propenyl)-(1-, 2- or 3-)piperazinyl group, 4-(3-(5-chloro(2-, 3-, 4-, 5- or
7-)benzofuranyl))-2-propenyl)-(1-, 2- or 3-)piperazinyl group, 4-(5-chloro(2-, 3-, 4-, 6- or
7-)benzofuranyl)methyl)-(1-, 2- or 3-)piperazinyl group,
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4-(2-(4-trifluoromethylphenyl)-4- or
5-)thiazolylmethyl)-(1-, 2- or 3-)piperazinyl group, 4-
(2-(4-trifluoromethoxyphenoxy)ethyl)-(1-, 2- or
3-)piperazinyl group, 4-(3-(4-trifluoromethoxyphenyl)-
2-propenyl)-(1-, 2- or 3-)piperazinyl group, 4-(5-
trifluoromethoxy (1-, 2-, 3-, 4-, 6- or
7-)indolylmethyl)-(1-, 2- or 3-)piperazinyl group, 4-
(2-(4-chlorophenyl)-(3-, 4- or 5-)furylmethyl)-(1-, 2-
or 3-)piperazinyl group, 4-(2-(2-chloro-5-
trifluoromethylphenyl)-(3-, 4- or 5-)furylmethyl)-(1-,
2- or 3-)piperazinyl group or the like.

A benzothienyl C1-C6 alkyl group (wherein, on
the benzothiophene ring, at least one selected from the
group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkoxy group and a
halogen substituted or unsubstituted C1-C6 alkyl group
may be substituted) includes a benzothienyl C1-C6 alkyl
group having a linear or branched alkyl group
containing 1 to 6 carbon atoms on the alkyl moiety
(wherein, on the benzothiophene ring, 1 to 3
substituents selected from the group consisting of a
halogen substituted or unsubstituted C1-C6 alkoxy group
and a halogen substituted or unsubstituted C1-C6 alkyl
group may be substituted), for example, ((2-, 3-, 4-, 5-, 6- or 7-)benzothienyl)methyl group, 1-((2-, 3-, 4-, 5-, 6- or 7-)benzothienyl)ethyl group, 2-((2-, 3-, 4-, 5-, 6- or 7-)benzothienyl)ethyl group, 3-((2-, 3-, 4-, 5-, 6- or 7-)benzothienyl)propyl group, 2-((2-, 3-, 4-,
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5-, 6- or 7-)benzothienyl)propyl group, 4-((2-, 3-, 4-, 5-, 6- or 7-)benzothienyl)butyl group, 5-((2-, 3-, 4-, 5-, 6- or 7-)benzothienyl)pentyl group, 4-((2-, 3-, 4-, 5-, 6- or 7-)benzothienyl)pentyl group, 6-((2-, 3-, 4-, 5-, 6- or 7-)benzothienyl)hexyl group, 2-methyl-3-((2-, 3-, 4-, 5- 6- or 7-)benzothienyl)propyl group, 1,1-dimethyl-2-((2-, 3-, 4-, 5-, 6- or 7-)benzothienyl)ethyl group, 5-chloro-(2-, 3-, 4-, 5- or 7-)benzothienylmethyl group, 5-methyl-(2-, 3-, 4-, 5-, 6- or 7-)benzothienylmethyl group, 5-methoxy-(2-, 3-, 4-, 6- or 7-)benzothienylmethyl group, 5-trifluoromethyl-(2-, 3-, 4-, 6- or 7-)benzothienylmethyl group, 5-trifluoromethoxy-(2-, 3-, 4-, 6- or 7-)benzothienylmethyl group, 5,6-dichloro-(2-, 3-, 4-, 5- or 7-)benzothienylmethyl group, 4,5,6-trifluoro-(2-, 3- or 7-)benzothienylmethyl group, 5-chloro-6-trifluoromethoxy-(2-, 3-, 4- or 7-)benzothienylmethyl group, 2,5-dimethyl-(3-, 4-, 6- or 7-)benzothienylmethyl group, 2,5,6-trimethyl-(3-, 4-, 5-, 6- or 7-)benzothienylmethyl group or the like.

A thiazolyl C1-C6 alkyl group [wherein, on the thiazole ring, at least one phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted] may be substituted] includes a thiazolyl C1-C6 alkyl group a linear or branched alkyl
group containing 1 to 6 carbon atoms on the alkyl moiety [wherein, on the thiazole ring, 1 to 2 phenyl groups as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted; may be substituted], for example, a \((2-, 4- or 5-)\)thiazolyl)methyl group, 1-\((2-, 4- or 5-)\)thiazolyl)ethyl group, 2-\((2-, 4- or 5-)\)thiazolyl)ethyl group, 3-\((2-, 4- or 5-)\)thiazolyl)propyl group, 2-\((2-, 4- or 5-)\)thiazolyl)propyl group, 4-\((2-, 4- or 5-)\)thiazolyl)butyl group, 5-\((2-, 4- or 5-)\)thiazolyl)pentyl group, 4-\((2-, 4- or 5-)\)thiazolyl)pentyl group, 6-\((2-, 4- or 5-)\)thiazolyl)hexyl group, 2-methyl-3-\((2-, 4- or 5-)\)thiazolyl)propyl group, 1,1-dimethyl-2-\((2-, 4- or 5-)\)thiazolyl)ethyl group, 2-(4-trifluoromethylphenyl)- (4- or 5-)thiazolyl)methyl group, 2-(4-trifluoromethylphenyl)-(4- or 5-)thiazolyl)methyl group, 2-(4-trifluoromethoxyphenyl)-(4- or 5-)thiazolyl)methyl group, 2-(4-trifluoromethoxyphenyl)-(4- or 5-)thiazolyl)methyl group, 4-(3-methylphenyl)-(2- or 5-)thiazolyl)methyl group, 4-(2-methoxyphenyl)-(2- or 5-)thiazolyl)methyl group, 5-(2-methoxyphenyl)-(2- or 5-)thiazolyl)methyl group, 4-(4-chlorophenyl)-(2- or 5-)thiazolyl)methyl group, 2-(2,4-dimethylphenyl)-(4- or 5-)thiazolyl)methyl group, 2-(2,4,6-trimethylphenyl)-(4- or 5-)thiazolyl)methyl group, 2-(3, 4-
dimethoxyphenyl)-(4- or 5-)thiazolymethyl group, 2-(3,4,5-trimethoxyphenyl)-(4- or 5-)thiazolymethyl group, 2-(3-chloro-4-trifluoromethylphenyl)-(4- or 5-)thiazolymethyl group, 4-(3,4-dichlorophenyl)-(2- or 5-)thiazolymethyl group, 2-(3,4,6-trifluorophenyl)-(4- or 5-)thiazolymethyl group, 2,4-diphenyl(4- or 5-)thiazolymethyl group or the like.

An indolyl Cl-C6 alkyl group (wherein, on the indole ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) includes an indolyl Cl-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety (wherein, on the indole ring, 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), for example, a (1-, 2-, 3-, 4-, 5-, 6- or 7-)indolyl)methyl group, 1-((1-, 2-, 3-, 4-, 5-, 6- or 7-)indolyl)ethyl group, 2-((1-, 2-, 3-, 4-, 5-, 6- or 7-)indolyl)ethyl group, 3-((1-, 2-, 3-, 4-, 5-, 6- or 7-)indolyl)propyl group, 2-((1-, 2-, 3-, 4-, 5-, 6- or 7-)indolyl)propyl group, 4-((1-, 2-, 3-, 4-, 5-, 6- or 7-)indolyl)butyl group, 5-((1-, 2-, 3-, 4-, 5-, 6- or 7-)indolyl)pentyl group, 4-((1-, 2-, 3-, 4-, 5-, 6- or 7-)indolyl)pentyl group, 6-((1-, 2-, 3-, 4-,
5 indolylmethyl group, 5-trifluoromethyl-(1-,
2-, 3-, 4-, 6- or 7-)indolylmethyl group, 2-trifluoromethoxy-(1-, 3-, 4-, 5-, 6-
or 7-)indolylmethyl group, 4-methyl-(1-, 2-, 3-, 5-, 6- or 7-)indolylmethyl group,
5-methoxy-(1-, 2-, 3-, 4-, 6- or 7-)indolylmethyl group, 4-
chloro-(1-, 2-, 3-, 5-, 6- or 7-)indolylmethyl group,
2,4-dimethyl-(1-, 3-, 5-, 6- or 7-)indolylmethyl group,
2,4,6-trimethyl-(1-, 3-, 5- or 7-)indolylmethyl group,
3,4-dimethoxy-(1-, 2-, 5-, 6- or 7-)indolylmethyl group,
3,4,5-trimethoxy-(1-, 2-, 6- or 7-)indolylmethyl group,
3-chloro-4-trifluoromethyl-(1-, 2-, 5-, 6- or 7-)indolylmethyl group,
3,4-dichloro-(1-, 2-, 5-, 6- or 7-)indolylmethyl group,
3,4,6-trifluoro-(1-, 2-, 5- or 7-)indolylmethyl group,
5-trifluoromethoxy-(1-, 2-, 3-, 4-, 6- or 7-)indolylmethyl group,
5-trifluoromethoxy-6-
chloro-(1-, 2-, 3-, 4- or 7-)indolylmethyl group, 1,3-
dimethyl-5-fluoro-(2-, 4-, 6- or 7-)indolylmethyl group or the like.

A phenyl C1-C6 alkyl group (wherein, on the
phenyl ring, at least one selected from the group
consisting of a benzofuryl group, a halogen atom, a
halogen substituted or unsubstituted C1-C6 alkyl group
and a halogen substituted or unsubstituted C1-C6 alkoxy
group may be substituted) includes, in addition to a
phenyl Cl-C6 alkyl group as described above (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), a phenyl Cl-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a benzofuryl group, a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted), for example, 4-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)benzyl group, 2-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)benzyl group, 3-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)benzyl group, 3,4-di((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)benzyl group, 2,4,6-tri((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)benzyl group, 3-chloro-4-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)benzyl group or the like.

A phenyl Cl-C6 alkyl group (wherein, on the phenyl group, at least one phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) may be substituted) includes a phenyl Cl-
C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety [wherein, on the phenyl ring, 1 to 3 phenyl groups as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted], for example, a 4-
phenylbenzyl group, 3-phenylbenzyl group, 2-
phenylbenzyl group, 2,4-diphenylbenzyl group, 2,4,6-
triphenylbenzyl group, 4-(4-
trifluoromethoxyphenyl)benzyl group, 2-(3-
trifluoromethylphenyl)benzyl group, 4-(2-
fluorophenyl)benzyl group, 3-(4-chlorophenyl)benzyl
group, 4-(4-methoxyphenyl)benzyl group, 3-(4-
methylphenyl)benzyl group, 2-(3,4-
dimethoxyphenyl)benzyl group, 4-(3,4-
dimethylphenyl)benzyl group, 3-(3,4,6-
trimethoxyphenyl)benzyl group, 2-(2,4,5-
trimethylphenyl)benzyl group, 4-(3,4-
dichlorophenyl)benzyl group, 2-(2,4,6-
trifluorophenyl)benzyl group, 4-(3-chloro-4-
trifluoromethoxyphenyl)benzyl group, 2-(4-(2-
fluorophenyl)phenyl)ethyl group, 3-(2-(3,4-
dimethoxyphenyl)phenyl)propyl group, 4-(2-(2,4,5-
trimethylphenyl)phenyl)butyl group, 5-(4-(3-chloro-4-
trifluoromethoxyphenyl)phenyl)pentyl group, 6-(2-(3-
trifluoromethylphenyl)phenyl)hexyl group, 1-(4-(4-
trifluoromethoxyphenyl)phenyl)ethyl group or the like.

A phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group is substituted) includes is a phenoxy group having 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group as defined above, examples of which include a 2-fluorophenoxy group, 3-fluorophenoxy group, 4-fluorophenoxy group, 2-chlorophenoxy group, 3-chlorophenoxy group, 4-chlorophenoxy group, 2-bromophenoxy group, 3-bromophenoxy group, 4-bromophenoxy group, 2-iodophenoxy group, 3-iodophenoxy group, 4-iodophenoxy group, 2,3-difluorophenoxy group, 3,4-difluorophenoxy group, 3,5-difluorophenoxy group, 2,4-difluorophenoxy group, 2,6-difluorophenoxy group, 2,3-dichlorophenoxy group, 3,4-dichlorophenoxy group, 3,5-dichlorophenoxy group, 2,4-dichlorophenoxy group, 2,6-dichlorophenoxy group, 3,4,5-trifluorophenoxy group, 3,4,5-trichlorophenoxy group, 2,4,6-trifluorophenoxy group, 2,4,6-trichlorophenoxy group, 2-fluoro-4-bromophenoxy group, 4-chloro-3-fluorophenoxy group, 2,3,4-trichlorophenoxy group, 3,4,5-trifluorophenoxy group, 2,3,4,5,6-
pentfluorophenoxy group, 2, 4, 6-trimethylphenoxy group, 4-n-butylphenoxy group, 2,4-dimethylphenoxy group, 2,3-dimethylphenoxy group, 2,6-dimethylphenoxy group, 3,5-dimethylphenoxy group, 2,5-dimethylphenoxy group, 3,5-difluoromethylphenoxy group, 4-n-butoxyphenoxy group, 2,4-dimethoxyphenoxy group, 2,3-dimethoxyphenoxy group, 2,6-dimethoxyphenoxy group, 3,5-dimethoxyphenoxy group, 2,5-dimethoxyphenoxy group, 2,4,6-trimethoxyphenoxy group, 3,5-

difluoromethoxyphenoxy group, 3-chloro-4-methoxyphenoxy group, 2-chloro-4-trifluoromethoxyphenoxy group, 3-methyl-4-fluorophenoxy group, 4-bromo-3-trifluoromethylphenoxy group, 2-methylphenoxy group, 3-methylphenoxy group, 4-methylphenoxy group, 2-methyl-3-chlorophenoxy group, 3-methyl-4-chlorophenoxy group, 2-chloro-4-methylphenoxy group, 2-methyl-3-fluorophenoxy group, 2-trifluoromethylphenoxy group, 3-trifluoromethylphenoxy group, 4-trifluoromethylphenoxy group, 2-
pentafluoroethylphenoxy group, 3-
pentafluoroethylphenoxy group, 4-
pentafluoroethylphenoxy group, 2-isopropylphenoxy group, 3-isopropylphenoxy group, 4-isopropylphenoxy group, 2-tert-butylphenoxy group, 3-tert-butylphenoxy group, 4-tert-butylphenoxy group, 2-sec-butylphenoxy group, 3-sec-butylphenoxy group, 4-sec-butylphenoxy group, 2-n-heptafluoropropylphenoxy group, 3-n-heptafluoropropylphenoxy group, 4-n-
heptafluoropropylphenoxy group, 4-n-pentylphenoxy
group, 4-n-hexylphenoxy group, 2-methoxyphenoxy group,
3-methoxyphenoxy group, 4-methoxyphenoxy group, 3-
chloro-2-methoxyphenoxy group, 2-fluoro-3-
methoxyphenoxy group, 2-fluoro-4-methoxyphenoxy group,
2,6-dimethoxyphenoxy group, 2,3,4-trifluorophenoxy
group, 2,4,6-trifluorophenoxy group, 2-
trifluoromethoxyphenoxy group, 3-
trifluoromethoxyphenoxy group, 4-
trifluoromethoxyphenoxy group, 3-fluoro-2-
trifluoromethoxyphenoxy group, 2-fluoro-3-
trifluoromethoxyphenoxy group, 3-fluoro-4-
trifluoromethoxyphenoxy group, 3-chloro-2-
trifluoromethoxyphenoxy group, 2-chloro-3-
trifluoromethoxyphenoxy group, 3-chloro-4-
trifluoromethoxyphenoxy group, 2-
pentafluoroethoxyphenoxy group, 3-
pentafluoroethoxyphenoxy group, 4-
pentafluoroethoxyphenoxy group, 3-chloro-2-
pentafluoroethoxyphenoxy group, 2-chloro-3-
pentafluoroethoxyphenoxy group, 3-chloro-4-
pentafluoroethoxyphenoxy group, 2-isopropoxyphenoxy
group, 3-isopropoxyphenoxy group, 4-isopropoxyphenoxy
group, 2-tert-butoxyphenoxy group, 3-tert-butoxyphenoxy
group, 4-tert-butoxyphenoxy group, 2-sec-butoxyphenoxy
group, 3-sec-butoxyphenoxy group, 4-sec-butoxyphenoxy
group, 2-n-heptafluoropropoxyphenoxy group, 3-n-
heptafluoropropoxyphenoxy group, 4-n-
heptafluoropropoxyphenoxy group, 4-n-pentoxyphenoxy group, 4-n-hexyloxyphenoxy group or the like.

A phenyl C1-C6 alkyl group [wherein, on the phenyl ring, at least one phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group is substituted, is substituted] includes a phenyl C1-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety [wherein, on the phenyl ring, 1 to 3 phenoxy groups as described above (wherein, on the phenyl ring, 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group are substituted), for example, a 4-(4-trifluoromethoxyphenyl)benzyl group, 2,4-di(4-

trifluoromethoxyphenyl)benzyl group, 2-(3-

trifluoromethylphenoxy)benzyl group, 4-(2-

fluorophenoxy)benzyl group, 2,4,6-tri(2-

fluorophenoxy)benzyl group,

3-(4-chlorophenoxy)benzyl group, 4-(4-

methoxyphenoxy)benzyl group, 3-(4-methylphenoxy)benzyl group, 2-(3, 4-dimethoxyphenoxy)benzyl group, 4-(3,4-
dimethylphenoxy)benzyl group, 3-(3,4,6-
trimethoxyphenoxy)benzyl group, 2-(2,4,5-
trimethylphenoxy) benzyl group, 4- (3, 4-
dichlorophenoxy) benzyl group, 2- (2, 4, 6-
trifluorophenoxy) benzyl group, 4- (3-chloro-4-
trifluoromethoxyphenoxy) benzyl group, 2- (4- (2-
fluorophenoxy) phenyl) ethyl group, 3- (2- (3, 4-
dimethoxyphenoxy) phenyl) propyl group, 4- (2- (2, 4, 5-
trimethylphenoxy) phenyl) butyl group, 5- (4- (3-chloro-4-
trifluoromethoxyphenoxy) phenyl) pentyl group, 6- (2- (3-
trifluoromethoxyphenoxy) phenyl) hexyl group, 1- (4- (4-
trifluoromethoxyphenoxy) phenyl) ethyl group or the like.

A thiazolyl group (wherein, on the thiazole
ring, at least one phenyl group may be substituted)
includes a thiazolyl group (wherein, on the thiazole
ring, 1 or 2 phenyl groups may be substituted), for
example, (2-, 4- or 5-) thiazolyl group, 2- phenyl- (4- or
5-) thiazolyl group, 4- phenyl- (2- or 5-) thiazolyl group,
5- phenyl- (2- or 4-) thiazolyl group, 2, 5-diphenyl-4-
thiazolyl group, 2, 4-diphenyl-5-thiazolyl group, 4, 5-
diphenyl- 2-thiazolyl group.

A phenoxy C1-C6 alkyl group (wherein, on the
phenyl ring, at least one selected from the group
consisting of a phenyl group (wherein, on the phenyl
ring, at least one selected from the group consisting
of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted), a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be substituted) includes, in addition to a phenoxy C1-C6 alkyl group as described above (which may be substituted by at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group), a phenoxy C1-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety (wherein, on the phenyl ring, 1 to 3 substituents selected from the group consisting of a phenyl group as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), for example, a 4-phenylphenoxy methyl group, 3-phenylphenoxy methyl group, 2-phenylphenoxy methyl group, 2,4-diphenylphenoxy methyl group, 2,4,6-triphenylphenoxy methyl group, 4-(4-trifluoromethoxyphenyl)phenoxy methyl group, 2-(3-trifluoromethylphenyl)phenoxy methyl group, 4-(2-fluorophenyl)phenoxy methyl group, 3-(4-chlorophenyl)phenoxy methyl group, 4-(4-methoxyphenyl)phenoxy methyl group, 3-(4-methylphenyl)phenoxy methyl group, 3-(4-methylphenyl)phenoxy methyl group, 3-(4-methylphenyl)phenoxy methyl group, 3-(4-methylphenyl)phenoxy methyl group, 3-(4-methylphenyl)phenoxy methyl group, 3-(4-methylphenyl)phenoxy methyl group, 3-(4-methylphenyl)phenoxy methyl group, 3-(4-methylphenyl)phenoxy methyl group, 3-(4-methylphenyl)phenoxy methyl group, 3-(4-methylphenyl)phenoxy methyl group, 3-(4-methylphenyl)phenoxy methyl group, 3-(4-methylphenyl)phenoxy methyl group, 3-(4-methylphenyl)phenoxy methyl group.
group, 2-(3,4-methoxyphenyl)phenoxyethyl group, 4-
(3,4-dimethylphenyl)phenoxyethyl group, 3-(3,4,6-
trimethoxyphenyl)phenoxyethyl group, 2-(2,4,5-
trimethylphenyl)phenoxyethyl group, 4-(3,4-
dichlorophenyl)phenoxyethyl group, 2-(2,4,6-
trifluorophenyl)phenoxyethyl group, 4-(3-chloro-4-
trifluoromethoxyphenyl)phenoxyethyl group, 2-(4-
phenylphenoxy)ethyl group, 2-(4-(2-
fluorophenyl)phenoxy)ethyl group, 3-(2-(3,4-
dimethoxyphenyl)phenoxy)propyl group, 4-(2-(2,4,5-
trimethylphenyl)phenoxy)butyl group, 5-(4-(3-chloro-4-
trifluoromethoxyphenyl)phenoxy)pentyl group, 6-(2-(3-
trifluoromethylphenyl)phenoxy)hexyl group, 2-(4-(4-
trifluoromethylphenyl)phenoxy)ethyl group, 2-(4-(4-
trifluoromethoxyphenyl)phenoxy)ethyl group or the like.

A piperidyl group [wherein, on the piperidine
ring, at least one selected from the group consisting
of a phenoxy group (on the phenyl ring, at least one
selected from the group consisting of a halogen atom, a
halogen substituted or unsubstituted C1-C6 alkyl group
and a halogen substituted or unsubstituted C1-C6 alkoxy
group may be substituted) and a phenyl C1-C6 alkyl
group may be substituted] includes, in addition the
above-described piperidyl group, a piperidyl group

[wherein, on the piperidine ring, at least one phenoxy
group (wherein, on the phenyl ring, at least one
selected from the group consisting of a halogen atom, a
halogen substituted or unsubstituted C1-C6 alkyl group
and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted], a piperidyl group [wherein, on the piperidine ring, 1 to 3 substituents selected from the group consisting of a phenoxy group as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) and a phenyl C1-C6 alkyl group may be substituted], for example, a 4-benzyl-(1-, 2- or 3-)piperidyl group, 3-benzyl-(1-, 2-, 4-, 5- or 6-)piperidyl group, 2-benzyl-(1-, 3-, 4-, 5- or 6-)piperidyl group, 2,4-dibenzyl-(1-, 3-, 5- or 6-)piperidyl group, 2,3,4-tribenzyl-(1-, 5- or 6-)piperidyl group, 4-phenoxy-3-benzyl-(1-, 2-, 5- or 6-)piperidyl group or the like.

A benzofuryl C1-C6 alkyl group (wherein, on the benzofuran ring, at least one halogen substituted or unsubstituted C1-C6 alkyl group may be substituted) includes a benzofuryl C1-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety (wherein, on the benzofuran ring, 1 to 3 halogen substituted or unsubstituted C1-C6 alkyl groups may be substituted), for example, a ((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)methyl group, 1-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)ethyl group, 2-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)ethyl group, 3-((2-, 3-, 4-, 5-,
4-, 5-, 6- or 7-)benzofuryl)propyl group, 2-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)propyl group, 4-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)butyl group, 5-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)pentyl group, 4-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)pentyl group, 6-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)hexyl group, 2-methyl-3-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)propyl group, 1,1-dimethyl-2-((2-, 3-, 4-, 5-, 6- or 7-)benzofuryl)ethyl group, 2-trifluoromethyl-(3-, 4-,
5-, 6- or 7-)benzofurylmethyl group, 5-trifluoromethyl-(2-, 3-, 4-, 6- or 7-)benzofurylmethyl group, 4-methyl-(2-, 3-, 4-, 6- or 7-)benzofurylmethyl group, 2,4-dimethyl-(3-, 5-, 6- or 7-)benzofurylmethyl group, 2,4,6-trimethyl-(3-, 5- or 7-)benzofurylmethyl group,
4-trifluoromethyl-(2-, 3-, 5-, 6- or 7-)benzofurylmethyl group, 6-trifluoromethyl-(2-, 3-, 4-, 5- or 7-)benzofurylmethyl group or the like.

A piperidylcarbonyl C1-C6 alkyl group
(wherein, on the piperidine ring, at least one phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted) includes

a piperidylcarbonyl C1-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety (wherein, on the piperidine ring 1 to 3 phenoxy groups as described above) (wherein, on
the phenyl ring, 1 to 5, preferably 1 to 3 substituents
selected from the group consisting of a halogen atom, a
halogen substituted or unsubstituted C1-C6 alkyl group
and a halogen substituted or unsubstituted C1-C6 alkoxy
group may be substituted) is substituted, for example,
(4-phenoxy-1-piperidylcarbonyl)methyl group, 2-(3-
phenoxy-2-piperidylcarbonyl)ethyl group, 3-(2-phenoxy-
3-piperidylcarbonyl)propyl group, 4-(1-phenoxy-4-
piperidylcarbonyl)butyl group, 5-(4-phenoxy-1-
piperidylcarbonyl)pentyl group, 6-(1-phenoxy-2-
piperidylcarbonyl)hexyl group, 1-(4-
trifluoromethoxyphenoxy)-4-piperidylcarbonylmethyl
group, 4-(4-trifluoromethoxyphenoxy)-1-
piperidylcarbonylmethyl group, 4-(4-
trifluoromethylphenoxy)-1-piperidylcarbonylmethyl
group, 4-(3-methoxyphenoxy)-1-piperidylcarbonylmethyl
group, 1-(2-methylphenoxy)-4-piperidylcarbonylmethyl
group, 4-(4-chlorophenoxy)-1-piperidylcarbonylmethyl
group, 4-(3,4-di(trifluoromethoxy)phenoxy)-1-
piperidylcarbonylmethyl group, 4-(2,4,6-
tri(trifluoromethyl)phenoxy)-1-piperidylcarbonylmethyl
group, 4-(3,4-dimethylphenoxy)-1-
piperidylcarbonylmethyl group, 4-(2,4,6-
trimethoxyphenoxy)-4-piperidylcarbonylmethyl group, 2-
(3,4-dichlorophenoxy)-1-piperidylcarbonylmethyl group,
3-(2,4,6-tribromophenoxy)-1-piperidylcarbonylmethyl
group, (1,2,6-triphenoxy-4-piperidylcarbonyl)methyl
group, (2,4-diphenoxy-1-piperidylcarbonyl)methyl group
or the like.

An oxazolyl C1-C6 alkyl group (wherein, on the oxazole ring, at least one phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted) includes an oxazolyl C1-C6 alkyl group having a linear or branched alkyl group containing 1 to 6 carbon atoms on the alkyl moiety (wherein, on the oxazole ring, 1 or 2 phenyl groups as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted; may be substituted), for example, (2-, 4- or 5-)oxazolyl)methyl group, 1-((2-, 4- or 5-)oxazolyl)ethyl group, 2-((2-, 4- or 5-)oxazolyl)propyl group, 2-((2-, 4- or 5-)oxazolyl)propyl group, 4-((2-, 4- or 5-)oxazolyl)butyl group, 5-((2-, 4- or 5-)oxazolyl)pentyl group, 4-((2-, 4- or 5-)oxazolyl)pentyl group, 6-((2-, 4- or 5-)oxazolyl)hexyl group, 2-methyl-3-((2-, 4- or 5-)oxazolyl)propyl group, 1,1-dimethyl-2-((2-, 4- or 5-)oxazolyl)ethyl group, 4-((4-trifluoromethoxyphenyl)-(2- or 5-)oxazolyl)methyl group, 4-((4-chlorophenyl)-(2-
or 5-)oxazolylmethyl group, 4-(4-
trifluoromethylphenyl)-(2- or 5-)oxazolylmethyl group, 4-(4-methylphenyl)-(2- or 5-)oxazolylmethyl group, 4-(4-methoxyphenyl)-(2- or 5-)oxazolylmethyl group, 4-(2, 5-dichlorophenyl)-(2- or 5-)oxazolylmethyl group, 4-(2,4,6-trifluorophenyl)-(2- or 5-)oxazolylmethyl group, 2-(3,4-dimethylphenyl)-(4- or 5-)oxazolylmethyl group, 5-(3,4,6-trimethylphenyl)-(2- or 4-)oxazolylmethyl group, 2-(3,4-dimethoxyphenyl)-(4- or 5-)oxazolylmethyl group, 4-(2,4,6-trimethoxyphenyl)-(2- or 5-)oxazolylmethyl group, 4-(3-chloro-4-trifluoromethoxyphenyl)-(2- or 5-)oxazolylmethyl group, 2,4-diphenyl-5-oxazolylmethyl group, 4,5-diphenyl-2-oxazolylmethyl group, 2,5-diphenyl-5-oxazolylmethyl group or the like.

An isoxazolyl group [wherein, on the isoxazoline ring, at least one phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) may be substituted] includes an isoxazolyl group [wherein, on the isoxazoline ring, 1 or 2 phenyl groups as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy
group may be substituted, for example, (3-, 4- or 5-)isooxazolyl group, 3-phenyl-(4- or 5-)isooxazolyl group, 4-phenyl-(3- or 5-)isooxazolyl group, 5-phenyl-(3- or 4-)isooxazolyl group, 3,4-diphenyl-5-isooxazolyl group, 3,5-diphenyl-4-isooxazolyl group, 4,5-diphenyl-3-isooxazolyl group, 3-(4-trifluorophenyl) -(4- or 5-)isooxazolyl group, 4-(4-chlorophenyl)-(3- or 5-)isooxazolyl group, 3-(4-trifluoromethylphenyl)-(4- or 5-)isooxazolyl group, 4-(4-methylphenyl)-(3- or 5-)isooxazolyl group, 3-(4-methoxyphenyl)-(4- or 5-)isooxazolyl group, 4-(2,4-dichlorophenyl)-(3- or 5-)isooxazolyl group, 3-(2,4,6-trifluorophenyl)-(4- or 5-)isooxazolyl group, 3-(3,4-diphenylmethyl)-(4- or 5-)isooxazolyl group, 5-(3,4,6-trimethylphenyl)-(3- or 4-)isooxazolyl group, 3-(3,4-dimethoxyphenyl)-(4- or 5-)isooxazolyl group, 4-(2,4,6-trimethoxyphenyl)-(3- or 5-)isooxazolyl group, 3-(3-chloro-4-trifluoromethoxyphenyl)-(4- or 5-)isooxazolyl group or the like.

A benzooxazolyl group (wherein, on the benzooxazole ring, at least one halogen atom may be substituted) includes a benzooxazolyl group (wherein, on the benzooxazole ring, 1 to 3 halogen atoms may be substituted), for example, a (2-, 4-, 5-, 6- or 7-)benzooxazolyl group, 5-chloro-(2-, 4-, 6- or 7-)benzooxazolyl group, 6-chloro-(2-, 4-, 5- or 7-)benzooxazolyl group, 5-fluoro(2-, 4-, 6- or 7-)benzooxazolyl group, 6-bromo-(2-, 4-, 5- or
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7-) benzooxazolyl group, 5-iodo-(2-, 4-, 6- or

7-) benzooxazolyl group, 5,6-dichloro-(2-, 4- or

7-) benzooxazolyl group, 4,5,6-trifluoro-(2- or

7-) benzooxazolyl group, 5-fluoro-6-chloro-(2-, 4- or

5 7-) benzooxazolyl group or the like.

A benzoimidazolyl group (wherein, on the
benzoimidazole ring, at least one selected from the
group consisting of a halogen atom and a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) may be substituted) includes a benzoimidazolyl group (wherein, on the benzoimidazole ring, 1 to 3 substituents selected from the group consisting of a halogen atom and a phenyl Cl-C6 alkyl group as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group and a halogen substituted or unsubstituted Cl-C6 alkoxy group may be substituted) may be substituted), for example, a (2-, 4-, 5-, 6- or 7-) benzoimidazolyl group, 1-(4-trifluoromethoxybenzyl)-5,6-dichloro-(2-, 4- or

25 7-) benzoimidazolyl group, 5-chloro-(1-, 2-, 4-, 6- or

7-) benzoimidazolyl group, 6-chloro-(1-, 2-, 4-, 5- or

7-) benzoimidazolyl group, 5-fluoro-(1-, 2-, 4-, 6- or

7-) benzoimidazolyl group, 6-bromo-(1-, 2-, 4-, 5- or
7-substituted benzimidazolyl group, 5-ido- (1-, 2-, 4-, 6- or 7-)benzimidazolyl group, 5,6-dichloro- (1-, 2-, 4- or 7-)benzimidazolyl group, 4,5,6-trifluoro- (1-, 2- or 7-)benzimidazolyl group, 5-fluoro-6-chloro- (1-, 2-, 4- or 7-)benzimidazolyl group, 1-benzyl- (2-, 4-, 5-, 6- or 7-)benzimidazolyl group, 1-(4-trifluoromethylbenzyl)- (2-, 4-, 5-, 6- or 7-)benzimidazolyl group, 1-(4-chlorobenzyl)- (2-, 4-, 5-, 6- or 7-)benzimidazolyl group, 1-(3-methylbenzyl)- (2-, 4-, 5-, 6- or 7-)benzimidazolyl group, 1-(2-methoxybenzyl)- (2-, 4-, 5-, 6- or 7-)benzimidazolyl group, 1-(3,4-dimethylbenzyl)- (2-, 4-, 5-, 6- or 7-)benzimidazolyl group, 1-(2,4,6-trimethylbenzyl)- (2-, 4-, 5-, 6- or 7-)benzimidazolyl group, 1-(3,4-dimethoxybenzyl)- (2-, 4-, 5-, 6- or 7-)benzimidazolyl group, 1-(2,4,5-trimethoxybenzyl)- (2-, 4-, 5-, 6- or 7-)benzimidazolyl group, 1-(3,4-dichlorobenzyl)- (2-, 4-, 5-, 6- or 7-)benzimidazolyl group, 1-(2,4,6-trifluorobenzyl)- (2-, 4-, 5-, 6- or 7-)benzimidazolyl group, 1-(3-chloro-4-trifluoromethylbenzyl)- (2-, 4-, 5-, 6- or 7-)benzimidazolyl group, (1,5-benzyl- (2-, 4-, 6- or 7-)benzimidazolyl group, 1,5,6-tribenzyl- (2-, 4- or 7-)benzimidazolyl group, or the like.

An imidazolyl group [wherein, on the imidazole ring, at least one phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be substituted) is substituted) includes an imidazolyl group [wherein, on the imidazole ring, 1 or 2 phenyl groups as described above (wherein, on the phenyl ring, 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted)}, for example, a 2-phenyl-(4- or 5-)imidazolyl group, 4-phenyl-(2- or 5-)imidazolyl group, 2,4-diphenyl-5-imidazolyl group, 2,4-diphenyl-5-imidazolyl group, 4,5-diphenyl-2-imidazolyl group, 2-(4-trifluoromethoxyphenyl)-(4- or 5-)imidazolyl group, 2-(4-trifluorophenyl)-(4- or 5-)imidazolyl group, 4-(4-chlorophenyl)-(2- or 5-)imidazolyl group, 4-(4-trifluoromethylphenyl)-(2- or 5-)imidazolyl group, 4-(4-methylphenyl)-2-imidazolyl group, 2-(4-methoxyphenyl)-(4- or 5-)imidazolyl group, 4-(2,4-dichlorophenyl)-(2- or 5-)imidazolyl group, 2-(2,4,6-trifluorophenyl)-(4- or 5-)imidazolyl group, 2-(3,4,6-triphenylmethyl)-(4- or 5-)imidazolyl group, 5-(3,4,6-trimethylphenyl)-(2- or 4-)-imidazolyl group, 2-(3,4-dimethoxyphenyl)-(4- or 5-)imidazolyl group, 4-(2,4,6-trimethoxyphenyl)-(2- or 5-)imidazolyl group, 5-(3-chloro-4-trifluoromethoxyphenyl)-(2- or 4-)-imidazolyl group or the like.

A phenylsulfinyl group [wherein, on the phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) is a phenylsulfonyl group unsubstituted or having 1 to 5, preferably 1 to 3 substituents selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group as defined above, examples of which include a phenylsulfonyl group, 2-fluorophenylsulfonyl group, 3-fluorophenylsulfonyl group, 4-fluorophenylsulfonyl group, 2-chlorophenylsulfonyl group, 3-chlorophenylsulfonyl group, 4-chlorophenylsulfonyl group, 2-bromophenylsulfonyl group, 3-bromophenylsulfonyl group, 4-bromophenylsulfonyl group, 2-iodophenylsulfonyl group, 3-iodophenylsulfonyl group, 4-iodophenylsulfonyl group, 2,3-difluorophenylsulfonyl group, 3,4-difluorophenylsulfonyl group, 3,5-difluorophenylsulfonyl group, 2,4-difluorophenylsulfonyl group, 2,6-difluorophenylsulfonyl group, 2,3-dichlorophenylsulfonyl group, 3,4-dichlorophenylsulfonyl group, 3,5-dichlorophenylsulfonyl group, 2,4-dichlorophenylsulfonyl group, 2,6-dichlorophenylsulfonyl group, 3,4,5-trifluorophenylsulfonyl group, 3,4,5-trichlorophenylsulfonyl group, 2,4,6-
trifluorophenylsulfanyl group, 2,4,6-
trichlorophenylsulfanyl group, 2-fluoro-4-
bromophenylsulfanyl group, 4-chloro-3-
fluorophenylsulfanyl group, 2,3,4-
trichlorophenylsulfanyl group, 2,3,4,5,6-
pentafluorophenylsulfanyl group, 2,4,6-
trimethylphenylsulfanyl group, 4-n-butylphenylsulfanyl group, 2,4-dimethylphenylsulfanyl group, 2,3-
dimethylphenylsulfanyl group, 2,6-
dimethylphenylsulfanyl group, 3,5-
dimethylphenylsulfanyl group, 2,5-
dimethylphenylsulfanyl group, 3,5-
ditrifluoromethoxyphenylsulfanyl group, 4-n-
butoxyphenylsulfanyl group, 2,4-dimethoxyphenylsulfanyl group, 2,3-dimethoxyphenylsulfanyl group, 2,6-
dimethoxyphenylsulfanyl group, 3,5-
dimethoxyphenylsulfanyl group, 2,5-
dimethoxyphenylsulfanyl group, 2,4,6-
trimethoxyphenylsulfanyl group, 3,5-
ditrifluoromethoxyphenylsulfanyl group, 3-chloro-4-
methoxyphenylsulfirnyl group, 2-chloro-4-
ditrifluoromethoxyphenylsulfanyl group, 3-methyl-4-
fluorophenylsulfanyl group, 4-bromo-3-
ditrifluoromethylphenylsulfanyl group, 2-
methylphenylsulfanyl group, 3-methylphenylsulfanyl group, 4-methylphenylsulfanyl group, 2-methyl-3-
chlorophenylsulfanyl group, 3-methyl-4-
chlorophenylsulfanyl group, 2-chloro-4-
methylphenylsulfinyl group, 2-methyl-3-fluorophenylsulfinyl group, 2-trifluoromethylphenylsulfinyl group, 3-trifluoromethylphenylsulfinyl group, 4-
trifluoromethylphenylsulfinyl group, 2-
pentafluoroethylphenylsulfinyl group, 3-
pentafluoroethylphenylsulfinyl group, 4-
pentafluoroethylphenylsulfinyl group, 2-
isopropylphenylsulfinyl group, 3-
isopropylphenylsulfinyl group, 4-
isopropylphenylsulfinyl group, 2-tert-
butylphenylsulfinyl group, 3-tert-butylphenylsulfinyl group, 4-tert-butylphenylsulfinyl group, 2-sec-
butylphenylsulfinyl group, 3-sec-butylphenylsulfinyl group, 4-sec-butylphenylsulfinyl group, 2-n-
heptafluoropropylphenylsulfinyl group, 3-n-
heptafluoropropylphenylsulfinyl group, 4-n-
heptafluoropropylphenylsulfinyl group, 4-n-
pentylphenylsulfinyl group, 4-n-hexylphenylsulfinyl group, 2-methoxyphenylsulfinyl group, 3-
methoxyphenylsulfinyl group, 4-methoxyphenylsulfinyl group, 3-chloro-2-methoxyphenylsulfinyl group, 2-fluoro-3-methoxyphenylsulfinyl group, 2-fluoro-4-
methoxyphenylsulfinyl group, 2,3,4-
trifluorophenylsulfinyl group, 2-
trifluoromethoxyphenylsulfinyl group, 3-
trifluoromethoxyphenylsulfinyl group, 4-
trifluoromethoxyphenylsulfinyl group, 3-fluoro-2-
trifluoromethoxyphenylsulfiny1 group, 2-fluoro-3-
trifluoromethoxyphenylsulfiny1 group, 3-fluoro-4-
trifluoromethoxyphenylsulfiny1 group, 3-chloro-2-
trifluoromethoxyphenylsulfiny1 group, 2-chloro-3-
trifluoromethoxyphenylsulfiny1 group, 3-chloro-4-
trifluoromethoxyphenylsulfiny1 group, 2-
pentafluoroethoxyphenylsulfiny1 group, 3-
pentafluoroethoxyphenylsulfiny1 group, 4-
pentafluoroethoxyphenylsulfiny1 group, 3-chloro-2-
pentafluoroethoxyphenylsulfiny1 group, 2-chloro-3-
pentafluoroethoxyphenylsulfiny1 group, 3-chloro-4-
pentafluoroethoxyphenylsulfiny1 group, 2-
isopropoxyphenylsulfiny1 group, 3-
isopropoxyphenylsulfiny1 group, 4-
isopropoxyphenylsulfiny1 group, 2-tert-
butoxyphenylsulfiny1 group, 3-tert-butoxyphenylsulfiny1
group, 4-tert-butoxyphenylsulfiny1 group, 2-sec-
butoxyphenylsulfiny1 group, 3-sec-butoxyphenylsulfiny1
group, 4-sec-butoxyphenylsulfiny1 group, 2-n-
heptafluoropropoxyphenylsulfiny1 group, 3-n-
heptafluoropropoxyphenylsulfiny1 group, 4-n-
heptafluoropropoxyphenylsulfiny1 group, 4-n-
pentoxyphenylsulfiny1 group, 4-n-hexyloxyphenylsulfiny1
group or the like.

A pyridyl C1-C6 alkyl group [wherein, on the
pyridyl ring, at least one phenyl group [wherein, on
the phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group and a halogen
substituted or unsubstituted C1-C6 alkoxy group may be
substituted) may be substituted) includes, in addition
to a pyridyl C1-C6 alkyl group as described above, a
pyridyl C1-C6 alkyl group having a linear or branched
alkyl group containing 1 to 6 carbon atoms on the alkyl
moiety (wherein, on the pyridine ring, 1 to 3 phenyl
groups as described above (wherein, on the phenyl ring,
1 to 5, preferably 1 to 3 substituents selected from
the group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group and a
halogen substituted or unsubstituted C1-C6 alkoxy group
may be substituted; may be substituted), for example, a
2-(4-trifluoromethoxyphenyl)-(3-, 4-, 5- or
6-)pyridylmethyl group, 2-(4-trifluoromethylphenyl)-
(3-, 4-, 5- or 6-)pyridylmethyl group, 2-(4-
methoxyphenyl)-(3-, 4-, 5- or 6-)pyridylmethyl group,
2-(4-methylphenyl)-(3-, 4-, 5- or 6-)pyridylmethyl
group, 2-(3-chloro-4-fluorophenyl)-(3-, 4-, 5- or
6-)pyridylmethyl group, 2-(2,4-dimethoxyphenyl)-(3-, 4-, 5- or
6-)pyridylmethyl group, 2-(3,4,5-trimethoxyphenyl)-(3-, 4-, 5- or 6-)pyridylmethyl group,
2-(2,4-dimethylphenyl)-(3-, 4-, 5- or 6-)pyridylmethyl
group, 2-(2,4,6-trimethylphenyl)-(3-, 4-, 5- or
6-)pyridylmethyl group, 2-(2,4,6-trichlorophenyl)-(3-, 4-, 5- or 6-)pyridylmethyl
group, 2,4,6-triphenyl-(3- or 5-)pyridylmethyl group,
2,5-diphenyl-(3-, 4- or 6-)pyridylmethyl group or the like.

A 4H-1,3-benzodioxinyl group (wherein, on the 4H-1,3-benzodioxine ring, at least one halogen atom may be substituted) includes a 4H-1,3-benzodioxinyl group (wherein, on the 4H-1,3-benzodioxine ring, 1 to 4 halogen atoms may be substituted), for example, a (2-, 4-, 5-, 6-, 7- or 8-)4H-1,3-benzodioxinyl group, 2,2,4,4-tetrafluoro-(5-, 6-, 7- or 8-)4H-1,3-benzodioxinyl group, 2-chloro-(2-, 4-, 5-, 6-, 7- or 8-)4H-1,3-benzodioxinyl group, 4-bromo-(2-, 4-, 5-, 6-, 7- or 8-)4H-1,3-benzodioxinyl group, 2,4-dichloro-(2-, 4-, 5-, 6-, 7- or 8-)4H-1,3-benzodioxinyl group, 2,4,6-trifluoro-(2-, 4-, 5-, 7- or 8-)4H-1,3-benzodioxinyl group or the like.
The methods for preparing the compounds of the present invention are explained in detail below.

Reaction scheme 1

wherein R', R'' and n are the same as above, and X' represents a halogen atom or nitro group.

According to reaction scheme 1, the compound of the present invention represented by general formula (1) is produced by reacting a 4-nitroimidazole compound represented by general formula (2) with an epoxy compound represented by general formula (3a); in the presence or absence of a basic compound to obtain a compound represented by general formula (4a), and then subjecting the obtained compound to a ring closure reaction.

The molar ratio of the compound of general formula (2) to the compound of general formula (3a) may be generally between 1:0.5 and 1:5, and preferably between 1:0.5 and 1:3.

Known compounds can be widely used as a basic compound herein. Examples of such a basic compound include inorganic basic compounds such as a metal hydride, metal alcoholate, hydroxide, carbonate or...
hydrogencarbonate, and organic basic compounds such as acetate.

Specific examples of a metal hydride include sodium hydride and potassium hydride. Specific examples of a metal alcoholate include sodium methoxide, sodium ethoxide and potassium tert-butoxide. Specific examples of a hydroxide include sodium hydroxide and potassium hydroxide. Specific examples of a carbonate include sodium carbonate and potassium carbonate. Specific examples of a hydrogencarbonate include sodium hydrogencarbonate and potassium hydrogencarbonate. In addition to the above compounds, sodium amide and the like may also be included in the inorganic basic compounds.

Specific examples of acetate include sodium acetate and potassium acetate. In addition to these compounds, specific examples of organic basic compounds include triethylamine, trimethylamine, diisopropyl-ethylamine, pyridine, dimethylaniline, 1-methyl-pyrrolidine, N-methylmorpholine, 1,5-diazabicyclo-[4.3.0]nonane-5(DBN), 1,8-diazabicyclo[5.4.0]undecene-7(DBU), and 1,4-diazabicyclo[2.2.2]octane(DABCO).

The molar ratio of the above basic compound to the compound of general formula (2) may be generally between 0.1 : 1 and 2 : 1, preferably between 0.1 : 1 and 1 : 1, and more preferably between 0.1 : 1 and 0.5 : 1.

The reaction of the compound of general
formula (2) with the compound of general formula (3a) is generally carried out in an appropriate solvent.

Common solvents can be widely used as the above solvent, as long as it does not inhibit the reaction. Examples of such a solvent include aprotic polar solvents such as dimethylformamide (DMF), dimethylsulfoxide (DMSO) or acetonitrile, ketone solvents such as acetone or methylethylketone, hydrocarbon solvents such as benzene, toluene, xylene, tetralin or liquid paraffin, alcohol solvents such as methanol, ethanol, isopropanol, n-butanol or tert-butanol, ether solvents such as tetrahydrofuran (THF), dioxane, dipropyl ether, diethyl ether or diglyme, ester solvents such as ethyl acetate or methyl acetate, and mixed solvents thereof. Water may be contained in these solvents.

The reaction of the compound of general formula (2) with the compound of general formula (3a) is carried out, for example, as follows: The compound of general formula (2) is dissolved in a reaction solvent, and while stirring, a basic compound is added to the mixture cooled on ice or at up to room temperature (30°C). Thereafter, the mixture is stirred at room temperature to 80°C for 30 minutes to 1 hour, and the compound of general formula (3a) is then added thereto. Thereafter, the mixture is further stirred generally at room temperature to 100°C, and preferably 50°C to 80°C, generally for 30 minutes to 60 hours, and
preferably for 1 to 50 hours.

The compound (2) used as a starting material is known. The compound (3a) includes a novel compound, and a method for producing the compound will be explained later.

The compound of the present invention represented by general formula (1) is produced by subjecting the compound represented by general formula (4a) to a ring closure reaction. The ring closure reaction is carried out by dissolving the above obtained compound represented by general formula (4a) in a reaction solvent and then adding a basic compound thereto followed by stirring.

Herein, as a reaction solvent and a basic compound, there can be used the same reaction solvent and the same basic compound as used in the above reaction of the compound of general formula (2) with the compound of general formula (3a).

The molar ratio of the basic compound to the compound of general formula (4a) is generally equal to 1:1 or higher, preferably between 1:1 and 5:1, and more preferably between 1:1 and 2:1.

The reaction temperature for the ring closure reaction is generally 0°C to 150°C, preferably room temperature to 120°C, and more preferably 50°C to 100°C. The reaction time is generally 30 minutes to 48 hours, preferably 1 to 24 hours, and more preferably 1 to 12 hours.
In the present invention, the reaction mixture can be directly subjected to the following ring closure reaction without isolating the compound of general formula (4a) generated as a result of the reaction of the compound of general formula (2) with the compound of general formula (3a). For example, the compound of general formula (2) is reacted with the compound of general formula (3a) at room temperature to 80°C, and thereafter, a basic compound is added to the obtained reaction mixture followed by stirring at 50°C to 100°C. Otherwise, after the compound of general formula (2) is reacted with the compound of general formula (3a) at room temperature to 80°C, the obtained reaction mixture is concentrated, and the residue is dissolved in a high boiling solvent. Thereafter, a basic compound is added to the obtained solution followed by stirring at 50°C to 100°C, so as to produce a compound of interest represented by general formula (1).

Alternatively, in the reaction of the compound of general formula (2) with the compound of general formula (3a), a basic compound is used at a molar ratio of the basic compound to the compound (2) that is between 0.9 : 1 and 2 : 1. The stirring is carried out at 50°C to 100°C, so that the reaction of the compound of general formula (2) with the compound of general formula (3a) is carried out in a single process to produce a compound of interest represented
by general formula (1).

Reaction scheme 2

\[
\begin{align*}
(3b) & \xrightarrow{R^{2a}H} (4c) & (1w)
\end{align*}
\]

wherein \(X^1\) is the same as above, \(R^{1b}\) represents a hydrogen atom or a C1-6 alkyl group and \(R^{2a}\) represents a group of (a) to (y) as defined above.

According to reaction scheme 2, the compound of the present invention represented by general formula (1w) is produced by reacting a compound represented by general formula (3b) with a compound represented by general formula (5) or a salt thereof, so as to obtain a compound represented by general formula (4c), and then subjecting the obtained compound represented by general formula (4c) to a ring closure reaction, in the presence of a basic compound.

The compound (3b) is novel, and a method for producing the compound will be explained later (reaction scheme 6). Further, the compound (5) includes a novel compound. An example of methods for producing the above compound will be described later in Reference Example 2.

The molar ratio of the compound of general formula (3b) to the compound of general formula (5) may
be generally between 1 : 0.5 and 1 : 5, and preferably between 1 : 0.5 and 1 : 2.

The reaction of the compound of general formula (3b) with the compound of general formula (5) is carried out in the presence of a basic compound in an appropriate solvent.

As a basic compound and a reaction solvent, there can be used the same basic compound and the same reaction solvent as used in the above reaction of the compound of general formula (2) with the compound of general formula (3a). The molar ratio of the basic compound to the compound of general formula (3b) is generally a catalytic amount, preferably between 0.1 : 1 and 3 : 1, and more preferably between 0.1 : 1 and 2 : 1.

The salt of the compound (5) can be used instead of using the compound (5) and a basic compound. Examples of such a salt include alkali metal salts such as a sodium salt or a potassium salt of the compound (5).

The reaction of the compound of general formula (3b) with the compound of general formula (5) is carried out, generally at room temperature to 150°C, preferably at room temperature to 120°C, and more preferably at room temperature to 80°C. The reaction time is generally 10 minutes to 48 hours, preferably 10 minutes to 24 hours, and more preferably 10 minutes to 2 hours.
The compound of the present invention represented by general formula (Iw) is produced by subjecting the compound represented by general formula (4c) to a ring closure reaction. The ring closure reaction is carried out by dissolving the above obtained compound represented by general formula (4c) in a reaction solvent and then adding a basic compound thereto followed by stirring at a certain temperature.

Herein, as a reaction solvent and a basic compound, there can be used the same reaction solvent and the same basic compound as used in the above reaction of the compound of general formula (3b) with the compound of general formula (5).

The molar ratio of the basic compound to the compound of general formula (4c) is generally equal to 1 : 1 or higher, preferably between 1 : 1 and 5 : 1, and more preferably between 1 : 1 and 2 : 1.

The reaction temperature for the ring closure reaction is generally 0°C to 150°C, preferably room temperature to 120°C, and more preferably 50°C to 100°C. The reaction time is generally 10 minutes to 48 hours, preferably 10 minutes to 24 hours, and more preferably 20 minutes to 4 hours.

In the present invention, the reaction mixture can be directly subjected to the following ring closure reaction without isolating the compound of general formula (4c) generated as a result of the reaction of the compound of general formula (3b) with
the compound of general formula (5), so as to produce a
compound of interest that is the compound of the
present invention represented by general formula (1w).

If a basic compound is used to the compound

(5) at a molar ratio of equal to 1 : 1 or higher and
the reaction is carried out at 50°C to 100°C, the
compound of the present invention represented by
general formula (1w) can be produced in a single
process without isolating an intermediate (4c). In the
case of using the alkali metal salt (e.g., a sodium
salt or a potassium salt) of the compound (5), the same
thing can be said.

Reaction scheme 3

\[
\begin{align*}
\text{(6)} & \quad \xrightarrow{\text{R}^{1A}H(5)} \quad \text{(1w)} \\
\end{align*}
\]

wherein \( R^{1A}, R^{2A} \) and \( n \) are the same as above, and \( R^{1A} \)
represents a Cl-6 alkylsulfonyl group, or a
benzenesulfonyl group which may be substituted Cl-6
alkyl group on the benzene ring.

Herein, a Cl-6 alkylsulfonyl group is a group
consisting of an alkyl group having 1 to 6 carbon atoms
and a sulfonyl group, and example of a Cl-6
alkylsulfonyl group includes a methanesulfonyl group,
ethanesulfonyle group, propanesulfonyle group,
butanesulfonyle group, pentanesulfonyle group,
hexanesulfonyle group and the like.

Examples of a benzenesulfonyle group which may
be substituted C1-6 alkyl group on the benzene ring
includes a benzenesulfonyle group which may have 1 to 3
C1-6 alkyl groups on the benzene ring, such as a
benzenesulfonyle group, o-toluenesulfonyle group, m-
toluenesulfonyle group, p-toluenesulfonyle group, 2-
ethylbenzenesulfonyle group, 3-ethylbenzenesulfonyle
group, 4-ethylbenzenesulfonyle group, 2-propyl-
benzenesulfonyle group, 3-propylbenzenesulfonyle group,
4-propylbenzenesulfonyle group, 2,3-dimethyl-
benzenesulfonyle group, 2,4-dimethylbenzenesulfonyle

group, 2,4,6-trimethylbenzenesulfonyle group and the
like.

The reaction of the compound (6) with the
compound represented by general formula (5) is carried
out in an appropriate solvent in the presence of a
basic compound.

Any known solvent can be used herein, as long
as it does not inhibit the present reaction. Examples
of such a solvent include water, aprotic polar solvents
such as DMF, CMSO or acetonitrile, hydrocarbon solvents
such as benzene, toluene, xylene, tetralin, liquid
paraffin or cyclohexane, alcohol solvents such as
ethanol, isopropanol, n-butanol or tert-butanol, ether
solvents such as THF, dioxane, diethyl ether, diethyl
ether or diglyme, ethyl acetate, acetone, and mixed solvents thereof.

As a basic compound, there can be used the same basic compound as used in the above reaction of the compound of general formula (2) with the compound of general formula (3a).

The molar ratio of the basic compound to the compound (6) is generally equal to 1 : 1 or higher, preferably between 1 : 1 and 5 : 1, and more preferably between 1 : 1 and 2 : 1.

The molar ratio of the compound represented by general formula (5) to the compound (5) may be generally equal to 1 : 1 or higher, preferably between 0.9 : 1 and 2 : 1, and more preferably between 0.9 : 1 and 1.5 : 1.

The reaction temperature is generally room temperature to 150°C, preferably room temperature to 100°C, and more preferably 60°C to 100°C. The reaction time is generally 10 minutes to 24 hours, preferably 10 minutes to 12 hours, and more preferably 20 minutes to 7 hours.

Next, the methods for preparing the starting materials and intermediates to obtain the compounds of the present invention are explained.
Reaction scheme 4

wherein $R^{14}$, $R^{15}$ and $n$ are the same as above, $R^{16}$ represents a C1-6 alkoxy-C1-6 alkoxyl group or a C1-6 alkanoyloxy group, and $X^2$ represents a halogen atom.

A compound of general formula (8) is produced by the hydrolysis of a compound of general formula (7).

Hydrolysis of the compound (7) is carried out under acidic conditions. The hydrolysis is carried out, for example, by suspending or dissolving the compound (7) in an appropriate solvent, and adding acid to the obtained solution followed by stirring at 0°C to 120°C. Example of the used solvent may include water, alcohol solvents such as methanol, ethanol, isopropanol or ethylene glycol, acetonitrile, acetone, toluene, DMF, DMSO, acetic acid, trifluoroacetic acid, and mixed solvents thereof. Examples of the used acid may include organic acids such as trifluoroacetic acid or acetic acid, and inorganic acids such as hydrochloric
acid, bromic acid, hydrobromic acid or sulfuric acid. Organic acids such as trifluoroacetic acid or acetic acid can also be used as reaction solvents. The reaction temperature is generally 0°C to 120°C, preferably room temperature to 100°C, and more preferably room temperature to 80°C. The reaction time is generally 30 minutes to 24 hours, preferably 30 minutes to 12 hours, and more preferably 1 to 8 hours.

Hydrolysis of the compound (7) can be carried out under basic condition. The hydrolysis is carried out, for example, by suspending or dissolving the compound (7) in an appropriate solvent, and adding base to the obtained solution followed by stirring at 0°C to 120°C. Example of the used solvent may include water, alcohol solvents such as methanol, ethanol, isopropanol or ethylene glycol, and mixed solvents thereof. Examples of the used base may include alkali metal hydroxides such as sodium hydroxide or potassium hydroxide, alkali metal carbonates such as sodium carbonate or potassium carbonate, and acetates such as sodium acetate. The reaction temperature is generally 0°C to 120°C, preferably room temperature to 100°C, and more preferably room temperature to 80°C. The reaction time is generally 30 minutes to 24 hours, preferably 30 minutes to 12 hours, and more preferably 1 to 8 hours.

For the reaction of the compound (8) with the compound (9), the reaction conditions for the common sulfonylation reaction of alcohol can be widely
applied. For example, the compound (8) is dissolved in an appropriate solvent, and the compound (9) is added to the obtained solution in the presence of a basic compound followed by stirring at 0°C to 150°C, so that the compound (6) can be obtained.

Any known solvent can be used herein, as long as it does not inhibit the sulfonylation reaction. Examples of such a solvent include halogenated hydrocarbon solvents such as methylene chloride or chloroform, aprotic polar solvents such as DMF, DMSO or acetonitrile, aromatic hydrocarbon solvents such as benzene, toluene or xylene, hydrocarbon solvents such as tetralin, liquid paraffin or cyclohexane, ether solvents such as THF, dioxane, diisopropyl ether, diethyl ether or diglyme, ethyl acetate, acetone, and mixed solvents thereof.

The compound (9) is used to the compound (8) at a molar ratio of generally equal to 1:1 or higher, preferably between 1:1 and 2:1, and more preferably between 1:1 and 1.1:1.

As a basic compound, there can be used the same basic compound as used in the above reaction of the compound of general formula (2) with the compound of general formula (3a).

The molar ratio of the basic compound to the compound (8) is generally equal to 1:1 or higher, preferably between 1:1 and 5:1, and more preferably between 1:1 and 2:1.
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In the present sulfonylation reaction, 4-dimethylaminopyridine, 4-(1-pyrrolidinyl)pyridine or the like can be used as a catalyst.

The reaction temperature is generally 0°C to 150°C, preferably 0°C to 100°C, and more preferably 0°C to 60°C. The reaction time is generally 30 minutes to 48 hours, preferably 1 to 24 hours, and more preferably 1 to 4 hours.

Reaction scheme 5

\[
\begin{align*}
\text{(4b)} & \xrightarrow{\text{R}^{1A}X'(9)} \text{(10)} & \xrightarrow{\text{R}^{2A}H(5)} \text{(4c)} \\
& \quad \text{wherein } \text{R}^{1A}, \text{R}^{2A}, \text{X}' \text{ and } n \text{ are the same as above.}
\end{align*}
\]

10 A reaction to lead from the compound (4b) into a compound (10) is carried out, for example, under the same reaction conditions for the reaction to lead from the compound (8) into the compound (6) as shown in reaction scheme 4.

15 A reaction to lead from the compound (10) into a compound (4c) is carried out, for example, under the same reaction conditions for the reaction to lead from the compound (6) into the compound (1w) as shown in reaction scheme 3.
Reaction scheme 6

wherein $R^{1A}$, $R^{15}$ and $X^1$ are the same as above.

A reaction to lead from a compound (10a) into a compound (3b) is carried out in an appropriate solvent in the presence of a basic compound.

Any solvent can be widely used herein, as long as it does not inhibit the reaction. Examples of such a solvent may include aprotic polar solvents such as DMSO or acetonitrile, hydrocarbon solvents such as benzene, toluene, xylene, tetralin or liquid paraffin, halogenated hydrocarbon solvents such as methylene chloride, chloroform or dichloromethane, ether solvents such as THF, dioxane, diisopropyl ether, diethyl ether or diglyme, acetone, ethyl acetate, and mixed solvents thereof.

The same basic compound as used in the reaction of the compound represented by the above general formula (2) with the compound represented by the above general formula (3a) can be used herein.

The molar ratio of such a basic compound to the compound (10a) may be generally equal to 1:1 or higher, preferably between 1:1 and 5:1, and more
preferably between 1:1 and 2:1.

The reaction temperature for this reaction is generally 0°C to 150°C, preferably 0°C to 100°C, and more preferably 0°C to 60°C. The reaction time is generally 5-30 minutes to 48 hours, preferably 1 to 24 hours, and more preferably 1 to 4 hours.

Reaction scheme 7

\[
\begin{align*}
\text{(11)} & \\
\text{(3a)} & \\
\text{(12)} &
\end{align*}
\]

wherein \( R^1, R^2 \) and \( n \) are the same as above.

A reaction to lead from a compound (11) into a compound (3a) is carried out, for example, by treating the compound (11) with trimethylsulfoxonium iodide in an appropriate solvent in the presence of a basic compound.

Any solvent can be widely used herein, as long as it does not inhibit the reaction. Examples of such a solvent may include aprotic polar solvents such as DMSO or acetonitrile, hydrocarbon solvents such as benzene, toluene, xylene, tetralin or liquid paraffin, ether solvents such as THF, dioxane, dipropyl ether, diethyl ether or diglyme, and mixed solvents thereof.

Examples of a basic compound may include sodium hydride, sodium amide, metal alcoholates such as
sodium methoxide, sodium ethoxide or potassium tert-butoxide.

The molar ratio of such a basic compound to the compound (11) may be generally equal to 1 : 1 or higher, preferably between 1 : 1 and 3 : 1, and more preferably between 1 : 1 and 1.5 : 1.

Moreover, the molar ratio of trimethylsulfoxonium iodide to the compound (11) may be generally equal to 1 : 1 or higher, preferably between 1 : 1 and 3 : 1, and more preferably between 1 : 1 and 1.5 : 1.

The reaction temperature for this reaction is generally 0°C to 80°C, preferably 10°C to 50°C, and more preferably 20°C to 35°C. The reaction time is generally 1 to 24 hours, preferably 1 to 12 hours, and more preferably 1 to 4 hours.

A reaction to lead from a compound (12) into the compound (3a) is carried out, for example, by treating the compound (12) with peroxide in an appropriate solvent.

Any reaction solvent can be widely used herein, as long as it does not inhibit the reaction. Examples of such a solvent may include water, alcohol solvents such as methanol or ethanol, aprotic polar solvents such as DMF, DMSO or acetonitrile, hydrocarbon solvents such as benzene, toluene, xylene, tetralin, liquid paraffin or cyclohexane, halogenated hydrocarbon solvents such as methylene chloride, chloroform or
dichloroethane, ether solvents such as THF, dioxane, dipropyl ether, diethyl ether or diglyme, and mixed solvents thereof.

Examples of peroxide include metachloro-5-perbenzoic acid (mCPBA), perbenzoic acid, peracetic acid and hydrogen peroxide.

The molar ratio of such peroxide to the compound (12) may be generally between 1 : 1 and 2 : 1, preferably between 1 : 1 and 1.5 : 1, and more preferably between 1 : 1 and 1.3 : 1.

The reaction temperature for this reaction is generally 0°C to 80°C, preferably 0°C to 50°C, and more preferably 20°C to 35°C. The reaction time is generally 10 minutes to 24 hours, preferably 1 to 12 hours, and more preferably 1 to 8 hours.

For example, one type of the compounds (3a) being optically active is produced from the compound (12) as follows.

Such an optically active compound (3a) can be produced by what is called Sharpless epoxidation. This is to say, the compound can be produced by epoxidation with cumene hydroperoxide or tert-butyl hydroperoxide, in the coexistence of Ti (O-iso-C₆H₅), and optically active C1-C6 alkyl tartarate such as diethyl tartarate (D- or L-form) as catalysts, instead of using a peroxide in the above reaction to lead from the compound (12) into the compound (3a).

Any solvent can be widely used herein, as
long as it does not inhibit the reaction. Examples of such a solvent may include aprotic polar solvents such as acetonitrile, hydrocarbon solvents such as benzene, toluene, xylene, tetralin, liquid paraffin or cyclohexane, halogenated hydrocarbon solvents such as methylene chloride, chloroform or dichloroethane, ether solvents such as THF, dioxane, dipropyl ether, diethyl ether or diglyme, and mixed solvents thereof.

The molar ratio of cumene hydroperoxide or tert-butyl hydroperoxide to the compound (6) may be generally between 0.1 : 1 and 2 : 1, preferably between 0.1 : 1 and 1.5 : 1, and more preferably between 0.1 : 1 and 1 : 1.

The molar ratio of Ti(O-iso-C₆H₇)₄ to the compound (12) may be generally between 0.1 : 1 and 2 : 1, preferably between 0.1 : 1 and 1.5 : 1, and more preferably between 0.1 : 1 and 1 : 1.

The molar ratio of optically active C1-C6 tartarates (D- or L-form) to the compound (12) may be generally between 1 : 1 and 2 : 1, preferably between 1 : 1 and 1.5 : 1, and more preferably between 1 : 1 and 1.3 : 1.

The reaction temperature for this reaction is generally -50°C to 30°C, preferably -20°C to 20°C, and more preferably -20°C to 5°C. The reaction time is generally 1 to 48 hours, preferably 4 to 24 hours, and more preferably 4 to 12 hours.
Reaction scheme 8

wherein $R^{1a}$, $R^{2a}$, $R^{15}$ and $n$ are the same as above.

A reaction to lead from a compound (13) into a compound (3c) is carried out, for example, under the same reaction conditions for the reaction to lead from the compound (6) into the compound (1w) as shown in reaction scheme 3.
Reaction Scheme 9

(14)

(15)

O2N

(16)

O2N

(1a)

(1b)

(17)

(18)

(19)

(20)

(21)

(wherein $R^{1a}$, $X$, $n$, $m$, $W$ and $o$ are the same as above. $R^{2a}$ represents a hydrogen atom, hydroxyl group, Cl-6)
alkoxy group or phenyl group (which may be substituted with a halogen atom(s) on the phenyl ring). The dotted line on the piperidine ring represents a bond which may be a double bond. When the dotted line is a double bond, a hydroxyl group should be substituted on the piperidine ring. \( R' \) represents a tetrahydropyrananyl group. \( R'' \) represents a Cl-6 alkyl group or phenyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring). \( M \) represents an alkali metal such as sodium, potassium, etc.).

A reaction to lead from a compound (14) into a compound (15) is carried out in the presence or absence of an appropriate solvent in the presence of an acid.

Any solvent can be widely used herein, as long as it does not affect the reaction. Examples of such a solvent may include water, halogenated hydrocarbons such as dichloromethane, chloroform or carbon tetrachloride, lower alcohols such as methanol, ethanol or isopropanol, ketones such as acetone or methyl ethyl ketone, ethers such as dioxane, tetrahydrofuran, ethylene glycol monomethyl ether or ethylene glycol dimethyl ether, aliphatic acids such as formic acid or acetic acid, an mixed solvents thereof.

Examples of such an acid may include, for
example, mineral acids such as hydrochloric acid, sulfuric acid or hydrobromic acid, organic acids such as formic acid, trifluoroacetic acid or acetic acid, or aromatic sulfonic acids such as pyridinium p-toluenesulfonic acid, p-toluenesulfonic acid or the like. Although the amount of such an acid used may be suitably selected from a wide range without any particular limitation, it may be generally about 0.1-10 moles to 1 mole of the usual compound (14), preferably about 0.1-2 moles.

The reaction proceeds suitably at generally about 0-200°C, preferably room temperature to about 150°C, and is generally completed in about 0.5-50 hours.

The reaction of the compound (15) with compound (16) or (17) may be carried out in the presence or absence of a basic compound, preferably in its absence in an appropriate inert solvent or without any solvent.

Examples of a basic compound used herein include, for example, organic bases such as triethylamine, trimethylamine, pyridine, dimethylaniline, N-ethylisopropylamine, dimethylaminopyridine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo[5.4.0]undecene-7 (DBU), or 1,4-diazabicyclo[2.2.2]octane (DARCO), and inorganic bases including carbonates such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate or
potassium hydrogen carbonate, metal hydroxides such as sodium hydroxide, potassium hydroxide or calcium hydroxide, potassium hydride, sodium hydride, potassium, sodium, sodium amide, metallic alcohohates such as sodium methyate or sodium ethylate, or the like.

Examples of a solvent used include, for example, halogenated hydrocarbons such as chloroform, dichloromethane, dichoroethane or carbon tetrachloride, aromatic hydrocarbons such as benzene, toluene or xylene, ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran or dimethoxyethane, esters such as methyl acetate, ethyl acetate or isopropyl acetate, alcohols such as methanol, ethanol, isopropanol, propanol, butanol, 3-methoxy-1-butanol, ethylcellulosolve or methylcellulosolve, and aprotic polar solvents such as acetonitrile, pyridine, acetone, water, N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide or hexamethylphosphoric triamide or mixed solvents thereof.

The molar ratio of the compound (16) or (17) to the compound (15) may be generally between about 1:1 and 5:1 each, preferably between about 1:1 and 3:1.

The reaction is performed generally at the temperature of about 0-200°C, preferably room temperature to around 150°C generally for about 5 minutes to 30 hours required.

In the reaction system, boron compounds such
as boron trifluoride etherate complex and halogenated copper compounds such as copper(I) chloride may be added.

In the reaction of the compound (15) with the compound (17), it proceeds advantageously when an organic acid such as trifluoroacetic acid is added in the reaction system.
Reaction Scheme 10

[Diagram showing chemical reactions and structures labeled (1a) to (1g).]

[wherein \( R^{1a}, X, n, m, W, R^{2a}, X^2 \) and \( \sigma \) are the same as above. Two \( Ws \) in general formulas (1c) to (1g) may be same or different. \( R^{5a} \) represents a hydrogen atom.]
R<sup>11a</sup> represents a hydrogen atom; C1-6 alkyl group which may have a hydroxyl group as a substituent; Cl-6 alkanoyl group; Cl-6 alkoxy carbonyl group; phenyl Cl-6 alkoxy carbonyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group, as a substituent on the phenyl ring); phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group, halogen-substituted or unsubstituted Cl-6 alkoxy group, amino group which may have a group selected from the group consisting of a Cl-6 alkanoyl group and Cl-6 alkyl group as a substituent, Cl-6 alkoxy carbonyl group, phenyl group, phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group, may be substituted), aminosulfonyl group, 1,2,3,4-tetrahydroquinolyl group (which may be substituted with at least one oxo group as substituent on the 1,2,3,4-tetrahydroquinoline ring), Cl-6 alkyl sulfonyl group, C3-8 cycloalkyl group, nitro group, cyano group, Cl-6 alkyl thio group, phenyl sulfonyl group (which may be substituted with at least one selected from the group consisting of a halogen atom, halogen-substituted or
unsaturated Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group, as a substituent on the phenyl ring), hydroxyl group-substituted Cl-6 alkyl group and a group:

\[
\begin{align*}
\text{O} & \quad \text{R}^{11} \\
\text{R} & \quad \text{W}_{1} \quad \text{P} \quad \text{R}^{12}
\end{align*}
\]

5 (wherein \( \text{W} \) represents a Cl-6 alkyne group. \( \text{R}^{11} \) and \( \text{R}^{12} \) represent a Cl-6 alkoxy group which may be same or different) may be substituted); a phenyl Cl-6 alkyl group (wherein, on the phenyl ring at least one selected from the group consisting of a Cl-4 alkyne
dioxy group, phenyl group (which may be substituted with at least one selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group, halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring), group

\[
-N(R^{11A})R^{12A}(R^{11A} \text{ and } R^{12A} \text{ represent a hydrogen atom, Cl-6 alkyl group or phenyl group which may be same or different, and } R^{11A} \text{ and } R^{12A} \text{ may be combined each other together with an adjacent nitrogen atom through a nitrogen atom, oxygen atom or sulfur atom or not}
\]

through them to form a 5- to 7-membered saturated heterocycle). phenoxy group (which may be substituted with at least one selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group, halogen-substituted or unsubstituted
Cl-6 alkoxy group on the phenyl ring), phenyl Cl-6 alkoxy group, Cl-6 alkoxy group substituted with an amino group which may have a Cl-6 alkyl group as a substituent, halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group, and halogen-substituted or unsubstituted Cl-10 alkoxy group, may be substituted as a substituent); benzo(furanyl Cl-6 alkyl group (which may be substituted with at least one selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group, halogen-substituted or unsubstituted Cl-6 alkoxy group on the benzofuran ring); phenylsulfonyl group (which may be substituted with at least one selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group, halogen-substituted or unsubstituted Cl-6 alkoxy group and Cl-4 alkylenedioxy group on the phenyl ring); phenoxydicarbonyl group (which may be substituted with at least one selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group, as a substituent on the phenyl ring); phenyl C2-6 alkenyl group (which may be substituted with at least one selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring); Cl-6 alkoxy-substituted Cl-6 alkyl group; C2-6 alkenyl group; Cl-6 alkoxy-substituted C2-6
alkanoyl group; C3-8 cycloalkyl-substituted Cl-6 alkyl group; phenoxy Cl-6 alkyl group (which may be substituted with at least one selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring); benzoyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring); phenylcarbamoyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring); pyridyl group; pyridyl Cl-6 alkyl group; imidazolyl Cl-6 alkyl group; 1,2,3,4-tetrahydroquinolyl group (which may be substituted with at least one group selected from the group consisting of an oxo group and Cl-6 alkyl group as substituent on the 1,2,3,4-tetrahydroquinoline ring); quinolyl group; indolyl group; amino group which may have a Cl-6 alkyl group as a substituent; indazolyl group; naphthyl group; C3-8 cycloalkyl group; amino-substituted Cl-6 alkyl group which may have a Cl-6 alkyl group as a substituent; cyano group-substituted Cl-6 alkyl group; furyl group Cl-6 alkyl group; group:
(wherein RR presents a phenyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group, as a substituent on the phenyl ring)); or piperazinyl-substituted Cl-6 alkyl group (which may be substituted with at least one phenyl group (which may be substituted with at least one selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring) as a substituent on the piperazine ring).

R^6 represents a hydrogen atom; Cl-6 alkyl group which may have a hydroxy group as a substituent; phenyl group (which may be substituted with at least one selected from the group consisting of a Cl-4 alkylenedioxy group, phenyl group (which may be substituted with at least one selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl group), group -N(R^{11a})R^{12a}(R^{11a} and R^{12a} represent a hydrogen atom, Cl-6 alkyl group or phenyl group which may be same or different, and R^{11a} and R^{12a} may be combined each
other together with an adjacent nitrogen atom through a
nitrogen atom, oxygen atom or sulfur atom or not
through them to form a 5- to 7-membered saturated
heterocycle), phenoxy group (which may be substituted
with at least one selected from the group consisting of
a halogen atom, halogen-substituted or unsubstituted
Cl-6 alkyl group and halogen-substituted or
unsubstituted Cl-6 alkoxy group on the phenyl ring),
phenyl Cl-6 alkoxy group, amino-substituted Cl-6 alkoxy
group which may have a Cl-6 alkyl group as a
substituent, a halogen atom, halogen-substituted or
unsubstituted Cl-6 alkyl group and halogen-substituted
or unsubstituted Cl-10 alkoxy group, as a substituent
on the phenyl ring); phenyl Cl-6 alkyl group (which may
be substituted with at least one selected from the
group consisting of a Cl-4 alkylenedioxy group, phenyl
group (which may be substituted with at least one
selected from the group consisting of a halogen atom,
halogen-substituted or unsubstituted Cl-6 alkyl group
and halogen-substituted or unsubstituted Cl-6 alkoxy
group on the phenyl ring), group –N(R^{11a})R^{12a}(R^{11b} and R^{12a}
represent a hydrogen atom, Cl-6 alkyl group or phenyl
group which may be same or different, and R^{11a} and R^{12a}
may be combined each other together with an adjacent
nitrogen atom through a nitrogen atom, oxygen atom or
sulfur atom or not through them to form a 5- to 7-
membered saturated heterocycle), phenoxy group (which
may be substituted with at least one selected from the
group consisting of a halogen atom, halogen-substituted or unsubstituted C1-6 alkyl group and halogen-substituted or unsubstituted C1-6 alkoxy group on the phenyl ring), phenyl C1-6 alkoxy group, amino-
substituted C1-6 alkoxy group which may have a C1-6 alkyl group as a substituent, halogen atom, halogen-substituted or unsubstituted C1-6 alkyl group and halogen-substituted or unsubstituted C1-10 alkoxy group, as a substituent on the phenyl ring); benzofuryl (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted C1-6 alkyl group, halogen-substituted or unsubstituted C1-6 alkoxy group on the benzofuran ring); benzofuryl C1-6 alkyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted C1-6 alkyl group and halogen-substituted or unsubstituted C1-6 alkoxy group on the benzofuran ring); C1-6 alkoxy-substituted C1-6 alkyl group; C3-8 cycloalkyl-substituted C1-6 alkyl group; C3-8 cycloalkyl group; phenoxy C1-6 alkyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted C1-6 alkyl group and halogen-substituted or unsubstituted C1-6 alkoxy group, as a substituent on the phenyl ring); pyridyl group; pyridyl C1-6 alkyl group; imidazolyl group; imidazolyl C1-6 alkyl group; amino-substituted
Cl-6 alkyl group which may have a Cl-6 alkyl group as a substituent; cyano-substituted Cl-6 alkyl group; furyl-substituted Cl-6 alkyl group; furyl group; piperazinyl group (which may be substituted with at least one phenyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring) as a substituent on the piperazine ring); or piperazinyl-substituted Cl-6 alkyl group (which may be substituted with at least one phenyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring) as a substituent on the piperazine ring).

R\(^{\circ}\) represents a Cl-6 alkyl group which may have a hydroxy group as a substituent; Cl-6 alkoxy carbonyl group; phenyl Cl-6 alkoxy carbonyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group, as a substituent on the phenyl group); phenyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl
group, halogen-substituted or unsubstituted Cl-6 alkoxy group, amino group which may have a group from the group consisting of a Cl-6 alkanoyl group and Cl-6 alkyl group as a substituent, Cl-6 alkoxy carbonyl group, phenyl group, phenoxy group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group, as a substituent on the phenyl ring), aminosulfonyl group, 1,2,3,4-tetrahydroquinolyl group (which may be substituted with at least one oxo group as substituent on the 1,2,3,4-tetrahydroquinoline ring), Cl-6 alkylsulfonyl group, C3-8 cycloalkyl group, nitro group, cyano group, Cl-6 alkylthio group, phenylsulfonyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group, as a substituent on the phenyl ring), a hydroxyl group-substituted Cl-6 alkyl group and a group:

\[ W_1 - R_{11}^{11} \]

\[ R_{12} \]

(Wherein \( W_1 \) represents a Cl-6 alkyene group, and \( R_{11}^{11} \) and \( R_{12} \) represent a Cl-6 alkoxy group which may be same or
different); a phenyl Cl-6 alkyl group (which may be substituted with at least one of groups selected from the group consisting of a Cl-4 alkyene dioxy group, phenyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring), group 
-N(R^{1A})R^{1A}; R^{1A} and R^{1A} represent a hydrogen atom, Cl-6 alkyl group or phenyl group which may be same or different, and R^{1A} and R^{1A} may be combined each other together with an adjacent nitrogen atom through a nitrogen atom, oxygen atom or sulfur atom or not through them to form a 5- to 7-membered saturated heterocycle), phenoxy group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring), phenyl Cl-6 alkoxy group, amino-substituted Cl-6 alkoxy group which may have a Cl-6 alkyl group as a substituent, halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-10 alkoxy group, as a substituent on the phenyl ring); benzofuryl Cl-6 alkyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and
halogen-substituted or unsubstituted C1-6 alkoxy group on the benzofuran ring; phenylsulfonyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted C1-6 alkyl group, halogen-substituted or unsubstituted C1-6 alkoxy group and halogen-substituted or unsubstituted C1-4 alkylene dioxy group on the phenyl ring); phenyl C2-6 alkenyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted C1-6 alkyl group and halogen-substituted or unsubstituted C1-6 alkoxy group on the phenyl ring); C1-6 alkoxy-substituted C1-6 alkyl group; C2-5 alkenyl group; C3-8 cycloalkyl group-substituted C1-6 alkyl group; phenoxy C1-6 alkyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted C1-6 alkyl group and halogen-substituted or unsubstituted C1-6 alkoxy group on the phenyl ring); pyridyl group; pyrrol C1-6 alkyl group; imidazolyl C1-6 alkyl group; 1,2,3,4-tetrahydroquinolyl group (which may be substituted with at least one group selected from the group consisting of an oxo group and C1-6 alkyl group as substituent on the 1,2,3,4-tetrahydroquinoline ring); quinolyl group; indolyl group; indazolyl group; naphthyl group; C3-8 cycloalkyl group; amino-substituted C1-6 alkyl group which may
have a C1-6 alkyl group as a substituent; cyano-
substituted C1-6 alkyl group; furyl-substituted C1-6
alkyl group; group:

\[ \text{N-RR} \]

(wherein RR presents a phenyl group (which may be
substituted with at least one of groups selected from
the group consisting of a halogen atom, halogen-
substituted or unsubstituted C1-6 alkyl group and
halogen-substituted or unsubstituted C1-6 alkoxy group,
as a substituent on the phenyl ring)); or piperazinyl-
substituted C1-6 alkyl group (which may be substituted
with at least one phenyl group (which may be
substituted with at least one selected from the group
consisting of a halogen atom, halogen-substituted or
unsubstituted C1-6 alkyl group and halogen-substituted
or unsubstituted C1-6 alkoxy group on the phenyl ring)
as a substituent on the piperazine ring).

R\(^{3d}\) represents a C1-6 alkanoyl group;
phenoxydicarbonyl group (which may be substituted with
at least one of groups selected from the group
consisting of a halogen atom, halogen-substituted or
unsubstituted C1-6 alkyl group and halogen-substituted
or unsubstituted C1-6 alkoxy group on the phenyl
group); C1-6 alkoxy-substituted C2-6 alkanoyl group or
benzoyl group (which may be substituted with at least
one of groups selected from the group consisting of a
halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring).

$R^\text{a}$ represents a phenyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl group).

$R^\text{a}$ represents a hydrogen atom or Cl-6 alkyl group.

The dotted line on the piperidine ring represents a bond which may be a double bond. When the dotted line is a double bond, a group-(W)ONR$^\text{a}$R$^\text{a}$, group-(W)ON(CHR$^\text{a}$R$^\text{a}$) R$^\text{a}$, group-(W)ONR$^\text{a}$R$^\text{a}$, group-(W)ONR$^\text{a}$R$^\text{a}$ or group-(W)ON(CONHR$^\text{a}$) R$^\text{a}$ should be substituted.

The total number of carbons of CHR$^\text{a}$R$^\text{a}$ constituting the group-N(R$^\text{a}$) CHR$^\text{a}$R$^\text{a}$ in general formula (1d) should not exceed 6.

The reaction of the compound (1c) with the compound (16) is carried out in the presence of a reducing agent without a solvent or in an appropriate solvent.

The molar ratio of the compound (16) to the compound (1c) may be generally at least 1:1, preferably 1:1 to large excess.

Examples of the solvents used in the reaction
may include, for example, water, lower alcohols such as methanol, ethanol, isopropanol, butanol, tert-butanol or ethylene glycol, acetonitrile, aliphatic acids such as formic acid, acetic acid or trifluoroacetic acid, ethers such as diethyl ether, tetrahydrofuran, dioxane, monoglyme or diglyme, aromatic hydrocarbons such as benzene, toluene or xylene, halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride or an mixed solvents thereof, or the like.

Examples of the reducing agents may include, for example, formic acid, alkali metal formates such as sodium formate, reducing agents such as sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, lithium aluminum hydride or mixed reducing agents thereof, catalytic hydrogen-reducing agents such as palladium-black, palladium-carbon, platinum oxide, platinum-black or Raney nickel, or the like.

When formic acid and the alkali metal formates are used as a reducing agent, the reaction temperature is appropriate generally at about room temperature to 200°C, preferably around about 50-150°C, and the reaction is completed in about 10 minutes to 10 hours. The molar ratio of formic acid to the compound (1c) may be large excess.

Also, when a reducing agent is used, the reaction temperature is appropriate generally at -80-
100°C, preferably at -80-70°C, and the reaction is completed in about 30 minutes to 100 hours. The molar ratio of the reducing agent to the compound (1c) may be generally between about 1:1 and 20:1, preferably between about 1:1 and 6:1. Particularly, when lithium aluminum hydride is used as a reducing agent, preferred is use of ethers such as diethyl ether, tetrahydrofuran, dioxane, monoglyme or diglyme and aromatic hydrocarbons such as benzene, toluene or xylene. Amines such as trimethylamine, triethylamine or N-ethyldiisopropylamine and molecular sieves such as molecular sieves 3A (MS-3A), molecular sieves 4A (MS-4A) or the like may be added in the reaction system.

Further, when the catalytic hydrogen-reducing agents are used, the reaction may be carried out generally in a hydrogen atmosphere of about ordinary pressure to 20 atm, preferably about ordinary pressure to 10 atm or in the presence of hydrogen-donating agents such as formic acid, ammonium formate, cyclohexene or hydrazine hydrate, generally at a temperature of about -30-130°C, preferably about 0-60°C, and the reaction is generally completed in about 1-12 hours. The catalytic hydrogen-reducing agents may be used generally in an amount of about 0.1-40 wt% based on the compound (1c), and preferably about 1-20 wt%.

The reaction of the compound (1c) with the compound (17) is conducted generally in an appropriate solvent in the presence or absence of a basic compound.
Examples of an inert solvent may include, for example, aromatic hydrocarbons such as benzene, toluene or xylene, ethers such as diethyl ether, tetrahydrofuran, dioxane, monoglyme or diglyme, halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform or carbon tetrachloride, lower alcohols such as methanol, ethanol, isopropanol, butanol, tert-butanol or ethylene glycol, aliphatic acids such as acetic acid, esters such as ethyl acetate or methyl acetate, ketones such as acetone or methylethyl ketone, acetonitrile, pyridine, dimethylsulfoxide, N,N-dimethylformamide, hexamethylphosphoric triamide or mixed solvents thereof.

The basic compounds may include, for example, carbonates such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate or cesium carbonate, metal hydroxides such as sodium hydroxide, potassium hydroxide or calcium hydroxide, sodium hydride, potassium hydride, potassium, sodium, sodium amide, metallic alcoholates such as sodium methylate, sodium ethylate or sodium n-butoxide, organic bases such as pyridine, imidazole, N-ethylidiosopropylamine, dimethylaminopyridine, triethylamine, trimethylamine, dimethylaniline, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo [5.4.0]undecene-7 (DBU) or 1,4-diazabicyclo[2.2.2]octane (DABCO) or a mixture
thereof.

The basic compounds may be used at the molar ratio to the compound (1c) of at least 1:1, preferably between 1:1 and 10:1.

The compound (17) be used at the molar ratio to the compound (1c) of at least 1:1, preferably between 1:1 and 10:1.

The reaction is carried out generally at 0-200°C, preferably at about 0-150°C, and is generally completed in about 5 minutes to 80 hours.

Alkali metal halides such as sodium iodide or potassium iodide may be added or phase-transfer catalysts may be added in the reaction system.

Examples of the phase-transfer catalysts herein may include, for example, catalysts such as tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium fluoride, tetrabutylammonium iodide, tetrabutylammonium hydroxide, tetrabutylammonium hydrogensulfite, tributylmethylammonium chloride, tributylbenzylammonium chloride, tetrapentylammonium chloride, tetrapentylammonium bromide, tetrahexylammonium chloride, benzyltrimethylammonium chloride, methyltrihexylammonium chloride, benzyltrimethyloctadecylammonium chloride, methyltridecylanmonium chloride, benzyltripropylammonium chloride, benzyltriethylammonium chloride, phenyltriethylammonium
chloride, tetracetyl ammonium chloride or tetramethylammonium chloride, quaternary ammonium salts substituted with groups selected from the group consisting of Cl-18 straight or branched chain alkyl groups, a phenyl Cl-6 alkyl group and phenyl group, phosphonium salts substituted with Cl-18 straight or branched chain alkyl groups such as tetrabutylphosphonium chloride or pyridinium salts substituted with Cl-18 straight or branched chain alkyl groups such as 1-dodecanylpyridinium chloride.

The phase-transfer catalysts may be used generally at the molar ratio to the compound (1c) of between 0.1:1 and 1:1, preferably between 0.1:1 and 0.5:1.

The reaction of the compound (1c) with the compound (18) is by a method wherein the compound (1c) and carboxylic acid of the compound (18) are reacted with usual amide-coupling generation reactions.

Conditions for a known amide bond formation reaction can be widely applied herein. Examples of such an amide bond formation reaction include (a) mixed acid anhydride method, that is, a method of reacting carboxylic acid (18) with alkyl haloformate to obtain a mixed acid anhydride and reacting the mixed acid anhydride with amine (1c), (b) active ester method, that is, a method of converting carboxylic acid (18) into active ester such as p-nitrophenyl ester, N-hydroxy succinimic acid imide ester or 1-
hydroxybenzotriazole ester, or into active amide such as benzoxazoline-2-thione, and then reacting this with amine (1c), (c) carbodiimide method, that is, a method of carrying out the condensation reaction of carboxylic acid (18) with amine (1c) in the presence of an activator such as dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSC) or carbonyldiimidazole, and (d) other methods including a method of converting carboxylic acid (18) into carboxylic anhydride by using a dehydrator such as acetic anhydride and reacting the carboxylic anhydride with amine (1c), a method of reacting ester of carboxylic acid (18) and lower alcohol with amine (1c) at high pressure and high temperature, and a method of reacting acid halide of carboxylic acid (18), i.e., carboxylic acid halide, with amine (1c).

The mixed acid anhydride used in (a) mixed acid anhydride method as described above is obtained by a common Schotten-Baumann reaction. The mixed acid anhydride is reacted with amine (1c) generally without subjecting to isolation, so as to produce the compound of the present invention represented by general formula (1f).

The above Schotten-Baumann reaction is carried out in the presence of a basic compound.

Compounds that are commonly used for the Schotten-Baumann reaction can be used herein as basic compounds. Examples of such a basic compound include:
organic bases such as triethylamine, trimethylamine, pyridine, dimethylaniline, N-ethyldiisopropylamine, dimethylaminopyridine, N-methylmorpholine, 1,5-diaza[4.3.0]nonene-5 (DBN), 1,8-
5 diaza[5.4.0]undecene-7 (DBU) or 1,4-
diaza[2.2.2]octane (DABCO); inorganic bases including carbonates such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate or potassium hydrogen carbonate, metal hydroxides such as sodium hydroxide, potassium hydroxide or calcium hydroxide, potassium hydride, sodium hydride, potassium, sodium, sodium amide, and metal alcohohlates such as sodium methyleate or sodium ethylate.

The reaction is carried out generally at -20°C to 100°C, and preferably at 0°C to 50°C. The reaction time is generally 5 minutes to 10 hours, and preferably 5 minutes to 2 hours.

The reaction of the obtained mixed acid anhydride with amine (Ic) is carried out generally at -20°C to 150°C, and preferably at 10°C to 50°C. The reaction time is generally 5 minutes to 10 hours, and preferably 5 minutes to 5 hours. The mixed acid anhydride method is generally carried out in a solvent.

Any solvent that is commonly used for the mixed acid anhydride method can be used herein. Examples of such a solvent include halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane or carbon tetrachloride, aromatic
hydrocarbons such as benzene, toluene or xylene, ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran or dimethoxyethane, esters such as methyl acetate, ethyl acetate or isopropyl acetate, aprotic polar solvents such as N,N-dimethylacetamide, N,N-dimethylformamide, dimethylsulfoxide or hexamethylphosphoric acid triamide, and mixed solvents thereof.

Examples of alkyl haloformate used for the mixed acid anhydride method include methyl chloroformate, methyl bromoformate, ethyl chloroformate, ethyl bromoformate, and isobutyl chloroformate. The molar ratio among carboxylic acid (18), alkyl haloformate and amine (1c) may be generally equal to 1:1. Each of alkyl haloformate and carboxylic acid (18) can also be used to amine (1c) within the molar range between 1:1 and 1.5:1.

The above method (c) involving the condensation reaction in the presence of the above activator is carried out in an appropriate solvent in the presence or absence of a basic compound.

As a solvent and a basic compound used herein, any solvent used in the reaction of carboxylic acid halide with amine (1c) described as above in (d) other methods can be used.

The molar ratio of the activator to the compound (1c) may be at least equal to 1:1, and preferably between 1:1 and 5:1. When WSC is used as an
activator, the reaction advantageously proceeds if 1-hydroxybenzotriazole is added into the reaction system.

The reaction is carried out generally at -20°C to 180°C, and preferably at 0°C to 150°C. The reaction time is generally 5 minutes to 90 hours.

When the method of reacting carboxylic acid halide with amine (1c) is adopted from (d) other methods described above, the reaction is carried out in the presence of a basic compound in an appropriate solvent.

Known basic compounds can be widely used herein. For example, any basic compound used in the above Schotten-Baumann reaction can be used.

Examples of the used solvent may include alcohols such as methanol, ethanol, isopropanol, propanol, butanol, 3-methoxy-1-butanol, ethyl cellosolve or methyl cellosolve, acetonitrile, pyridine, acetone, water, as well as solvents used for the above mixed acid anhydride method.

The molar ratio of amine (1c) to carboxylic acid halide is not particularly limited, but it may be appropriately selected from a wide range. The molar ratio of these compounds may be generally at least equal to 1:1, and preferably between 1:1 and 1:5.

The reaction is carried out generally at -20°C to 180°C, and preferably at 0°C to 150°C. The reaction time is generally 5 minutes to 50 hours.

The above amide bond formation reaction can
also be carried out by reacting carboxylic acid (18) with amine (1c) in the presence of a phosphorus condensing agent such as diphenylphosphinic chloride, phenyl-N-phenyl phosphoramidite chloridate, diethyl chlorophosphate, diethyl cyanophosphate, azide diphenyl phosphate, or bis(2-oxo-3-oxazolidinyl)phosphinic chloride.

This reaction is carried out in the presence of a solvent and a basic compound that are used for the above method of reacting carboxylic acid halide with amine (1c), generally at -20°C to 150°C, and preferably at 0°C to 100°C. The reaction time is generally 5 minutes to 30 hours. Each of the condensing agent and the carboxylic acid (18) is used to amine (1c) at a molar ratio of at least equal to 1:1, and preferably between 1:1 and 2:1.

The reaction of the compound (1c) with the compound (19) can be carried out under the same conditions for the reaction of the compound (15) with the compound (16) or (17) represented by the above reaction scheme 9.
Reaction Scheme 11

(wherein \( R^{1a} \), \( X \), \( n \), \( m \), \( W \), \( R^{1b} \), \( R^p \), \( R^{10} \) and \( o \) are the same as above. \( R^{9b} \) represents a C1-6 alkoxy carbonyl group. The dotted line on the piperidine ring represents a bond which may be a double bond. When the dotted line is a double bond, a group \( R^{9b} \), COOH or \(-CON \) R^9 R^{10} should be substituted.).

A compound (21) is produced by hydrolyzing a
compound (20).

The hydrolysis reaction is conducted in an appropriate solvent or without a solvent in the presence of an acid or basic compound.

The solvent used may include, for example, water, lower alcohols such as methanol, ethanol, isopropanol or tert-butanol, ketones such as acetone or methylethyl ketone, ethers such as diethyl ether, dioxane, tetrahydrofuran, monoglyme or diglyme, aliphatic acids such as acetic acid or formic acid, esters such as ethyl acetate or methyl acetate, halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane or carbon tetrachloride, dimethylsulfoxide, N,N-
dimethylformamide, hexamethylphosphoric triamide or mixed solvents thereof.

The acid may include, for example, mineral acids such as hydrochloric acid, sulfuric acid or hydrobromic acid, organic acids such as formic acid, acetic acid, trifluoroacetic acid, or sulfonic acids such as p-toluenesulfonic acid.

The basic compound may include, for example, carbonates such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate or potassium hydrogen carbonate, metal hydroxides such as sodium hydroxide, potassium hydroxide, calcium hydroxide or lithium hydroxide, or the like.

The acid or basic compound is used at its
molar ratio to the compound (20) of at least 1:1, and preferably between 1:1 and 10:1, or may be used in large excess as a reaction solvent.

The reaction proceeds generally at about 0-5 200°C, preferably at about 0-150°C and is generally completed in about 10 minutes to 30 hours.

After the above described hydrolysis treatment, a further treatment may be performed in about 1-30 minutes usually at 0-100°C, preferably at room temperature to around 70°C in an appropriate solvent in the presence of a basic compound to complete the reaction. A solvent and basic compound used herein may use any solvent and basic compound which is used in the method wherein the carboxylic acid halide is reacted with the amine (1c) of the method (d) among reactions of the compound (1c) with the compound (19) in the above described Reaction Scheme 10.

The reaction of the compound (21) with the compound (22) is performed under the reaction conditions similar to those of the reaction of the compound (1c) with the compound (19) in the above described Reaction Scheme 10. The amount of the carboxylic acid (19) was based on the amine (1c) in the above described Reaction Scheme 10, while the amount of the amine (22) is based on the carboxylic acid (19) in the present reaction.

Reaction Scheme 12
The reaction of a compound (1i) with a compound (23) is performed under the reaction conditions similar to those of the reaction of the compound (1c) with the compound (17) in the above described Reaction Scheme 10.
(wherein $R^{1A}$, $n$, $R^{1B}$, $X$, $m$, $W$, $o$, $R^t$ and $X^t$ are the same as above.)

$R^{1AB}$ represents a Cl-6 alkoxy carbonyl group.

$R^{2AB}$ represents: a Cl-6 alkyl group; phenyl group (which may be substituted with at least one of groups selected from the group consisting of a Cl-4 alkylenediokxy group, cyano group, nitro group, amino group which may have a Cl-6 alkyl group as a substituent, amino-substituted sulfanyl group which may have a Cl-6 alkyl group as a substituent, Cl-6 alkoxy carbonyl group, Cl-6 alkylthio group, phenoxy group, phenyl Cl-6 alkoxy group, pyrrolidinyl group (which may be substituted with at least one oxo group on the pyrrolidine ring), imidazolyl group, isoioxazolyl group, oxazolyl group, phenyl Cl-6 alkyl group, phenyl group, amino Cl-6 alkyl group which may have a Cl-6 alkyl group as a substituent, pyrrolidinyl Cl-6 alkoxy group, halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring); phenyl Cl-6 alkoxy carbonyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring); benzofuryl Cl-6 alkyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or
unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the benzofuran ring); benzofuryl C2-6 alkenyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the benzofuran ring); phenoxy Cl-6 alkyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring); thiazolyl Cl-6 alkyl group (which may be substituted with at least one phenyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring) on the thiazole ring); phenyl Cl-6 alkyl group (which may be substituted with at least one phenyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring), halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring); pyridyl Cl-6
alkyl group (which may be substituted with at least one phenyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring); Cl-6 alkoxy group on the pyridine ring); Cl-6 alkoxy carbonyl group; benzothiienyl group; benzothiienyl Cl-6 alkyl group (which may be substituted with at least one halogen atom on the benzothiophene ring); indolyl Cl-6 alkyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the indole ring); 4H-1,3-benzodioxinyl group (wherein, on the 4H-1,3-benzodioxine ring, at least one halogen atom may be substituted); naphthyl group; quinoyl group; benzochiazolyl group (which may be substituted with at least one Cl-6 alkyl group on the benzothiazole ring); 2,3-dihydro-1H-iridinyl group (which may be substituted with at least one oxo group on the 2,3-dihydro-1H-indane ring); 9H-fluorenyl group or phenyl C2-6 alkenyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring).

\( R^6 \) represents a benzoyl group (which may be
substituted with at least one of groups selected from
the group consisting of a halogen atom, halogen-
substituted or unsubstituted Cl-6 alkyl group and
halogen-substituted or unsubstituted Cl-6 alkoxy group
on the phenyl ring), halogen atom, halogen-substituted
or unsubstituted Cl-6 alkyl group and halogen-
substituted or unsubstituted Cl-6 alkoxy group on the
phenyl ring).

R^a represents: a hydrogen atom; phenyl group
(which may be substituted with at least one of groups
selected from a phenyl group (which may be substituted
with at least one of groups selected from the group
consisting of a halogen atom, halogen-substituted or
unsubstituted Cl-6 alkyl group and halogen-substituted
or unsubstituted Cl-6 alkoxy group on the phenyl ring),
a halogen atom, halogen-substituted or unsubstituted
Cl-6 alkyl group and halogen-substituted or
unsubstituted Cl-6 alkoxy group on the phenyl ring);
benzofuryl Cl-6 alkyl group (which may be substituted
with at least one of groups selected from the group
consisting of a halogen atom, halogen-substituted or
unsubstituted Cl-6 alkyl group and halogen-substituted
or unsubstituted Cl-6 alkoxy group on the benzofuran
ring); benzofuryl group (which may be substituted with
at least one of groups selected from the group
consisting of a halogen atom, halogen-substituted or
unsubstituted Cl-6 alkyl group and halogen-substituted
or unsubstituted Cl-6 alkoxy group on the benzofuran
ring); phenoxy C1-6 alkyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted C1-6 alkyl group and halogen-substituted or unsubstituted C1-6 alkoxy group on the phenyl ring); thiazolyl C1-6 alkyl group (which may be substituted with at least one phenyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted C1-6 alkyl group and halogen-substituted or unsubstituted C1-6 alkoxy group on the phenyl ring) on the thiazole ring); thiazolyl group (which may be substituted with at least one phenyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted C1-6 alkyl group and halogen-substituted or unsubstituted C1-6 alkoxy group on the phenyl ring) on the thiazole ring); phenyl C1-6 alkyl group (which may be substituted with at least one of groups selected from a phenyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted C1-6 alkyl group and halogen-substituted or unsubstituted C1-6 alkoxy group on the phenyl ring), halogen atom, halogen-substituted or unsubstituted C1-6 alkyl group and halogen-substituted or unsubstituted C1-6 alkoxy group on the phenyl ring); pyridyl C1-6
alkyl group (which may be substituted with at least one phenyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring); benzothienyl Cl-6 alkyl group (at least one halogen atom may be substituted on the benzothiophene ring); indolyl Cl-6 alkyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the indole ring); pyridyl group (which may be substituted with at least one phenyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring) on the pyridine ring); benzothienyl group (at least one halogen atom may be substituted on the benzothiophene ring); or indolyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the indole ring).

\( R^6 \) represents a phenyl group (which may be
substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alky1 group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring).

The total number of carbons of the group-CHR"R" in general formula (10) should not exceed 6. A reaction to lead from a compound (1k) into a compound (11) is performed under the reaction conditions similar to those of the reaction to lead from the compound (20) into the compound (21) in the above described Reaction Scheme 11.

A reaction of the compound (11) with a compound (24) is carried out under the reaction conditions similar to those of the reaction of the compound (1c) with the compound (17) in the above described Reaction Scheme 10.

A reaction of the compound (11) with a compound (25) is carried out under the reaction conditions similar to those of the reaction of the compound (1c) with the compound (13) in the above described Reaction Scheme 10.

A reaction of the compound (11) with a compound (26) is carried out under the reaction conditions similar to those of the reaction of the compound (1c) with the compound (16) in the above described Reaction Scheme 10.

A reaction of the compound (11) with a
compound (27) is carried out under the reaction conditions similar to those of the reaction of the compound (1c) with the compound (19) in the above described Reaction Scheme 10.

Reaction Scheme 14

\[
\begin{align*}
\text{(1q)} \\
\text{R}^{5f}\text{OH (35)} \\
\text{(1r)}
\end{align*}
\]

5 (wherein \( R^{1A}, n, X, m, W, 0 \) and \( R^4 \) are the same as above. \( R^{5f} \) represents a Cl-6 alkyl group or phenyl Cl-6 alkyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted Cl-6 alkyl group and halogen-substituted or unsubstituted Cl-6 alkoxy group on the phenyl ring).)

The reaction of a compound (1q) with the compound (26) is conducted in appropriate solvent in
the presence of a condensation agent.

Solvents used herein can use any solvent which is used in the method wherein the carboxylic acid halide is reacted with the amine (1c) of other methods (d) of reactions of the compound (1c) with the compound (18) in the above described Reaction Scheme 10.

A condensation agent may include, for example, N,N'-carbonyldiimidazole or the like. The molar ratio of the compound (26) and condensation agent used to the compound (1g) may be at least, preferably between about 1:1 and 2:1. The reaction is carried out generally at 0-150°C, preferably around 0-100°C and completed in about 1-30 hours.

Reaction Scheme 15

![Chemical Structure](attachment:image.png)

(27)

(28)

(1s)

(wherin R^{1A}, n, X, m, W, o, R^9 and R^{10} are the same as above.)
A reaction of the compound (27) with a compound (28) is carried out under reaction conditions similar to those of the reaction of the compound (1c) with the compound (16) in the above described Reaction Scheme 10.

Reaction Scheme 16

(1t) -> (1u)

R^{93}OH (29) -> (1v)

(wherewith R^{1A}, n, X, m, W, o, R^{7a} and R^{10a} are the same as
above. Two Ws in general formulas (1t)-(1v) may be same or different. R⁹ represents a C1-6 alkoxy carbonyl group. The dotted line on the piperidine ring represents a bond which may be a double bond. When the dotted line is a double bond, a group -(W)ONR⁹′R¹⁰′, group -(W)ONHR¹⁰ or group -(W)ONR¹⁰(COOR⁹) should be substituted. R⁹ represents a C1-6 alkyl group or phenyl C1-6 alkyl group (which may be substituted with at least one of groups selected from the group consisting of a halogen atom, halogen-substituted or unsubstituted C1-6 alkyl group and halogen-substituted or unsubstituted C1-6 alkoxy group on the phenyl ring).

A reaction to lead from the compound (1t) into the compound (1u) is carried out under reaction conditions similar to those of the reaction to lead from the compound (20) into the compound (21) in the above described Reaction Scheme 11.

A reaction of the compound (1u) with the compound (23) is carried out under reaction conditions similar to those of the reaction of the compound (1q) with the compound (26) in the above described Reaction Scheme 14.

The starting compound (14) in Reaction Scheme 9 and the starting compound (20) in Reaction Scheme 11 are new compounds. These compounds are readily manufactured, for example, according to the above Reaction Schemes 1 to 3 using the corresponding starting materials.
The compounds (final compounds) represented by general formula (1) of the present invention and intermediates obtained in the above described each Reaction Scheme embrace stereoisomers and optical isomers.

Each target compound obtained in the above described each Reaction Scheme can be isolated and purified from the reaction mixture, for example, by isolating crude reaction products by isolation operations such as filtration, concentration and extraction after cooling, followed by usual purification operations such as column chromatography and recrystallization.

The compound of the present invention includes a pharmaceutically acceptable salt of the compounds of the formula (1). Examples of such a salt include inorganic salts such as hydrochloride, hydrobromide, nitrate, sulfate or phosphate, and organic salts such as methanesulfonate, p-toluenesulfonate, acetate, citrate, tartrate, maleate, fumarate, maleate or lactate.

Next, a medical preparation containing the compound of the present invention as an active ingredient will be explained.

The above medical preparation is obtained by preparing the compound of the present invention in the form of a common medical preparation. It is prepared using commonly used diluents or excipients such as a
filler, expander, binder, wetting agent, disintegrator, surfactant or lubricant.

Such a medical preparation can be selected from among various forms, depending on therapeutic purposes. Typical examples of a preparation form include a tablet, pill, powder, liquid, suspension, emulsion, granule, capsule, suppository, and injection (liquid, suspension, etc.)

Known carriers can be widely used in making the medical preparation in a tablet form. Examples of such a carrier include excipients such as lactose, sucrose, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, or crystalline cellulose; binders such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethylcellulose, shellac, methylcellulose, potassium phosphate or polyvinylpyrrolidone; disintegrators such as dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogencarbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, monoglyceride stearate, starch or lactose; disintegration controllers such as sucrose, stearin, cacao butter or hydrogenated oil; absorption enhancers such as quaternary ammonium base or sodium lauryl sulfate, humectants such as glycerin or starch, adsorbents such as starch, lactose, kaolin, bentonite or colloidal silica, and lubricants such as purified
talc, stearate, boric acid powder or polyethylene glycol.

Moreover, such tablets can be prepared as tablets with common tablet coating, such as a sugar coated tablet, gelatin coated tablet, enteric coated tablet, film coated tablet, double coated tablet, or multi-coated tablet.

Known carriers can be widely used in making the medical preparation in a pill form. Examples of such a carrier include excipients such as glucose, lactose, starch, cacao butter, hydrogenated vegetable oil, kaoline or talc, binders such as gum arabic powder, tragacanth powder, gelatin or ethanol, and disintegrators such as laminaran or agar.

Known carriers can be widely used in making the medical preparation in a suppository form. Examples of such a carrier include polyethylene glycol, cacao butter, higher alcohol, higher alcohol esters, gelatin, and semisynthetic glyceride.

In a case where the medical preparation is prepared as an injection such as a liquid, emulsion or suspension, these solutions are preferably sterilized and prepared to be isotonic to blood. Known diluents can be widely used in making the medical preparation in such a liquid, emulsion or suspension form. Examples of such a diluent include water, ethanol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, and polyoxylethylene sorbitan fatty
acid esters. Moreover, in the case of using the medical preparation as an injection, a certain amount of common salts, glucose or glycerin that is sufficient to prepare an isotonic solution may be added to the medical preparation. Otherwise, a common solubilizing agent, buffer, soothing agent or the like may also be added to the medical preparation. Further, a coloring agent, preservative, perfume, flavor, sweetening agent or other pharmaceuticals may also be added thereto, if necessary.

The amount of the compound of the present invention contained in the medical preparation is not particularly limited, but it can be appropriately selected from a wide range. Generally, 1 to 70% by weight of the compound of the present invention is preferably contained in the medical preparation.

The method of administering the medical preparation of the present invention is not particularly limited. It is administered depending on various preparation forms, patients' age, sex, conditions of disease, or other conditions. For example, where the medical preparation adopts a tablet, pill, liquid, suspension, emulsion, granule or capsule form, it is administered orally. In the case of an injection, it can be administered intravenously, singly or in combination with a common auxiliary fluid such as glucose or amino acid. Moreover, if necessary, it can be singly administered intramuscularly, intradermally,
subcutaneously or intraperitoneally. In the case of a suppository, it can be administered intrarectally.

The dose of the above medical preparation may be appropriately selected depending on usage, patients' age, sex, level of disease, or other conditions. Generally 0.01 to 100 mg, preferably 0.1 to 50 mg per kg of body weight of the medical preparation is administered once or divided into several times per day.

Since the above dose is altered depending on various conditions, the dose smaller than the above range may be sufficient in some cases, or the dose greater than the above range may be required in other cases.

The compound of the present invention has a specific effect against Mycobacterium tuberculosis such as acid-fast bacteria (Mycobacterium, atypical acid-fast bacteria). The compound of the present invention has an excellent effect against multi-drug-resistant Mycobacterium tuberculosis. The compound of the present invention has an antimicrobial action against anaerobic bacteria.

The compound of the present invention does not only show the above described activities in vitro, but it also expresses the above activities in oral administration.

The compound of the present invention does not induce diarrhea, which is induced by known
antimicrobial agents having a wide spectrum for common bacteria such as Gram-positive bacteria or Gram-negative bacteria. In addition, it has lesser adverse reactions than existing agents. Accordingly, it can be a medical preparation, which can be administered for a long time.

The compound of the present invention can be distributed well in the tissues of the lung, the main organ that is infected by acid-fast bacteria, and it has properties such as sustained efficacy or excellent safety. Accordingly, a high therapeutic effect can be expected from the compound.

When compared with existing antitubercular agents, the compound of the present invention shows a strong bactericidal action even towards cytozoic bacteria such as Mycobacterium tuberculosis present in a human macrophage. Accordingly, it enables a reduction of reoccurrence rate of tuberculosis and the realization of a short-term chemotherapy. It is therefore expected that the compound of the present invention will also be used as a main preventive agent administered for a mixed infection by HIV and tuberculosis, which is considered to be a serious problem.

25 EXAMPLES

Formulation Example, Text Examples, Reference Examples and Examples will be described below.
Formulation Example 1

100 g of a compound of the invention, 40 g of Avicel (trade name, manufactured by Asahi Kasei Corporation), 30 g of corn starch and 2 g of magnesium stearate were mixed and ground, and then formed into tablets with a pestle of sugarcoat R10 mm.

A film coating agent containing 10 g of TC-5 (trade name, hydroxypropyl methylcellulose, manufactured by Shin-Etsu Chemical Co., Ltd.), 3 g of polyethylene glycol 6000, 40 g of castor oil and an appropriate amount of ethanol was used to coat the obtained tablets, producing a film-coated tablet having the composition described above.

Reference Example 1

Preparation of 1-(4-(tetrahydropyran-2-yloxy)phenyl)-4-(N-(4-chlorophenyl)-N-methylamino)piperidine

4-(N-(4-chlorophenyl)-N-methylamino)piperidine (2.52 g, 11.22 mmol), 2-(4-bromophenoxy)tetrahydropyran (2.89 g, 11.22 mmol), palladium acetate (50 mg, 0.22 mmol), (S)-(−)-2,2-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) (212 mg, 0.34 mmol) and tert-butoxy sodium (1.51 g, 15.71 mmol) were refluxed with heating in toluene (30 ml) under nitrogen atmosphere for 3 hours. Ethyl acetate and water were added into the reaction solution and stirred, then the resulting precipitate was removed by filtration through Celite, thereafter the filtrate was extracted with ethyl acetate. The organic phase was washed with saturated
brine, dried over magnesium sulfate, and then filtered. After the resulting filtrate was concentrated under reduced pressure, the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 20/1) to afford 1-(4-(tetrahydropyran-2-yloxy)phenyl)-4-(N-(4-chlorophenyl)-N-methylamino)piperidine (1.33 g, yield 30%) as a light yellow powder. 

$^1$H NMR (CDCl$_3$) δ ppm:

1.50 - 2.04 (10H, m), 2.68 - 2.80 (2H, m), 2.78 (3H, s), 3.50 - 3.70 (4H, m), 3.85 - 4.03 (1H, m), 5.31 (1H, t, J = 5.7 Hz), 6.72 (2H, d, J = 9.1 Hz), 6.90 (2H, d, J = 9.2 Hz), 6.98 (2H, d, J = 9.2 Hz), 7.17 (2H, d, J = 9.1 Hz).

Reference Example 2

Preparation of 4-(4-(N-(4-chlorophenyl)-N-methylamino)piperidine-1-yl)phenol

1-(4-(Tetrahydropyran-2-yloxy)phenyl)-4-(N-(4-chlorophenyl)-N-methylamino)piperidine (1.33 g, 3.32 mmol) was suspended in ethanol (80 ml). To this mixture, pyridinium p-toluenesulfonate (0.25 g, 1 mmol) was added and then stirred at 70°C for 8 hours. Ethanol was removed under reduced pressure, then to this residue, methylene chloride and a saturated aqueous sodium hydrogen carbonate solution were added and stirred. This was extracted with methylene chloride, dried over magnesium sulfate and then filtered. After the resulting filtrate was concentrated under reduced pressure, methylene chloride and n-hexane were added to
the residue and the resulting precipitate was filtered to afford 4-[(4-N-(4-chlorophenyl)-N-methylamino)piperidine-1-yl]phenol (922.5 mg, yield 88%) as a light pink powder.

5 \(^1\text{H}-\text{NMR (CDCl}_3\text{)}\) ppm:
1.79 - 2.04 (4H, m), 2.67 - 2.79 (2H, m), 2.79 (3H, s), 3.56 - 3.68 (2H, m), 4.48 (1H, s), 6.69 - 6.80 (4H, m), 6.85 - 6.92 (2H, m), 7.14 - 7.21 (2H, m).

The following compounds were prepared similarly to Reference Examples 1 and 2. In the following table, Ph means a phenyl group or phenylene group.

Reference Example 3

(4-Chlorophenyl)-(4-hydroxyphenyl)methanone O-methyloxime

Ms: 261 (M').

Reference Example 4

(4-Hydroxyphenyl)-(4-trifluoromethylphenyl)methanone O-methyloxime

Ms: 295 (M').
[Table 1]

<table>
<thead>
<tr>
<th>Reference Example</th>
<th>RI</th>
<th>( ^1{H} ) NMR (CDCl₃) δ</th>
<th>PMR or MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 ( \text{CH}_2 \text{CH}_2 \text{NH} )</td>
<td>4.63 (1H, brs), 6.74 (2H, d, J=8.0 Hz), 6.87 (2H, d, J=9.0 Hz), 7.27-7.36 (5H, m)</td>
<td>( ^1{H} ) NMR (CDCl₃) δ 1.79 - 1.85 (2H, m), 2.04 - 2.06 (2H, m), 2.77 - 2.87 (2H, m), 3.33 - 3.41 (2H, m), 3.52 - 3.56 (2H, m), 4.58 (2H, s)</td>
<td></td>
</tr>
<tr>
<td>6 4-CF₃OPhCH₂⁻</td>
<td>( ^1{H} ) NMR (CDCl₃) δ 1.67 - 1.90 (2H, m), 2.00 - 2.10 (2H, m), 2.84 (2H, m), 3.33 - 3.42 (2H, m), 3.51 - 3.60 (1H, m), 4.53 (1H, brs), 4.63 (2H, d, J=6.74 Hz), 6.74 (2H, d, J=9.0 Hz), 6.87 (2H, d, J=9.0 Hz), 7.46 (2H, d, J=8.1 Hz), 7.60 (2H, d, J=8.1 Hz)</td>
<td>( ^1{H} ) NMR (CDCl₃) δ 1.71 - 1.93 (2H, m), 1.95 - 2.15 (2H, m), 2.71 - 2.93 (2H, m), 3.26 - 3.48 (2H, m), 3.46 - 3.58 (1H, m), 4.36 (1H, s), 4.57 (2H, d, J=8.74 Hz), 6.37 (2H, d, J=8.5 Hz), 7.18 (2H, d, J=8.0 Hz), 7.36 (2H, d, J=8.0 Hz)</td>
<td></td>
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<tr>
<td>7 4-CF₃OPhCH₂⁻</td>
<td>( ^1{H} ) NMR (CDCl₃) δ 1.67 - 1.90 (2H, m), 2.00 - 2.10 (2H, m), 2.72 - 2.90 (2H, m), 3.26 - 3.48 (2H, m), 3.44 - 3.63 (1H, m), 4.41 (1H, br, broad s), 4.54 (2H, s), 6.74 (2H, d, J=9.0 Hz), 6.87 (2H, d, J=9.0 Hz), 7.20 - 7.33 (4H, m)</td>
<td>( ^1{H} ) NMR (CDCl₃) δ 1.71 - 1.93 (2H, m), 1.93 - 2.18 (2H, m), 2.70 - 2.83 (2H, m), 3.22 - 3.45 (2H, m), 3.46 - 3.63 (1H, m), 4.52 (2H, s), 4.85 (1H, brs), 5.70 (2H, d, J=9.0 Hz), 5.82 (2H, d, J=8.0 Hz), 7.19 (1H, dd, J=8.3 Hz, 2.0 Hz), 7.41 (1H, d, J=8.2 Hz), 7.46 (1H, d, J=8.1 Hz)</td>
<td></td>
</tr>
<tr>
<td>8 4-OPhCH₂⁻</td>
<td>( ^1{H} ) NMR (CDCl₃) δ 1.67 - 1.90 (2H, m), 2.00 - 2.10 (2H, m), 2.72 - 2.90 (2H, m), 3.26 - 3.48 (2H, m), 3.44 - 3.63 (1H, m), 4.41 (1H, br, broad s), 4.54 (2H, s), 6.74 (2H, d, J=9.0 Hz), 6.87 (2H, d, J=9.0 Hz), 7.20 - 7.33 (4H, m)</td>
<td>( ^1{H} ) NMR (CDCl₃) δ 1.71 - 1.93 (2H, m), 1.93 - 2.18 (2H, m), 2.70 - 2.83 (2H, m), 3.22 - 3.45 (2H, m), 3.46 - 3.63 (1H, m), 4.52 (2H, s), 4.85 (1H, brs), 5.70 (2H, d, J=9.0 Hz), 5.82 (2H, d, J=8.0 Hz), 7.19 (1H, dd, J=8.3 Hz, 2.0 Hz), 7.41 (1H, d, J=8.2 Hz), 7.46 (1H, d, J=8.1 Hz)</td>
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<tr>
<td>9 3,4-OPhCH₂⁻</td>
<td>( ^1{H} ) NMR (CDCl₃) δ 1.67 - 1.90 (2H, m), 2.00 - 2.10 (2H, m), 2.72 - 2.90 (2H, m), 3.26 - 3.48 (2H, m), 3.44 - 3.63 (1H, m), 4.41 (1H, br, broad s), 4.54 (2H, s), 6.74 (2H, d, J=9.0 Hz), 6.87 (2H, d, J=9.0 Hz), 7.19 (1H, dd, J=8.3 Hz, 2.0 Hz), 7.41 (1H, d, J=8.2 Hz), 7.46 (1H, d, J=8.1 Hz)</td>
<td>( ^1{H} ) NMR (CDCl₃) δ 1.71 - 1.93 (2H, m), 1.93 - 2.18 (2H, m), 2.70 - 2.83 (2H, m), 3.22 - 3.45 (2H, m), 3.46 - 3.63 (1H, m), 4.52 (2H, s), 4.85 (1H, brs), 5.70 (2H, d, J=9.0 Hz), 5.82 (2H, d, J=8.0 Hz), 7.19 (1H, dd, J=8.3 Hz, 2.0 Hz), 7.41 (1H, d, J=8.2 Hz), 7.46 (1H, d, J=8.1 Hz)</td>
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<tr>
<td>10 4-CF₃OPhCH₂⁻</td>
<td>Ms 381 (1H)</td>
<td>Ms 381 (1H)</td>
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<tr>
<td>11 4-CF₃OPhCH₂⁻</td>
<td>Ms 393 (1H)</td>
<td>Ms 393 (1H)</td>
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</tr>
<tr>
<td>12 4-CF₃OPhCH₂⁻</td>
<td>Ms 395 (1H)</td>
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**Table 2**

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<th>R1</th>
<th>R2</th>
<th>NMR or MS</th>
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<td>13</td>
<td>4-ClPh-</td>
<td>-CH₃</td>
<td>H NMR (CDCl₃) δ 7.74-2.06 (4H, m), 2.87-2.75 (2H, m), 7.06 (4H, d, J=8.04 Hz), 7.62 (4H, d, J=8.04 Hz), 5.88 (2H, m).</td>
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<td>14</td>
<td>4-OTfPh-</td>
<td>-H</td>
<td>H NMR (CDCl₃) δ 1.56-7.21 (8H, m), 7.23-2.06 (2H, m), 7.76 (4H, d, J=8.04 Hz), 7.60-2.75 (2H, m), 7.02 (4H, d, J=8.04 Hz), 7.62 (4H, d, J=8.04 Hz).</td>
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<tr>
<td>15</td>
<td>CH₂CH₂H</td>
<td>-H</td>
<td>H NMR (CDCl₃) δ 1.29-2.41 (3H, m), 2.51-2.06 (3H, m), 7.06 (4H, d, J=8.04 Hz), 7.62 (4H, d, J=8.04 Hz).</td>
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<td>16</td>
<td>4-CF₃CH₂-</td>
<td>-H</td>
<td>H NMR (CDCl₃) δ 0.91-1.18 (6H, m), 1.84-2.11 (2H, m), 2.51-2.74 (4H, m), 3.38-3.57 (2H, m), 7.33 (2H, d, J=8.04 Hz), 7.65-2.75 (2H, m), 7.00-7.41 (4H, m).</td>
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<td>17</td>
<td>3.4-ClPhCH₂-</td>
<td>-H</td>
<td>H NMR (CDCl₃) δ 7.14-1.70 (2H, m), 1.84-2.11 (2H, m), 7.06 (4H, d, J=8.04 Hz), 7.62 (4H, d, J=8.04 Hz), 5.88 (2H, m), 7.02 (4H, d, J=8.04 Hz), 7.62 (4H, d, J=8.04 Hz).</td>
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<td>18</td>
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<td>-H</td>
<td>H NMR (CDCl₃) δ 0.86-2.06 (4H, m), 2.40-2.83 (2H, m), 3.33-3.57 (2H, m), 3.65 (2H, d, J=8.04 Hz), 5.88 (2H, m), 6.00-6.93 (2H, m), 7.17 (2H, d, J=8.04 Hz), 7.67 (2H, d, J=8.04 Hz).</td>
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<td>19</td>
<td>4-CF₂OPhCH₂-</td>
<td>-H</td>
<td>H NMR (CDCl₃) δ 1.53-1.80 (2H, m), 2.17-2.16 (2H, m), 2.76-3.92 (2H, m), 3.33-3.57 (2H, m), 5.88 (2H, d, J=8.04 Hz), 6.00-6.93 (2H, m).</td>
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<td>20</td>
<td>4-CH₂OPh-</td>
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<td>H NMR (CDCl₃) δ 7.14-1.70 (2H, m), 1.84-2.11 (2H, m), 2.76-3.92 (2H, m), 3.33-3.57 (2H, m), 5.88 (2H, d, J=8.04 Hz), 6.00-6.93 (2H, m), 7.01-7.05 (2H, m).</td>
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<td>21</td>
<td>4-OPh-</td>
<td>-H</td>
<td>H NMR (CDCl₃) δ 1.52-1.80 (2H, m), 2.17-2.16 (2H, m), 2.76-3.92 (2H, m), 3.33-3.57 (2H, m), 6.00-6.93 (2H, m).</td>
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<tr>
<td>28</td>
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<td>Ms: 257(M+)</td>
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<td>29</td>
<td>4-CF3OPh-</td>
<td>1H NMR (CDCl3) δ 1.48 - 1.63 (2H, m), 1.87 - 1.98 (3H, m), 2.62 - 2.72 (2H, m), 3.61 - 3.57 (2H, m), 3.83 (2H, d, J=5.85Hz), 4.50 (2H, bs), 6.73 - 6.78 (2H, m), 6.84 - 6.91 (4H, m), 7.12 - 7.16 (2H, m).</td>
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<td>28</td>
<td>4-CF3OPh-</td>
<td>1H NMR (CDCl3) δ 1.36 - 1.90 (5H, m), 2.56 - 2.68 (2H, m), 3.38 (2H, d, J=6.31Hz), 3.44 - 3.53 (2H, m), 4.51 (2H, s), 4.65 (4H, brs), 6.70 - 6.77 (2H, m), 6.83 - 6.89 (2H, m), 7.17 - 7.21 (2H, m), 7.34 - 7.39 (2H, m).</td>
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<td>31</td>
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<td>1H NMR (CDCl3) δ 1.31 - 1.98 (5H, m), 2.43 - 2.77 (4H, m), 3.34 - 3.58 (2H, m), 4.57 (4H, bs), 6.69 - 6.80 (2H, m), 6.80 - 6.92 (2H, m), 7.28 (2H, d, J=7.7Hz), 7.65 (2H, d, J=8.1Hz).</td>
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<tr>
<td>36</td>
<td>4-CIFPh</td>
<td>1H NMR (CDCl3) δ 1.37 - 1.54 (2H, m), 1.58 - 1.90 (3H, m), 2.57 - 2.68 (2H, m), 3.39 (2H, d, J=6.29Hz), 3.46 - 3.52 (2H, m), 4.57 (2H, s), 5.26 (1H, s), 6.67 - 6.74 (2H, m), 6.83 - 6.89 (2H, m), 7.43 - 7.47 (2H, m), 7.59 - 7.62 (2H, m).</td>
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<td>37</td>
<td>4-CIFPh</td>
<td>1H NMR (CDCl3) δ 1.48 - 1.63 (2H, m), 1.69 - 1.98 (3H, m), 2.61 - 2.71 (2H, m), 3.51 - 3.56 (2H, m), 3.82 (2H, d, J=5.95Hz), 4.49 (1H, s), 6.73 - 6.81 (8H, m), 7.19 - 7.29 (2H, m).</td>
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<tr>
<td>38</td>
<td>4-CIFPh</td>
<td>1H NMR (CDCl3) δ 1.38 - 1.54 (2H, m), 1.64 - 1.79 (1H, m), 1.58 (2H, d, J=12.9Hz), 2.52 (2H, d, J=11.95Hz), 3.32 (2H, m), 3.34 (2H, t, J=6.27Hz), 3.52 (2H, d, J=11.98Hz), 4.60 - 4.74 (1H, brs), 4.39 - 4.55 (1H, brs), 6.60 (2H, d, J=8.55Hz), 6.75 (2H, d, J=8.59Hz), 6.87 (2H, d, J=8.69Hz), 7.40 (2H, d, J=8.65Hz).</td>
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<tr>
<td>39</td>
<td>4-CIFPh</td>
<td>1H NMR (CDCl3) δ 1.37 - 1.57 (2H, m), 1.61 - 1.77 (1H, m), 1.79 - 1.97 (2H, m), 2.52 - 2.70 (2H, m), 3.04 (2H, d, J=6.70Hz), 3.51 (2H, d, J=11.88Hz), 3.76 - 4.76 (2H, br), 6.48 - 6.53 (2H, m), 6.71 - 8.81 (2H, m), 6.83 - 8.92 (2H, m), 7.05 - 7.17 (2H, m).</td>
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<tr>
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<td>1H NMR (CDCl3) δ 1.37 - 1.81 (4H, m), 1.90 (2H, d, J=6.20Hz), 2.53 (2H, t, J=11.68Hz), 3.05 (2H, d, J=6.65Hz), 3.52 (2H, d, J=11.89Hz), 3.69 - 4.07 (1H, br), 4.18 - 4.74 (1H, br), 6.49 - 6.63 (2H, m), 6.67 - 8.92 (2H, m), 6.87 (2H, d, J=8.64Hz), 7.03 (2H, d, J=8.64Hz).</td>
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<td>41</td>
<td>4-CIFPh</td>
<td>1H NMR (DMSO) δ 1.35 - 1.45 (2H, m), 1.68 - 1.80 (3H, m), 2.46 - 2.56 (2H, m), 3.40 - 3.46 (2H, m), 4.00 (2H, d, J=5.90Hz), 6.81 - 8.65 (2H, m), 6.87 - 8.81 (2H, m), 7.31 - 7.36 (2H, m), 7.45 - 7.51 (2H, m), 7.78 (1H, s), 8.75 (1H, s).</td>
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(Table 4)

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<th>R²</th>
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<td>42</td>
<td>4-Cl-OPhCH=CHCH₂-</td>
<td>H</td>
<td>4-OF₂</td>
<td>δ 3.58 (1H, brs), 3.85 (2H, d, J=5.7Hz), 4.24 (1H, brs), 6.31 (1H, d, J=15.9, 6.7Hz), 7.36-8.82 (8H, m), 8.01-8.72 (2H, m), 7.13-7.16 (2H, m), 7.26-7.30 (2H, m).</td>
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<td>Reference Example</td>
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<td>R&lt;sub&gt;2&lt;/sub&gt;</td>
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<tr>
<td>43</td>
<td>-H</td>
<td></td>
<td>H NMR (CDCl&lt;sub&gt;3&lt;/sub&gt;)  δ 1.21 - 1.36 (2H, m), 1.48 (8H, s), 1.84 - 2.09 (2H, m), 2.78 - 3.00 (2H, brm), 3.08 - 3.25 (1H, br), 3.27 - 3.34 (1H, m), 3.87 - 4.22 (2H, br), 4.29 - 4.58 (1H, br), 5.50 - 6.58 (2H, m), 6.86 - 7.75 (2H, m)</td>
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<td>44</td>
<td>-H</td>
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<td>H NMR (CDCl&lt;sub&gt;3&lt;/sub&gt;)  δ 3.44 - 3.59 (2H, m), 2.10 (4H, d, J=1.54 Hz), 2.32 - 2.50 (2H, m), 2.14 - 2.22 (2H, br), 1.94 - 2.10 (2H, br), 3.48 - 3.57 (1H, m), 2.77 (2H, d, J=2.34 Hz), 3.30 - 4.15 - 4.33 (1H, br), 6.57 (2H, d, J=8.60 Hz), 6.97 (2H, d, J=8.60 Hz), 7.47 (2H, d, J=8.60 Hz)</td>
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<td>45</td>
<td>-H</td>
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<td>H NMR (CDCl&lt;sub&gt;3&lt;/sub&gt;)  δ 3.44 - 3.59 (2H, m), 2.07 - 2.22 (2H, m), 2.78 - 2.93 (2H, m), 3.25 - 3.40 (1H, m), 3.83 - 3.87 (2H, m), 6.52 - 6.53 (2H, m), 6.87 - 6.96 (2H, m), 6.81 - 6.91 (2H, m), 7.14 - 7.24 (2H, m)</td>
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<tr>
<td>46</td>
<td>-H</td>
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<td>H NMR (CDCl&lt;sub&gt;3&lt;/sub&gt;)  δ 1.41 - 1.60 (2H, m), 2.08 - 2.24 (2H, m), 2.63 - 2.87 (2H, m), 3.83 - 3.96 (2H, br), 3.93 - 3.84 (1H, m), 6.53 - 7.03 (2H, m), 4.16 - 4.73 (1H, br), 6.50 - 8.62 (2H, m), 6.56 - 6.77 (2H, m), 6.85 - 6.97 (2H, m), 7.03 - 7.17 (2H, m)</td>
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<td>-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Cl</td>
<td>H NMR (CDCl&lt;sub&gt;3&lt;/sub&gt;)  δ 1.70 - 1.86 (4H, br), 2.59 - 2.65 (5H, m), 3.39 - 3.58 (1H, m), 3.80 - 3.92 (2H, m), 4.34 (1H, t, J=5.32 Hz), 6.53 - 6.92 (4H, m), 7.15 - 7.21 (2H, m)</td>
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<td>-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Cl</td>
<td>H NMR (CDCl&lt;sub&gt;3&lt;/sub&gt;)  δ 1.75 - 1.92 (4H, br), 2.34 - 2.46 (5H, m), 3.37 - 3.52 (1H, m), 3.63 - 3.79 (2H, m), 4.34 (1H, t, J=5.32 Hz), 6.57 - 6.87 (4H, m), 6.87 - 6.94 (2H, m), 7.06 - 7.15 (2H, m)</td>
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<td>49</td>
<td>-OCH&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>H NMR (CDCl&lt;sub&gt;3&lt;/sub&gt;)  δ 1.05 (3H, t, J=6.94 Hz), 1.65 - 1.82 (2H, m), 2.02 - 2.10 (2H, m), 2.25 - 2.36 (2H, m), 3.04 - 3.15 (2H, br), 3.97 - 4.06 (2H, br), 3.66 - 3.80 (2H, brm), 4.42 - 4.66 (2H, br), 6.63 - 6.84 (5H, m), 7.03 - 7.15 (2H, m)</td>
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<td>H NMR (CDCl&lt;sub&gt;3&lt;/sub&gt;)  δ 2.90 (3H, d, J=5.18 Hz), 4.20 (1H, br), 6.24 (1H, d, J=16.9, 3.41 Hz), 6.55 (1H, d, J=15.9 Hz), 6.71 - 6.76 (4H, m), 7.42 - 7.44 (2H, m), 7.50 - 7.55 (2H, m)</td>
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<td>H NMR (CDCl&lt;sub&gt;3&lt;/sub&gt;)  δ 1.72 - 1.84 (4H, m), 2.77 - 2.91 (2H, m), 3.45 - 3.58 (2H, m), 3.87 (2H, d, J=12.74 Hz), 4.36 (1H, d, J=8.92 Hz), 6.82 (2H, d, J=8.59 Hz), 6.93 (2H, d, J=8.76 Hz), 7.47 (2H, d, J=8.76 Hz)</td>
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<tr>
<td>Reference Example</td>
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<tr>
<td>52</td>
<td>4-CF₃Ph-</td>
<td>¹H NMR (CDCl₃)  δ 3.96 (2H, s), 4.66 (1H, s).</td>
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</tr>
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<td>6.75-6.79 (2H, m), 7.01-7.06 (2H, m), 7.26-7.29 (2H, m), 7.51-7.54 (2H, m).</td>
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<td>¹H NMR (CDCl₃)  δ 3.87 (3H, brs), 6.74-6.76 (2H, m), 7.01-7.04 (2H, m), 7.07-7.10 (2H, m), 7.22-7.29 (2H, m).</td>
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**Table 7**

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<td>56</td>
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<td>¹H NMR (CDCl₃)  δ 1.21 (9H, t, J=7.03Hz), 1.90-1.96 (4H, m), 2.91-2.99 (2H, m), 3.37 (3H, q, J=7.00Hz), 3.74-3.83 (3H, m), 4.75 (1H, s), 6.73-6.82 (2H, m), 6.86-6.89 (2H, m), 6.98-7.04 (2H, m), 7.40-7.44 (6H, m).</td>
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<td>57</td>
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<td>¹H NMR (CDCl₃)  δ 3.33 (3H, s), 4.80 (1H, brs), 8.67-8.91 (2H, m), 6.94-7.02 (2H, m), 7.07-7.14 (4H, m), 7.42-7.51 (4H, m).</td>
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<td>¹H NMR (CDCl₃)  δ 1.66-2.02 (3H, m), 2.07-2.16 (2H, m), 3.09-3.28 (2H, m), 3.43-3.59 (2H, m), 4.41-4.50 (1H, m), F 4.74 (1H, s), 6.84-6.99 (4H, m), 6.98-7.00 (2H, m), 7.12-7.17 (2H, m), 7.40-7.49 (4H, m).</td>
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<td>59</td>
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<td>¹H NMR (CDMSO)  δ 2.62-2.68 (2H, m), 7.06-7.20 (3H, m), 7.26-7.49 (4H, m), 7.58-7.72 (6H, m), 9.52 (1H, s).</td>
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<td>60</td>
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<td>¹H NMR (CDCl₃)  δ 4.73 (1H, s), 4.88-6.53 (2H, m), 7.01-7.12 (4H, m), 7.17-7.22 (2H, m), 7.43-7.55 (4H, m).</td>
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### Table 8

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<td>62</td>
<td>4-CF₃OPhN(CH₃)₂⁻</td>
<td>224 (M⁺)</td>
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<td>63</td>
<td>4-ClPhN(CH₃)₂⁻</td>
<td>224 (M⁺)</td>
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### Table 9

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### Table 10

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<td>4-CF&lt;sub&gt;3&lt;/sub&gt;PCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;O(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CDCl&lt;sub&gt;3&lt;/sub&gt;; 1.35-1.57 (5H, m), 1.76-1.82 (2H, m), 2.55-2.66 (2H, m), 3.44-3.50 (2H, m), 3.57 (2H, t, J = 6.3Hz), 4.38 (1H, s), 4.57 (2H, s), 6.72-6.78 (2H, m), 6.84-6.89 (2H, m), 7.43-7.48 (2H, m), 7.58-7.62 (2H, m)</td>
</tr>
<tr>
<td>66</td>
<td>-H</td>
<td>4-CF&lt;sub&gt;3&lt;/sub&gt;OPhCH&lt;sub&gt;2&lt;/sub&gt;OCH&lt;sub&gt;2&lt;/sub&gt;-</td>
</tr>
<tr>
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<td>CDCl&lt;sub&gt;3&lt;/sub&gt;; 1.36-1.53 (2H, m), 1.55-1.82 (1H, m), 1.84-1.90 (2H, m), 2.56-2.67 (2H, m), 3.38 (2H, d, J = 6.3Hz), 3.44-3.63 (2H, m), 4.51 (2H, s), 4.66 (1H, bs), 6.70-6.77 (2H, m), 6.83-6.89 (2H, m), 7.17-7.21 (2H, m), 7.34-7.39 (2H, m)</td>
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<td>67</td>
<td>-H</td>
<td>4-CF&lt;sub&gt;3&lt;/sub&gt;OPhCH&lt;sub&gt;2&lt;/sub&gt;O(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
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<tr>
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<td>CDCl&lt;sub&gt;3&lt;/sub&gt;; 1.37-1.66 (5H, m), 1.76-1.81 (2H, m), 2.55-2.65 (2H, m), 3.44-3.50 (2H, m), 3.55 (2H, t, J = 6.3Hz), 4.44 (1H, s), 4.50 (2H, s), 6.72-6.78 (2H, m), 6.83-6.89 (2H, m), 7.18-7.22 (2H, m), 7.35-7.39 (2H, m)</td>
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<td>68</td>
<td>-H</td>
<td>4-FPhNH-</td>
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<td>CDCl&lt;sub&gt;3&lt;/sub&gt;; 1.51-1.66 (2H, m), 2.13-2.18 (2H, m), 2.74-2.85 (2H, m), 3.30-3.50 (4H, m), 4.50 (1H, s), 6.53-6.56 (2H, m), 6.73-6.78 (2H, m), 6.93-6.94 (4H, m)</td>
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<tr>
<td>69</td>
<td>-H</td>
<td>4-CF&lt;sub&gt;3&lt;/sub&gt;OPhNHC&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;-</td>
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<td></td>
<td>CDCl&lt;sub&gt;3&lt;/sub&gt;; 1.03 (2H, d, J=6.6Hz), 1.87 (2H, d, J=6.8Hz), 6.62-6.67 (2H, m), 6.63-6.49 (2H, m), 4.74-4.18 (1H, br), 4.07-3.89 (1H, br), 3.53 (2H, d, J=12.0Hz), 3.05 (2H, d, J=6.7Hz), 2.63 (2H, q, J=6.7Hz), 1.90 (2H, d, J=12.4Hz), 1.81-1.37 (3H, m)</td>
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<td>70</td>
<td>-H</td>
<td>4-CiPhNHCH&lt;sub&gt;2&lt;/sub&gt;-</td>
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<td>CDCl&lt;sub&gt;3&lt;/sub&gt;; 7.17-7.08 (2H, m), 8.92-8.83 (2H, m), 6.816.71 (2H, m), 6.58-6.48 (2H, m), 4.76-3.76 (2H, br), 3.51 (2H, d, J=12.0Hz), 3.04 (2H, d, J=6.7Hz), 2.702.52 (2H, m), 1.88 (2H, d, J=12.3Hz), 1.77-1.61 (1H, m), 1.57-1.37 (2H, m)</td>
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<td>71</td>
<td>-H</td>
<td>3.5-C&lt;sub&gt;6&lt;/sub&gt;PhNH-</td>
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<tr>
<td></td>
<td></td>
<td>CDCl&lt;sub&gt;3&lt;/sub&gt;; 4.48-1.64 (2H, m), 2.05-2.19 (2H, m), 2.71-2.83 (2H, m), 3.21-3.48 (3H, m), 3.75 (1H, d, J = 8.0Hz), 4.71 (1H, bs), 6.42 (2H, d, J = 1.8Hz), 3...</td>
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<tr>
<td>72</td>
<td>-H</td>
<td>4-n-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;-PhNH-</td>
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<tr>
<td></td>
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<td>CDCl&lt;sub&gt;3&lt;/sub&gt;; 0.94 (3H, t, J = 7.3Hz), 1.45-1.71 (4H, m), 2.09-2.21 (2H, m), 2.47 (2H, t, J = 7.3Hz), 2.64-2.63 (2H, m), 3.29-3.52 (3H, m), 4.83 (1H, br), 6...</td>
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### Table 11

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<th>Example</th>
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<th>NMR</th>
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<tr>
<td>76</td>
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</tbody>
</table>

**Example 73**

- R1: 
  - CDCl₃: 1.36-1.92 (10H, m), 2.56-2.63 (2H, m), 3.28 (1H, dd, J = 6.2 Hz, 9.6 Hz), 3.47-3.56 (2H, m), 3.65 (1H, dd, J = 6.6 Hz, 9.5 Hz), 3.82-3.92 (1H, m), 4.83-4.81 (1H, m), 4.76 (1H, bs), 8.76-8.78 (2H, m), 6.84-6.91 (2H, m)

**Example 74**

- R1: 
  - CDCl₃: 7.34-7.70 (4H, m), 6.85 (2H, d, J = 8.03 Hz), 6.75 (2H, d, J = 8.79 Hz), 4.50 (1H, s), 4.54-4.35 (2H, m), 3.55-3.40 (2H, m), 3.24-3.02 (2H, m), 2.86-2.44 (2H, m), 1.85-1.60 (3H, m), 1.56-1.31 (11H, m)

**Example 75**

- R1: 
  - CDCl₃: 7.36-7.24 (2H, m), 7.23-7.07 (2H, m), 6.93-6.80 (2H, m), 6.80-6.72 (2H, m), 4.53 (1H, s), 4.51-4.34 (2H, m), 3.57-3.41 (2H, m), 3.36-2.90 (2H, m), 2.67-2.46 (2H, m), 1.85-1.81 (3H, m), 1.81-1.31 (11H, m)

**Example 76**

- R1: 
  - CDCl₃: 7.59 (2H, d, J = 7.8 Hz), 7.42-7.28 (2H, m), 6.93-6.80 (2H, m), 6.75 (2H, d, J = 8.7 Hz), 4.69-4.41 (3H, m), 3.58-3.41 (2H, m), 3.26-3.02 (2H, m), 2.71-2.44 (2H, m), 1.91-1.62 (3H, m), 1.62-1.28 (11H, m)
<table>
<thead>
<tr>
<th>Reference</th>
<th>R1</th>
<th>R2</th>
<th>MS</th>
</tr>
</thead>
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<td>Example</td>
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<td></td>
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<tr>
<td>77</td>
<td>-H</td>
<td>4-CF&lt;sub&gt;3&lt;/sub&gt;OPhCH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>351 (M&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>78</td>
<td>-H</td>
<td>4-CF&lt;sub&gt;3&lt;/sub&gt;OPh(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;O-</td>
<td>395 (M&lt;sup&gt;+&lt;/sup&gt;)</td>
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<tr>
<td>79</td>
<td>-OH</td>
<td>4-CIPh&lt;sup&gt;-&lt;/sup&gt;</td>
<td>303 (M&lt;sup&gt;+&lt;/sup&gt;)</td>
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<tr>
<td>80</td>
<td>-H</td>
<td>4-CF&lt;sub&gt;3&lt;/sub&gt;OPhCH&lt;sub&gt;2&lt;/sub&gt;OCH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>364 (M-1)&lt;sup&gt;*&lt;/sup&gt;</td>
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<tr>
<td>81</td>
<td>-H</td>
<td>4-CIPhCH&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>345 (M&lt;sup&gt;+&lt;/sup&gt;)</td>
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<tr>
<td>82</td>
<td>-H</td>
<td>4-CIPhNHCO(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>374 (M&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>83</td>
<td>-H</td>
<td>4-CF&lt;sub&gt;3&lt;/sub&gt;OPh(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>365 (M&lt;sup&gt;+&lt;/sup&gt;)</td>
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<tr>
<td>84</td>
<td>-H</td>
<td>3,4-Cl&lt;sub&gt;2&lt;/sub&gt;PhNH&lt;sup&gt;-&lt;/sup&gt;</td>
<td>336 (M-1)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>85</td>
<td>-H</td>
<td>3-CF&lt;sub&gt;3&lt;/sub&gt;OPhCH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>351 (M&lt;sup&gt;+&lt;/sup&gt;)</td>
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<tr>
<td>86</td>
<td>-H</td>
<td>2-CF&lt;sub&gt;3&lt;/sub&gt;OPhCH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>351 (M&lt;sup&gt;+&lt;/sup&gt;)</td>
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</table>
[Table 13]

<table>
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<tr>
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<tr>
<td>Example</td>
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<tr>
<td>87</td>
<td>N,N,NCl</td>
<td>353 (M⁺)</td>
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<tr>
<td>88</td>
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<td>402 (M⁺)</td>
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<tr>
<td>89</td>
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<td>404 (M⁺)</td>
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<tr>
<td>90</td>
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<td>320(M-1)⁺</td>
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<tr>
<td>91</td>
<td></td>
<td>400 (M⁺)</td>
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<tr>
<td>92</td>
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<td>403 (M⁺)</td>
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**Table 14**

<table>
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<th>MS</th>
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</thead>
<tbody>
<tr>
<td>Example 93</td>
<td>404 (M²)</td>
</tr>
<tr>
<td>Example 94</td>
<td>402 (M²)</td>
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</table>

**Diagram:**
- Example 93: Structure with R1 = \(\text{R1}^3\)
- Example 94: Structure with R1 = \(\text{R1}^4\)
Table 15

<table>
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<th>MS</th>
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<tbody>
<tr>
<td>Example 95</td>
<td>409 (M⁺)</td>
</tr>
<tr>
<td>Example 96</td>
<td>410 (M⁺)</td>
</tr>
<tr>
<td>Example 97</td>
<td>408 (M⁺)</td>
</tr>
<tr>
<td>Example 98</td>
<td>261 (M⁺)</td>
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<tr>
<td>Example 99</td>
<td>387 (M⁺)</td>
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### Table 16

<table>
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<td>4-CF₃PhCH₂⁻</td>
<td>307 (M⁺)</td>
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<td>101</td>
<td>4-CF₂OPhCH₂⁻</td>
<td>323 (M⁺)</td>
</tr>
<tr>
<td>102</td>
<td>4-CIPhCH₂⁻</td>
<td>273 (M⁺)</td>
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### Table 17

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<td>103</td>
<td>4-CF₂OPhCH₂⁻</td>
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<td>104</td>
<td>4-CIPhCH₂⁻</td>
<td>237 (M⁺)</td>
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### Table 18

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<td>105</td>
<td>-Cl</td>
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<td>106</td>
<td>-H</td>
<td>211 (M⁺)</td>
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<td>Reference R1:</td>
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<tr>
<td>-------------</td>
<td>-----</td>
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<tr>
<td>CDC:3.52-3.75(1H, br), 3.86(2H, dd, J=5.7, 1.4Hz), 4.17-4.32(1H, br), 6.31(1H, td, J=15.9, 5.7Hz), 5.50-5.65(3H, m), 6.61(2H, d, J=9.9Hz), 7.15(2H, d, J=8.4Hz), 7.37(2H, d, J=8.4Hz).</td>
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<tr>
<td>(DMSO-D6): 6.72(2H, d, J=8.7Hz), 6.79(1H, d, J=15.7Hz), 7.41-7.49(4H, m), 7.55(1H, d, J=15.7), 7.73(2H, d, J=8.7Hz), 9.10-9.34(1H, br), 9.90-10.02(1H, br).</td>
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<tr>
<td>(DMSO-D6): 3.38(3H, s), 6.11-6.18(1H, br), 6.35(1H, d, J=15.5Hz), 6.93(2H, d, J=8.6Hz), 7.97-7.15(4H, m), 7.33(1H, d, J=8.6Hz), 7.63(1H, d, J=15.6Hz).</td>
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<tr>
<td>CDC:7.08(4H, d, J=8.9Hz), 8.87(4H, d, J=8.9Hz), 6.76(2H, d, J=8.9Hz), 6.65(2H, d, J=8.9Hz), 4.42-4.29(1H, br), 3.83(4H, d, J=12.2Hz), 3.14(4H, d, 6.5Hz), 2.68(4H, t, J=12.2Hz), 1.81(6H, d, J=9.8Hz), 1.44-1.27(4H, m)</td>
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<tr>
<td>CDC:7.09(2H, d, J=8.8Hz), 8.94-8.84(2H, m), 8.81-8.73(2H, m), 6.93(2H, d, J=9.8Hz), 4.28(1H, s), 3.85(2H, d, J=12.3Hz), 3.12(2H, d, J=8.8Hz), 2.90(3H, s), 2.73-2.62(2H, m), 1.93-1.75(3H, m), 1.46-1.30(2H, m)</td>
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<tr>
<td>CDC:3.19(6H, s), 4.08(1H, s), 6.74(2H, d, J=8.5Hz), 7.24(2H, d, J=8.5Hz), 7.49-7.56(4H, m)</td>
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<tr>
<td>CDC:7.40(2H, d, J=8.6Hz), 6.87(2H, d, J=8.9Hz), 6.75(2H, d, J=8.9Hz), 6.60(2H, d, J=8.6Hz), 4.48(1H, s), 4.18-4.00(1H, br), 3.52(2H, d, J=11.9Hz), 3.11(2H, t, J=8.3Hz), 2.71-2.54(2H, m), 1.89(2H, d, J=12.9Hz), 1.79-1.64(1H, m), 1.53-1.38(2H, m)</td>
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### Table 20

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<tr>
<td>114 4-CF₃PhCH=CHCH₂NH-</td>
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<td>115 4-CF₃PhCH=CHCON(C₂H₅)⁻</td>
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<tr>
<td>116 4-CF₃OPhCH₂OCONH⁻</td>
<td>327 (M⁺)</td>
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<td>117</td>
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<td>354 (M⁺)</td>
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<td>119</td>
<td>321 (M⁺)</td>
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<td>120</td>
<td>271 (M⁺)</td>
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<td>121</td>
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<td>122</td>
<td>321 (M⁺)</td>
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<tr>
<td>Example</td>
<td><img src="image" alt="Chemical Structure" /></td>
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Example 1

Preparation of (R)-2-methyl-6-nitro-2-(2-(4-(4-
trifluoromethoxybenzyl)-piperazine-1-yl)-benzothiazole-
6-yloxyethyl)-2,3-dihydroimidazo[2, 1-b]oxazole

(R)-2-Chloro-1-(2-methyl-2-oxyranylmethyl)-4-
nitro-1H-imidazole (51 mg, 0.23 mmol) and 6-hydroxy-2-
(4-(4-trifluoromethoxybenzyl)-piperazine-1-yl)-
benzothiazole (80 mg, 0.20 mmol) were dissolved in DMF
(5 ml). To this mixture, sodium hydride (10 mg, 0.25
mmol) was added and stirred at 60°C for 1.5 hours.
After allowing to stand at room temperature, water was
added to the reaction solution and extracted with ethyl
acetate. The combined organic layer was washed with
water and saturated brine, then dried over magnesium
sulfate. This was filtered and then the filtrate was
concentrated under reduced pressure. The residue was
purified by silica gel column chromatography (n-hexane:
etyl acetate = 1:3 → ethyl acetate) and recrystallized
from ethanol to afford (R)-2-methyl-6-nitro-2-(2-(4-(4-
trifluoromethoxybenzyl)-piperazine-1-yl)-benzothiazole-
6-yloxyethyl)-2,3-dihydroimidazo[2, 1-b]oxazole (49 mg,
yield 33%) as colorless powdered crystals.

Melting point: 205.6-207.4°C.

Example 2

Preparation of (R)-2-methyl-6-nitro-2-(2-(4-(4-
trifluoromethoxyphenoxy)piperidine-1-yl)pyridine-5-
oxyl)-methyl-2,3-dihydro-imidazo[2, 1-b]oxazole
5-hydroxy-2-(4-(4-trifluoromethoxy)-
phenoxypiperidine-1-yl)pyridine (0.67 g, 1.9 mmol) and (R)-2-chloro-1-[(2-methyl-2-oxacyclemethyl)-4-nitro-1H-imidazole (0.51 g, 2.4 mmol) were dissolved in DMF (6.7 ml). To this mixture, sodium hydride (91 mg, 2.3 mmol) was added and stirred at 50-55°C for 1 hour. Water was added to the reaction solution and extracted with methylene chloride. The organic layer was washed with saturated brine, dried over magnesium sulfate and then filtered under suction. The resulting filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate = 10/9, 9/1, 8/2), and further crystallized from methylene chloride/diisopropyl ether/ethyl acetate to afford (R)-2-methyl-6-nitro-2-(2-[(4-(4-trifluoromethoxyphenoxypiperidine-1-yl)pyridine-5-oxymethyl]-2,3-dihydro-imidazo[2, 1-b]oxazole (0.30 g, yield 29%) as a light yellow powder.

$^1$H-NMR (CDCl$_3$) δppm:

1.77 (3H, s), 1.80 - 1.94 (2H, m), 1.94 - 2.17 (2H, m), 3.21 - 3.44 (2H, m), 3.67 - 3.89 (2H, m), 3.96 - 4.11 (2H, m), 4.19 (1H, d, J = 10.4 Hz), 4.36 - 4.59 (2H, m), 6.65 (1H, d, J = 9.2 Hz), 6.83 - 6.97 (2H, m), 7.02 - 7.20 (3H, m), 7.56 (1H, s), 7.87 (1H, d, J = 3.0 Hz).

The following compounds were prepared similarly to the above described Example 2. In the following table, Ph means a phenyl group or phenylene group.

Example 3
(R)-2-(4-(4-N-(4-chlorophenyl)-N-methylamino)piperidine-1-yl)phenoxy)methyl)-2-methyl-6-nitro-2,3-dihydro-imidazo[2, 1-b]oxazole

Melting point: 173.7-175.1°C.

Example 4

(R)-2-methyl-6-nitro-2-(4-(4-(4-trifluoromethoxybenzyl)piperidine-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2, 1-b]oxazole

$^1$H-NMR (CDCl$_3$) δ ppm:

1.23 - 1.52 (2H, m), 1.55 - 1.65 (3H, m), 1.66 - 1.39 (3H, m), 2.43 - 2.70 (4H, m), 3.50 (2H, d, $J = 12.1$ Hz), 3.91 - 4.09 (2H, m), 4.16 (1H, d, $J = 10.1$ Hz), 4.48 (1H, d, $J = 10.2$ Hz), 6.66 - 6.81 (2H, m), 6.81 - 6.95 (2H, m), 7.05 - 7.23 (4H, m), 7.54 (1H, s).

Melting point: 210.9-212.4°C.

[$\alpha$]$_D$-9.0° (concentration: 1.0, CHCl$_3$).

Example 5

(R)-2-(4-(4-(3,4-dichlorobenzyl)piperidine-1-yl)phenoxy)methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2, 1-b]oxazole

$^1$H-NMR (CDCl$_3$) δ ppm:

1.24 - 1.52 (2H, m), 1.55 - 1.64 (4H, m), 1.64 - 1.73 (1H, m), 1.73 - 1.87 (4H, m), 2.33 - 2.68 (4H, m), 3.49 (2H, d, $J = 12.1$ Hz), 3.91 - 4.09 (2H, m), 4.16 (1H, d, $J = 10.2$ Hz), 4.49 (1H, d, $J = 10.2$ Hz), 6.67 - 6.81 (2H, m), 6.81 - 6.92 (2H, m), 6.94 - 7.07 (1H, m), 7.25 (1H, s), 7.35 (1H, d, $J = 8.2$ Hz), 7.55 (1H, s).

Melting point: 180.0-181.2°C.
$\text{[a]}_p^{\text{D}} = -8.5^\circ$ (concentration: 1.0, CHCl$_3$).

**Example 6**

(R)-6-nitro-2-(4-(4-(4-trifluoromethoxybenzyl)oxymethyl)piperidine-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2, 1-b]oxazole

Melting point: 140.4-141.7°C.

**Example 7**

(R)-2-methyl-6-nitro-2-(4-(4-(4-trifluoromethylbenzyl)oxymethyl)-piperidine-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2, 1-b]oxazole

Melting point: 172.3-172.9°C.

**Example 8**

(R)-2-methyl-6-nitro-2-(4-(4-(3-(4-trifluoromethylenyl)-2-propenyl)piperidine-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2, 1-b]oxazole

Melting point: 199.7-202°C.

**Example 9**

(R)-2-methyl-6-nitro-2-(4-(4-(2-(4-trifluoromethoxyphenoxy)ethyl)piperazine-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2, 1-b]oxazole

Melting point: 194.8-195.6°C.

**Example 10**

(R)-2-(4-(4-(N-(4-chlorophenyl)-N-ethylamino)piperidine-1-yl)phenoxy)methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2, 1-b]oxazole

Melting point: 121.4-125°C.

**Example 11**

(R)-2-(4-(4-(N-ethyl-N-(4-
trifluoromethoxyphenyl)amino)piperidine-1-yl)phenoxy)methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point: 122.5-122.8°C.

Example 12

(R)-2-[(4-((N-ethyl-N-(4-trifluoromethyl)phenyl)amino)piperidine-1-yl)phenoxy)methyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point: 105-108.5°C.

Example 13

(R)-2-[(4-((5-chlorobenzofuran-2-yl)methyl)piperidine-1-yl)phenoxy)methyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Melting point: 210.6-211.6°C.

Example 14

(R)-2-methyl-6-nitro-2-(2-(4-(4-trifluoromethoxybenzyl)piperidine-1-yl)benzothiazole-6-yloxymethyl)-2,3-dihydroimidazo[2,1-b]oxazole

Melting point: 203.9-205.2°C.

Example 15

2-Methyl-6-nitro-2-(4-(4-(4-trifluoromethoxybenzyl)piperidine-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole

Melting point: 180.9-182.7°C.

Example 16

2-(4-(4-(3,4-Dichlorobenzyl)piperidine-1-yl)phenoxy)methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole
Melting point: 191.4-192.1°C.

Example 17
2-(4-(4-(N-(4-chlorophenyl)-N-methylamino)piperidine-1-yl)phenoxy)methyl)-2-methyl-6-nitro-2,3-dihydroimidazo-[2,1-b]oxazole

Melting point: 137.6-141.5°C.

Example 18
(R)-2-(4-(4-(N-(4-chlorophenyl)-N-methylamino)piperidine-1-yl)phenoxy)methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole, 4-toluenesulfonate.

Melting point: 212.6-214.1°C.

Example 19
(R)-2-(4-(4-(N-(4-chlorophenyl)-N-methylamino)-piperidine-1-yl)phenoxy)methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole, methanesulfonate.

Melting point: 171.2-172.8°C.

Example 20
(R)-2-(4-(4-(N-(4-chlorophenyl)-N-methylamino)-piperidine-1-yl)phenoxy)methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole, hydrochloride.

Melting point: 170.0-173.7°C.
Example 21
2-Methyl-6-nitro-2-((4-(4-(4-trifluoromethoxybenzyloxy)methyl)piperidine-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole

Melting point: 153.1-153.7°C.

Example 22
(R)-(4-chlorophenyl)carbamic acid 1-(4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole-2-ylmethoxy)phenyl)piperidine-4-ylmethyl ester

Melting point: 211.6-212.3°C (decomposed).

Example 23
2-Methyl-6-nitro-2-(4-(4-(4-trifluoromethylbenzyloxy)methyl)piperidine-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole

Melting point: 138.7-139.5°C.
### Table 22

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<td><img src="image5" alt="Structure" /></td>
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### Table 23

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(Table 24)

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### Table 25

<table>
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<th>Example</th>
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<th>mp (°C)</th>
<th>δ H NMR (DMSO) (D, s, °)</th>
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<td>84</td>
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<td>-Cl</td>
<td>211.7 - 213.1</td>
<td>2.82 - 2.77 (2H, m), 3.52 (2H, d, J=12.9Hz), 4.15 (1H, d, J=1.9Hz), 4.17 (2H, s), 4.35 (1H, d, J=10.9Hz), 4.61 (2H, brs), 6.62 - 6.91 (4H, m), 7.11 - 7.28 (1H, m), 7.36 - 7.61 (3H, m), 8.01 (1H, s)</td>
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### Table 26

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## Table 27

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<td>Example</td>
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<td>R3</td>
<td>R4</td>
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(Table 29)

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<td>4-CF$_3$Ph</td>
<td>C$_2$H$_5$</td>
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<tr>
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<td>4-CF$_3$Ph</td>
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$^1$H NMR (CDCl$_3$) $\delta$ 1.21(3H, t, J=7.0(1 Hz), 1.91-1.98(4H, m), 2.82-2.94(2H, m), 3.37(2H, q, $\beta$=7.01 Hz), 3.74-3.99(3H, m), 4.30-4.51(4H, m), 5.68-5.69(1H, m), 6.74-6.79(2H, m), 6.90-6.95(2H, m), 6.99-7.04(2H, m), 7.42-7.52(1H, m).

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<tr>
<td>126</td>
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(Table 30)

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$^1$H NMR (DMSC) $\delta$ 1.71(3H, s), 4.21(1H, d, $J$=11.0(1 Hz), 4.34(2H, s), 4.40(1H, d, $J$=11.0(1 Hz), 6.99(2H, d, $J$=8.4(1 Hz), 7.10-7.20(2H, m), 7.42(2H, d, J=8.4(1 Hz), 7.57-7.72(3H, m), 8.22(1H, s).

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<td>190.5 - 191.3</td>
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<tr>
<td>134</td>
<td>S F F</td>
<td>194.6 - 195.4</td>
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<tr>
<td>135</td>
<td>Cl</td>
<td>219.9 - 220.5</td>
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<tr>
<td>Example</td>
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<tr>
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'H NMR (CDCl₃)  δ 1.49–1.62(2H, m), 1.76(3H, s), 2.08–2.21(2H, m), 2.90–3.05(2H, m), 3.25–3.47(1H, m), 3.78–3.83(2H, m), 3.94–4.08(2H, m), 4.16(1H, d, J=10.20Hz), 4.50(1H, d, J=10.29Hz), 6.53–6.65(2H, m), 6.69–6.77(2H, m), 6.89–6.88(2H, m), 7.43–7.51(2H, m), 7.55(1H, s)

'H NMR (CDCl₃)  δ 1.20–1.37(2H, m), 1.46(3H, s), 1.76(3H, s), 1.94–2.07(2H, brm), 2.77–3.01(2H, brm), 3.23–3.41(2H, brm), 3.84–4.11(4H, m), 4.14(1H, d, J=10.19Hz), 4.49(1H, d, J=10.15Hz), 6.50–6.59(2H, m), 6.87–6.98(2H, m), 7.55(1H, s)
### Table 33

<table>
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### Table 34

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<td>CH₄</td>
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</table>

¹H NMR (CDCl₃): δ 1.74-1.87(5H, m), 2.50-2.68(2H, m), 2.68-2.83(2H, m), 2.97(3H, s), 3.42-3.56(2H, m), 4.55-4.66(1H, m), 6.49-6.55(1H, br), 6.84-6.92(2H, m), 7.10-7.18(2H, m), 7.37-7.44(2H, m), 7.49-7.57(2H, m), 7.58(1H, s)
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[Table 36]

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δH NMR (CDCl₃): 8 1.29-1.54 (2H, brm), 1.67-1.86 (8H, brm), 2.13 (3H, s), 2.20 (1H, s), 2.48-2.72 (2H, brm), 3.15-3.23 (2H, brm).

308     | -CH₃  | 4-CF₃OPhCH₂⁻ | COCH₃ | 3.27-3.38 (2H, brm), 3.46-3.83 (2H, brm), 3.93-4.10 (2H, brm), 4.10-4.20 (1H, brm), 4.4K (H, d, J=10.15 Hz), 7.28 (1H, s), 6.83-6.96 (2H, brm), 7.12-7.30 (4H, m), 7.58 (1H, s), 7.66 (1H, s). |

309     | -CH₃  | 4-CF₃OPh⁻    | H     | 101.0 - 102.5                             |
| 310     | -CH₃  | 4-CF₃OPh⁻    | H     | 177.5 - 179.1                             |
| 311     | -CH₃  | 4-CF₃Ph⁻     | H     | 164.7 - 165.8                             |
| 312     | -CH₃  | 4-CF₃OPhCH₂⁻ | C₂H₅  | 163.9 - 165.2                             |
| 313     | -CH₃  | 4-CF₃OPhCH₂⁻ | CH₃   | 160.5 - 160.0                             |
| 314     | -CH₃  | 4-CF₃PhCH₂⁻  | CH₃   | 169.5 - 170.6                             |
| 315     | -CH₃  | 4-CF₃PhCH₂⁻  | H     | 166.7 - 167.6                             |
| 316     | -CH₃  | 4-CF₃PhCH₂⁻  | H     | 163.9 - 167.6                             |
| 317     | -CH₃  | 4-CF₃PhCH₂⁻  | H     | 157.1 - 160.2                             |

δH NMR (CDCl₃): 8 1.29-1.54 (1H, brm), 1.60-1.84 (6H, m), 2.48-2.60 (2H, brm), 3.00-3.24 (2H, brm), 3.46-3.57 (2H, brm), 3.97-4.08 (2H, m), 4.17 (1H, d, J=10.12 Hz), 4.35-4.55 (2H, m), 6.76-6.94 (2H, m), 6.81-6.95 (2H, m), 7.12-7.20 (2H, m), 7.20-7.35 (2H, m), 7.59 (1H, s), 7.66 (1H, s). |

319     | -CH₃  | 4-CF₃OPhCH₂⁻ | (CH₃)₂COO⁻ | 5.17 (1H, d, J=10.10 Hz), 4.34-4.38 (2H, brm), 4.46 (1H, d, J=10.10 Hz), 6.76 (2H, d, J=6.97 Hz), 6.81-6.93 (2H, brm), 7.07-7.21 (2H, brm), 1.24 (2H, d, J=2.0 Hz), 7.65 (1H, s), 7.66 (1H, s). |

320     | -CH₃  | 4-CF₃PhCH₂⁻  | (CH₃)₂COO⁻ | 5.17 (1H, d, J=10.15 Hz), 4.49-4.51 (2H, brm), 5.07 (2H, d, J=6.95 Hz), 6.83-6.96 (2H, brm), 7.26-7.42 (2H, brm), 7.56 (1H, s), 7.58 (1H, d, J=7.30 Hz). |

δH NMR (CDCl₃): 8 1.31-1.51 (1H, brm), 1.61-1.85 (6H, m), 2.45-2.72 (2H, brm), 3.03-3.28 (2H, brm), 3.52 (2H, d, J=12.6 Hz), 6.96-7.09 (2H, m), 4.17 (1H, d, J=10.15 Hz), 4.49-4.51 (2H, brm), 5.07 (2H, d, J=6.95 Hz), 6.83-6.96 (2H, brm), 7.26-7.42 (2H, brm), 7.56 (1H, s), 7.58 (1H, d, J=7.30 Hz). |
### Table 49

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[Table 80]

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<td>-H</td>
<td>-H</td>
<td>172.7 - 175.2</td>
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<td>-H</td>
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<td>-H</td>
<td>-H</td>
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(Table 81)

![Chemical structure](image)

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<td>4-CF₃OPhCH₂⁻</td>
<td>238.2-240.3 dec</td>
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<td>247.8-248.5 dec</td>
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<td>695</td>
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<td>4-CF₂PhCH₂⁻</td>
<td>247.7-248.4 dec</td>
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<td>221.0-226.0</td>
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<td>248.0-252.0</td>
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<td>4-FPhCH₂⁻</td>
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<tr>
<td>700</td>
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<td>(CH₂)₂COCO⁻</td>
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</tr>
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<tr>
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<td>286.4-289.2 dec</td>
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<tr>
<td>708</td>
<td>-H</td>
<td>4-CF₃Ph⁻</td>
<td>250 dec</td>
</tr>
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<td>4-CF₃OPh⁻</td>
<td>270 dec</td>
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<tr>
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<td>N,N,N,N-Cl</td>
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<tr>
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**Table 83**

<table>
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### Table 85

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### Table 86

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[Table 97]

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[Table 91]

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### Table 95

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### Table 96

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[Table 98]

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[Table 99]

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**Table 100**

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<td>864</td>
<td>-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>4-CF&lt;sub&gt;3&lt;/sub&gt;OPhOCH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>201.3-202.2</td>
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<tr>
<td>865</td>
<td>-H</td>
<td>4-CF&lt;sub&gt;3&lt;/sub&gt;OPhOCH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>191.5-194.5</td>
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[Table 101]

```
<table>
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<th>Example</th>
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<tr>
<td>867</td>
<td>-CH₃</td>
<td>109.3 - 112.7</td>
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### Table 102

<table>
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| 868     | -CH₃ | \[
\begin{array}{c}
\text{N} \\
\text{O}
\end{array}
\] | 223.8 - 225.6         |
| 869     | -CH₃ | \[
\begin{array}{c}
\text{N} \\
\text{O}
\end{array}
\] | 168.3 - 171.2         |
| 870     | -CH₃ | \[
\begin{array}{c}
\text{N} \\
\text{O}
\end{array}
\] | 119.9 - 122.0         |

### Table 103

<table>
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<tr>
<td>871</td>
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<td>-C₆H₅</td>
<td>249.3 - 250.0</td>
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<tr>
<td>872</td>
<td>-CH₃</td>
<td>4-ClPh</td>
<td>257.8 - 258.2</td>
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<tr>
<td>873</td>
<td>H</td>
<td>-C₆H₅</td>
<td>249.2 - 252.1 dec</td>
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<tr>
<td>874</td>
<td>H</td>
<td>4-ClPh</td>
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</tr>
</tbody>
</table>
[Table 104]

Example | R1 | R2
--- | --- | ---
875 | -CH₃ | -CF₃

[Table 105]

Example | R1 | R2 | mp(°C)
--- | --- | --- | ---
876 | -CH₃ | -C₆H₅ | 221.2 - 222.1
877 | -CH₃ | 4-ClPh | 229.3 - 232.1
878 | -H | -C₆H₅ | 246.2 - 247.0
879 | -H | 4-ClPh | 260.4 - 260.9
### Table 106

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<tr>
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<td>-H</td>
<td>4-C1Ph</td>
<td>191.0 - 193.9 dec</td>
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<tr>
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<td>-H</td>
<td>C₆H₅</td>
<td></td>
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<tr>
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<td>-H</td>
<td>-H</td>
<td>4-C1Ph</td>
<td>161.0 - 165.0 dec</td>
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<tr>
<td>884</td>
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<td>-CH₃</td>
<td>C₆H₅</td>
<td>121.0 - 126.1 dec</td>
</tr>
<tr>
<td>885</td>
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<td>-CH₃</td>
<td>4-C1Ph</td>
<td>216.0 - 217.5 dec</td>
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<td>C₆H₅</td>
<td>218.0 - 219.1 dec</td>
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<td>887</td>
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### Table 107

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<td>4-CF₃PhCH₂</td>
<td>151.1 - 154.1</td>
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[Table 106]

![Chemical Structure 1](image1)

[Table 107]

![Chemical Structure 2](image2)
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<td>897</td>
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<td>4-CF₃OPh</td>
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### Table 110

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[Table 111]

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### [Table 112]

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<th>R5</th>
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### Table 113

<table>
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[Table 114]

<table>
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[Table 116]

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*(Table 124)*

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(Table 125)

Example R1 R2

1096 -CH₃

1097 -CH₃
Example 1098
(R)-2-methyl-2-(4-(N-methyl-N-(1-methylpiperidine-4-yl)amino)phenoxy)methyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

Example 1099
(R)-4-(1-(4-(2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole-2-ylmethoxy)phenyl)-3-(4-trifluoromethoxyphenyl)ureido)-piperidine-1-carboxylic acid(4-trifluoromethoxyphenyl)amide

Example 1100
6-Nitro-2-((4-(4-(4-trifluoromethylbenzyloxy)methyl)piperidine-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole
Melting point: 140.2-141.7°C.

Example 1101
(R)-2-methyl-6-nitro-2-(4-(4-(tetrahydropyran-2-yl)oxy)methyl)piperidine-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole
Melting point: 217.6-218.6°C.

Example 1102
(R)-2-methyl-6-nitro-2-(4-(4-(hydroxymethyl)piperidine-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole

Example 1103
2-methyl-6-nitro-2-(4-(4-(4-trifluoromethoxyphenoxy)piperidine-1-yl)benzyl)-2,3-dihydroimidazo[2,1-b]oxazole
Melting point: 184.9-186.8°C.
Example 1104
(R)-2-methyl-6-nitro-2-(4-(4-(4-
trifluoromethoxyphenyl)carbamoyloxy)methyl)piperidin-1-
yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole
5 Melting point: 211.6°C-212.0°C (decomposition)

Example 1105
(R)-2-4-(4-(biphenyl-4-yloxy)methyl)piperidin-1-
yl)phenoxy)methyl)-2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole
Melting point: 245°C (decomposition)

Example 1106
(R)-2-(1-benzyl-2-(4-(4-
trifluoromethoxybenzyl)piperazin-1-yl)-1H-benzimidazol-
5-yloxy)methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-
b]oxazole
Melting point: 101.3°C-104.0°C

Example 1107
(R)-2-methyl-6-nitro-2-(4-(4-(4-
trifluoromethoxybenzyl)piperidin-1-
yl)methyl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-
b]oxazole
25 Melting point: 172.5°C-174.1°C

Example 1108
2-(4-(4-(N-methyl-tert-butoxycarbonyl)amino)piperidin-1-
ylmethy1)phenoxy)methyl)-2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole
Melting point: 138.5°C-141.9°C

Example 1109
(R)-2-(4'-(4-tert-butoxycarbonyl-1,4-diazepan-1-
yl)biphenyl-4-yloxy)methyl)-2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole
Melting point: 213.8°C-215.7°C

Example 1110
(R)-2-(4'-(4-tert-butoxycarbonyl-1,4-diazepan-1-
yl)biphenyl-4-yloxy)methyl)-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole
Melting point: 235.5°C-237.5°C

Example 1111
(S)-2-methyl-2-(N-methyl-N-(4-(N-methyl-N-(4-
trifluoromethyl)cinnamyl)amino)benzyl)aminomethyl)-6-
nitro-2,3-dihydroimidazo[2,1-b]oxazole
Melting point: 153.5°C-154.5°C

Example 1112
(R)-2-methyl-6-nitro-2-[4-(2-oxo-2-(4-(4-
trifluoromethoxyphenoxy)piperidin-1-
yl)ethylaminocarbonyl)phenoxy)methyl)-2,3-
dihydroimidazo[2,1-b]oxazole
Melting point: 186.9°C-189.5°C
Example 1113
2-methyl-6-nitro-2-(2-(4-(4-
trifluoromethoxybenzyl)piperazin-1-yl)benzothiazol-6-
yloxymethyl)-2,3-dihydroimidazo[2,1-b]oxazole
Melting point: 172.6°C-174.6°C

Example 1114
2-(4-(4-(4-chlorophenoxyethyl)piperidin-1-
yl)phenoxyethyl)-2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole
Melting point: 190.0°C-190.4°C

Example 1115
2-(4-(4-(4-chlorophenoxyethyl)piperidin-1-
yl)phenoxyethyl)-6-nitro-2,3-dihydroimidazo[2,1-
b]oxazole
Melting point: 191.2°C-192.5°C

Example 1116
6-nitro-2-(4-(4-(4-trifluoromethoxybenzyl)piperidin-1-
yl)phenoxyethyl)-2,3-dihydroimidazo[2,1-b]oxazole
Melting point: 132.7°C-135.0°C

Example 1117
2-methyl-6-nitro-2-(4-(4-(4-
trifluoromethoxycinnamyl)piperazin-1-yl)phenoxyethyl)-
2,3-dihydroimidazo[2,1-b]oxazole
Melting point: 181.1°C-182.2°C
[Table 126]

<table>
<thead>
<tr>
<th>Example</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>R5</th>
<th>R6</th>
<th>mp(°C)</th>
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**Table 127**

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**Table 128**

<table>
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<td>-H</td>
<td>¹H NMR (CDCl₃) δ 1.76 (3H, t), 2.49-2.74 (4H, m), 2.97-3.22 (4H, m), 3.51 (2H, s), 3.89-4.10 (2H, m), 4.17 (1H, d, J=10.2 Hz), 4.49 (1H, d, J=10.2 Hz), 6.66-6.81 (2H, m), 6.81-6.95 (2H, m), 7.28 (2H, d, J=8.6 Hz), 7.49 (2H, d, J=8.2 Hz), 7.48-7.67 (5H, m).</td>
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<td>-H</td>
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<td>¹H NMR (CDCl₃) δ 2.53-2.73 (4H, m), 3.02-3.21 (4H, m), 3.57 (2H, s), 4.15-4.50 (4H, m), 5.49-5.66 (1H, m), 6.72-6.95 (4H, m), 7.28 (2H, d, J=20.1 Hz), 7.43 (2H, d, J=8.2 Hz), 7.52 (2H, d, J=8.3 Hz), 7.58-7.67 (3H, m).</td>
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**Table 129**

![Chemical Structure](image)

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<th>mp (°C)</th>
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Table 131

<table>
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### Table 132

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<th>R3</th>
<th>R4</th>
<th>R5</th>
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<tr>
<td>1176</td>
<td>-H</td>
<td>-CH₃</td>
<td>-CF₃</td>
<td>-H</td>
<td>-CF₃</td>
<td>-H</td>
<td>-H</td>
<td>135.7-137.6</td>
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<tr>
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<td>-H</td>
<td>4-CF₃Ph⁻</td>
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<td>-H</td>
<td>226.0-229.3</td>
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<tr>
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<td>-H</td>
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<td>4-ClPhO⁻</td>
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<td>-H</td>
<td>189.5-194.1</td>
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<td>-H</td>
<td>200.0-203.5</td>
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<tr>
<td>1181</td>
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<td>-H</td>
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<td>4-ClPh⁻</td>
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<td>-H</td>
<td>237.4-239.0</td>
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<tr>
<td>1183</td>
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<td>-H</td>
<td>-H</td>
<td>4-CF₃OPh⁻</td>
<td>-H</td>
<td>-H</td>
<td>233.7-235.8</td>
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</tbody>
</table>
[Table 133]

![Chemical Structure Image]

<table>
<thead>
<tr>
<th>Example</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>R5</th>
<th>R6</th>
<th>R7</th>
<th>'H NMR</th>
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<tr>
<td>1188</td>
<td>-</td>
<td>CH₃</td>
<td>-H</td>
<td>-H</td>
<td>4-CF₃OPh-</td>
<td>-H</td>
<td>-H</td>
<td>1H NMR(CDC₃) δ 1.66-2.06(7H, m), 2.26(3H, s), 2.47-2.77(3H, m), 3.51-3.72(4H, m), 3.92-4.09(2H, m), 4.17(1H, d, J=10.2Hz), 4.49(1H, d, J=10.2Hz), 6.66-6.82(2H, m), 6.82-6.97(2H, m), 7.27(2H, d, J=5.5Hz), 7.40(2H, d, J=8.2Hz), 7.46-7.66(5H, m).</td>
</tr>
<tr>
<td>1189</td>
<td>-H</td>
<td>CH₃</td>
<td>-H</td>
<td>-H</td>
<td>4-CF₃Ph-</td>
<td>-H</td>
<td>-H</td>
<td>1H NMR(CDC₃) δ 1.70-2.06(4H, m), 2.30(3H, s), 2.44-2.78(3H, s), 3.48-3.75(4H, m), 4.17-4.53(4H, m), 5.48-5.70(1H, m), 6.71-6.85(2H, m), 6.85-6.93(2H, m), 7.42(2H, d, J=8.2Hz), 7.51-7.61(3H, m), 7.72(4H, s).</td>
</tr>
</tbody>
</table>
**[Table 134]**

<table>
<thead>
<tr>
<th>Example</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>mp(°C)</th>
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<tbody>
<tr>
<td>1190</td>
<td>-CH₃</td>
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<td>CF₃</td>
<td>-CH₃</td>
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<td></td>
<td></td>
<td></td>
<td>181.4 - 183.3</td>
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| 1191    | -CH₃|     | CF₃  | H          |
|         |     |     |       | 183.0 - 188.8 |

**[Table 135]**

<table>
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<tr>
<th>Example</th>
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<tbody>
<tr>
<td>1192</td>
<td>-CH₃</td>
<td>-CH₃</td>
<td>252-255 dec.</td>
</tr>
<tr>
<td>1193</td>
<td>-CH₃</td>
<td>4-CF₂PhCH=CHCH₂⁻</td>
<td>232-234</td>
</tr>
<tr>
<td>1194</td>
<td>-CH₃</td>
<td>4-CIPhCH=CHCH₂⁻</td>
<td>231-232</td>
</tr>
<tr>
<td>1195</td>
<td>-CH₃</td>
<td>4-CF₂OPhCH=CHCH₂⁻</td>
<td>228-230</td>
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### Table 136

<table>
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<tr>
<th>Example</th>
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<th>R3</th>
<th>mp(°C)</th>
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<tbody>
<tr>
<td>1196</td>
<td>-CH₃</td>
<td>4-C₅F₃Ph⁻</td>
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<td>188-195</td>
</tr>
<tr>
<td>1197</td>
<td>-H</td>
<td>4-C₅F₃Ph⁻</td>
<td>-CH₃</td>
<td>172-174</td>
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<td>1198</td>
<td>-CH₃</td>
<td>4-C₅F₃OPh⁻</td>
<td>-C₂H₅</td>
<td>198.5-199.3</td>
</tr>
<tr>
<td>1199</td>
<td>-CH₃</td>
<td>4-CIPh⁻</td>
<td>-C₂H₅</td>
<td>184.5-186.5</td>
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<tr>
<td>1200</td>
<td>-CH₃</td>
<td>-CH₃</td>
<td>-CH₃</td>
<td>250-252</td>
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### Table 137

<table>
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<th>R3</th>
<th>R4</th>
<th>R5</th>
<th>R6</th>
<th>mp(°C)</th>
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<td>-H</td>
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<td>-H</td>
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<td>-H</td>
<td>4-C₅F₃OPh⁻</td>
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<td>-H</td>
<td>229.4-230.1</td>
</tr>
<tr>
<td>1203</td>
<td>-H</td>
<td>-H</td>
<td>-H</td>
<td>4-C₅F₃OPh⁻</td>
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<td>-H</td>
<td>183.7-187.2</td>
</tr>
<tr>
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<td>-H</td>
<td>4-CIPh⁻</td>
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<td>248.9-250.0</td>
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<tr>
<td>1205</td>
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<td>-H</td>
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<td>4-CIPh⁻</td>
<td>-H</td>
<td>-H</td>
<td>236.2-236.8</td>
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<tr>
<td>1206</td>
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<td>-H</td>
<td>-C₂H₅</td>
<td>-H</td>
<td>-H</td>
<td>224.2-227.4</td>
</tr>
<tr>
<td>1207</td>
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<td>-H</td>
<td>-H</td>
<td>-C₂H₅</td>
<td>-H</td>
<td>-H</td>
<td>235.8-237.4</td>
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**Table 138**

<table>
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<tr>
<th>Example</th>
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<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>R5</th>
<th>R6</th>
<th>H NMR</th>
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<tr>
<td>1208</td>
<td>-CH₃</td>
<td>-H</td>
<td>-H</td>
<td>-4-CF₃</td>
<td>Ph</td>
<td>-H</td>
<td>1H NMR (CDCl₃) δ 1.30-1.64 (2H, m), 1.58-1.98 (5H, m), 2.44-2.72 (4H, m), 3.38-3.62 (2H, m), 3.91-4.08 (2H, m), 4.16 (1H, d, J=10.2 Hz), 4.48 (1H, d, J=10.3 Hz), 6.86-6.91 (2H, m), 6.81-6.94 (2H, m), 7.18-7.32 (2H, m), 7.44-7.59 (3H, m), 7.61-7.75 (4H, m).</td>
</tr>
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</table>

**Table 139**

<table>
<thead>
<tr>
<th>Example</th>
<th>R1</th>
<th>R2</th>
<th>mp (°C)</th>
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<tbody>
<tr>
<td>1209</td>
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<td>-CH₂OCH₃</td>
<td>194.0-195.6</td>
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<td>1210</td>
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<td>-H</td>
<td>216.3-218.4 (dec)</td>
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<tr>
<td>1211</td>
<td>-H</td>
<td>-CH₂OCH₃</td>
<td>150.0-151.2</td>
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Table 140

<table>
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<th>mp(°C)</th>
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<td>-CH₃OCH₂OCH₃</td>
<td>208.7-210.7</td>
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<tr>
<td>1213</td>
<td>-CH₃</td>
<td>-CH₂OH</td>
<td>171.0-173.8</td>
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<td>1214</td>
<td>-H</td>
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<td>236.7-237.2</td>
</tr>
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<td>1215</td>
<td>-CH₃</td>
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<td>166.0-168.9</td>
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<td>1216</td>
<td>-CH₃</td>
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<td>196.8-200.3</td>
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### Table 141

<table>
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<th>mp (°C)</th>
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<td>196.0-199.4</td>
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<td>212.4-214.9</td>
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<td>1220</td>
<td>-CH₃</td>
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<td>198.6-199.7</td>
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<td>-CH₃</td>
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<td>224.1-227.6</td>
</tr>
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<td>1222</td>
<td>-CH₃</td>
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<td>192.2-195.3</td>
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<tr>
<td>1223</td>
<td>-CH₃</td>
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<td>182.2-183.5</td>
</tr>
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<td>1224</td>
<td>-CH₃</td>
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<td>219.6-221.9</td>
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<tr>
<td>Example</td>
<td>R1</td>
<td>R2</td>
<td>R3</td>
</tr>
<tr>
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<tr>
<td>1225</td>
<td>-CH₃</td>
<td>-CH₃</td>
<td>F-F</td>
</tr>
<tr>
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<td>-CH₃</td>
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</tr>
<tr>
<td>1227</td>
<td>-H</td>
<td>-CH₃</td>
<td>F-F</td>
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<td>-CH₃</td>
<td>F-F</td>
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<td>1229</td>
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<td>-CH₃</td>
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(Table 142)
<table>
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<tr>
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<th>R3</th>
<th>mpT(°C)</th>
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<td>1H NMR(CDCl₃) 6 1.48(9H, s), 1.54-</td>
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<td></td>
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<td>1.64(4H, m), 2.57-2.85(6H, m), 3.39-</td>
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<td></td>
<td>3.65(1H, m), 4.04-4.32(7H, m), 5.49-</td>
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<tr>
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<td>5.07(1H, m), 6.69-6.96(4H, m), 7.58(1H, s).</td>
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<table>
<thead>
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<th>R1</th>
<th>R2</th>
</tr>
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<tbody>
<tr>
<td>1231</td>
<td>-CH₃</td>
<td>4-CF₃OPhCH₂-</td>
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<td>1232</td>
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### Table 145

<table>
<thead>
<tr>
<th>Example</th>
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<th>mp (°C)</th>
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<tbody>
<tr>
<td>1233</td>
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<td>4-ClPhS⁻</td>
<td>182.8-184.6</td>
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<td>1234</td>
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<td>4-CF₃OpHs⁻</td>
<td>147.2-150.0</td>
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<td>4-ClPhSO₂⁻</td>
<td>223.5-224.9</td>
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<td>1236</td>
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<td>4-CF₃OpHsO⁻</td>
<td>128.0-130.7</td>
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<td>1237</td>
<td>-CH₃</td>
<td>4-CF₃OpHsO₂⁻</td>
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### Table 146

<table>
<thead>
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<th>R3</th>
<th>mp (°C)</th>
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<td>-CH₃</td>
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<td>1239</td>
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<td>H</td>
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<td>231.4-234.1</td>
</tr>
<tr>
<td>1240</td>
<td>-CH₃</td>
<td>-CH₃</td>
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<td>133.9-134.9</td>
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### Table 147

<table>
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<th>R2</th>
<th>R3</th>
<th>1H NMR</th>
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<tr>
<td>1241</td>
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<td>-CH₃</td>
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<td>1H NMR (CDCl₃) δ 1.75 (3H, s),</td>
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<td>2.98 (3H, s), 4.00 (1H, d, J=10.1 Hz),</td>
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<td>4.02 (1H, d, J=10.1 Hz), 4.18 (1H, d, J=10.1 Hz),</td>
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<td>4.49 (2H, s), 4.50 (1H, d, J=10.1 Hz),</td>
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<td>5.70 (2H, d, J=9.2 Hz),</td>
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<td>5.77 (2H, d, J=9.2 Hz), 7.23-7.31 (4H, m),</td>
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<td>7.50 (2H, d, J=9.2 Hz), 7.54 (1H, s),</td>
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<td></td>
<td>7.57 (2H, d, J=8.7 Hz)</td>
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<tr>
<td>Example</td>
<td>R1</td>
<td>R2</td>
<td>mp (°C)</td>
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<td>--------</td>
<td>-----------</td>
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<td>-CH₃</td>
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<td>1243</td>
<td>-CH₃</td>
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<td>145.3-147.4</td>
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<td>1244</td>
<td>-CH₃</td>
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<td>241.2-242.5</td>
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<td>148.1-150.9</td>
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<td>-CH₃</td>
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<td>202.9-204.0</td>
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<td>190.0-191.5</td>
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**Table 145**

<table>
<thead>
<tr>
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<th>R2</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1252</td>
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<td>1253</td>
<td>-CH₃</td>
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<td>264.6-266.4</td>
</tr>
<tr>
<td>1254</td>
<td>-CH₃</td>
<td></td>
<td>285.4-285.8</td>
</tr>
<tr>
<td>1255</td>
<td>-CH₃</td>
<td></td>
<td>169.6-163.3</td>
</tr>
<tr>
<td>1256</td>
<td>-CH₃</td>
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<td>206.4-209.7</td>
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<td>2.15-2.23 (2H, m)</td>
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<td>2.93 (3H, s)</td>
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<td>3.23-3.32 (2H, m)</td>
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<td>3.41-3.50 (2H, m)</td>
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<td>3.59-3.69 (1H, m)</td>
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<td>4.02 (1H, d, J = 10.2 Hz)</td>
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<td>6.96 (1H, d, J = 3.0 Hz)</td>
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<td>7.23 (1H, d, J = 9.0 Hz)</td>
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<td>7.59 (1H, s)</td>
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1H NMR (CDCl₃) δ ppm:
- 1.78 (3H, s)
- 2.15-2.23 (2H, m)
- 2.93 (3H, s)
- 3.23-3.32 (2H, m)
- 3.41-3.50 (2H, m)
- 3.59-3.69 (1H, m)
- 4.00 (1H, d, J = 10.1 Hz)
- 4.02 (1H, d, J = 10.2 Hz)
- 4.16 (1H, d, J = 9.0 Hz)
- 6.79 (2H, d, J = 9.0 Hz)
- 6.96 (1H, d, J = 3.0 Hz)
- 7.23 (1H, d, J = 9.0 Hz)
- 7.59 (1H, s)
### Table 151

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**Table 153**

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### Table 154

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### Table 155

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[Table 156]

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### Table 157

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Table 158

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### Table 159

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### Table 160

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### Table 161

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[Table 163]

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[Table 164]

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<th>R2</th>
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Example 1463

(R)-2-(4-(4-(4-chlorophenyl)oxazol-2-yl)phenoxymethyl)-2-methyl-5-nitro-2,3-dihydropyrimidazo[2,1-b]oxazole

1.73 g (7.9 mmol) of (R)-2-chloro-1-(2-methyl-2-oxyranyl)methyl)-4-nitro-1H-imidazole, 1.80 g (6.6 mmol) of 4-(4-(4-chlorophenyl)oxazol-2-yl)phenol, and 0.42 g (2.0 mmol) of potassium phosphate were suspended in 15 ml of ethanol, and the mixture was heated under reflux with stirring for 3 hours in an argon atmosphere. The reaction solution was concentrated, and dichloromethane was then added to the residue to precipitate non-soluble product, which was then filtered off. The filtrate was concentrated, and the residue was dissolved in 20 ml of DMF to give a solution. 0.29 g (7.3 mmol) of 60% sodium hydride was added to the solution while cooled by ice, and the obtained mixture was stirred for 6 hours. Thereafter, the solvent was removed under a reduced pressure, and 100 ml of acetone and 10 ml of silica gel were added to the residue, followed by concentration. The residue was purified by silica gel column chromatography (dichloromethane : methanol = 50 : 1 to 30 : 1), and the resultant product was crystallized from a mixed solvent consisting of dichloromethane and ethanol. The resultant product was then recrystallized from a mixed solvent consisting of acetone and water to obtain 1.15 g (yield: 38%) of light brown powders, (R)-2-(4-(4-(4-chlorophenyl)oxazol-2-yl)phenoxymethyl)-2-methyl-6-
nitro-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 248.8°C-251.5°C

Example 1464

5 6-([R]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)-2-(4-(4-
trifluoromethoxybenzyl)piperidin-1-yl)quinoline

0.65 g of ([R]-2-chloro-1-(2-methyl-2-
pyranylmethyl)-4-nitro-1H-imidazole, 1.50 g of 6-
10 hydroxy-2-(4-(4-trifluoromethoxybenzyl)piperidin-1-
yl)quinoline, and 0.16 g of potassium phosphate were
suspended in 10 ml of ethanol, and the mixture was
heated under reflux with stirring for 4 hours in an
argon atmosphere. The reaction solution was
concentrated, and the residue was purified by silica
gel column chromatography (from hexane: ethyl acetate
= 1 : 3 to ethyl acetate). The resultant product was
concentrated, the residue was then dissolved in DMF (10
ml), and 99 mg of sodium hydride was then added

20 thereto. The mixture was stirred at room temperature
for 1 hour. Thereafter, water was added to the
reaction solution, and repeated extraction was then
carried out with ethyl acetate. The combined organic
layer was washed with water and then with a saturated
aqueous solution of sodium chloride, and then dried
over sodium sulfate. The sodium sulfate was filtered
off, and the filtrate was concentrated under a reduced
pressure. The residue was purified by silica gel
column chromatography (hexane : ethyl acetate from 1 : 1 to 1 : 3). The resultant product was recrystallized from ethanol to obtain 0.57 g (yield: 36%) of light yellow powdery crystals, 6-((R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)-2-(4-(4-trifluoromethoxybenzyl)piperidin-1-yl)quinoline.

Melting point: 184.9°C-185.9°C

Example 1465

6-((R)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-ylmethoxy)-2-(4-(4-trifluoromethoxybenzylidene)piperidin-1-yl)quinoline

0.65 g of (R)-2-chloro-1-(2-methyl-2-oxiranylethyl)-4-nitro-1H-imidazole, 0.94 g of 6-hydroxy-2-(4-(4-trifluoromethoxybenzylidene)piperidin-1-yl)quinoline, and 0.15 g of potassium phosphate were suspended in 10 ml of ethanol, and the mixture was heated under reflux with stirring for 6 hours in an argon atmosphere. The reaction solution was concentrated, and the residue was purified by silica gel column chromatography (from hexane : ethyl acetate = 1 : 3 to ethyl acetate). The resultant product was concentrated, the residue was then dissolved in DMF (10 ml), and 99 mg of sodium hydride was then added thereto. The mixture was stirred at room temperature for 3 hours. Thereafter, ethyl acetate was added to the reaction solution, and the mixture was then concentrated under a reduced pressure. The residue was
purified by silica gel column chromatography
(dichloromethane : methanol = 50 : 1). The resultant
product was recrystallized from ethanol to obtain 1.37
\( \text{g (yield: 51\%)} \) of yellow powdery crystals, 6-\{(R)-2-
5 methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazol-2-
ylmethoxy\}-2-(4-(4-
trifluoromethoxybenzylidene)piperidin-1-yl)quinoline.
Melting point: 193.9-195.9°C

Example 1466

\( \{R\}-2\text{-methyl}-6\text{-nitro-2-}(6-\{4-\{4-
trifluoromethoxyphenoxy\}piperidin-1-yl\}naphthalene-2-
yloxymethyl\}-2,3\text{-dihydroimidazo[2,1-b]oxazole} \)

2.12 g of \( \{R\}-2\text{-chloro-1-} \{2\text{-methyl-2-
15 oxyranylmethyl\}}-4\text{-nitro-1H-imidazole}, 3.02 \text{g of } 6-\{4-
(4\text{-trifluoromethoxyphenoxy}\}piperidin-1-yl\}naphthalene-
2-ol, and 0.48 g of potassium phosphate were suspended
in 30 ml of ethanol, and the mixture was heated under
reflux with stirring for 6 hours in a nitrogen
atmosphere. Thereafter, water was added to the
reaction solution, and repeated extraction was carried
out with dichloromethane. The combined organic layer
was washed with a saturated aqueous solution of sodium
chloride and then dried over anhydrous magnesium
sulfate, followed by concentration. The residue was
purified by silica gel column chromatography (from
hexane : ethyl acetate = 1 : 3 to ethyl acetate). The
resultant product was concentrated to obtain 2.73 g of
yellow powders. The obtained powders were dissolved in DMF (27 ml), and 0.21 g of sodium hydride was then added thereto, followed by stirring at room temperature for 2.5 hours. Thereafter, a saturated aqueous solution of sodium chloride was added to the reaction solution, and repeated extraction was then carried out with dichloromethane. The combined organic layer was washed with water and then with a saturated aqueous solution of sodium chloride, and then dried over anhydrous magnesium sulfate. The magnesium sulfate was filtered, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : ethyl acetate = 4 : 1). The resultant product was recrystallized from a mixed solvent consisting of dichloromethane, ethyl acetate, and diisopropyl ether to obtain 1.05 g (yield: 24%) of light yellow powdery crystals, (R)-2-methyl-6-nitro-2-(6-(4-(4-trifluoromethoxyphenoxy)piperidin-1-yl)naphthalene-2-yloxymethyl)-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 204.8°C-207.9°C

Example 1467

(R)-2-methyl-6-nitro-2-(4-(4-(4-trifluoromethoxybenzyloxy)piperidin-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole

0.305 g of 4-(4-(4-trifluoromethoxybenzyloxy)piperidin-1-yl)phenol was
dissolved in DMF (5 ml), and 10 mg of sodium hydride was added thereto, followed by stirring at 70°C to 80°C for 20 minutes. Thereafter, 0.252 g of (R)-2-chloro-1-(2-methyl-2-oxiranymethyl)-4-nitro-1H-imidazole was added to the reaction solution while cooled by ice, followed by stirring at 70°C to 80°C for 20 minutes. Thereafter, the reaction solution was cooled to room temperature. Water was added to the reaction solution, and repeated extraction was carried out with ethyl acetate. The combined organic layer was washed with water and then with a saturated aqueous solution of sodium chloride, and then dried over sodium sulfate. The sodium sulfate was filtered off, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (from hexane : ethyl acetate = 1 : 3 to ethyl acetate). The resultant product was recrystallized from a mixed solvent consisting of dichloromethane and ethyl acetate to obtain 88 mg (26.7%) of colorless powdery crystals, (R)-2-methyl-6-nitro-2-(4-(4-(4-trifluoromethoxybenzyloxy)piperidin-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 214.3°C-217.7°C

Example 1468
(R)-2-methyl-6-nitro-2-(4-(4-(4-trifluoromethylbenzyloxy)piperidin-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole
0.217 g of 4-((4-(4-
trifluoromethylbenzyloxy)piperidin-1-yl)phenol was
dissolved in DMF (5 ml), and 27 mg of sodium hydride
was added thereto, followed by stirring at 70°C to 80°C
for 20 minutes. Thereafter, 0.188 g of (R)-2-chloro-1-
(2-methyl-2-oxyranyl)methyl)-4-nitro-1H-imidazole was
added to the reaction solution while cooled by ice,
followed by stirring at 70°C to 80°C for 20 minutes.
Thereafter, the reaction solution was cooled to room
temperature. Water was added to the reaction solution,
and repeated extraction was carried out with ethyl
acetate. The combined organic layer was washed with
water and then with a saturated aqueous solution of
sodium chloride, and then dried over sodium sulfate.
The sodium sulfate was filtered off, and the filtrate
was concentrated under a reduced pressure. The residue
was purified by silica gel column chromatography (from
hexane : ethyl acetate = 1 : 3 to ethyl acetate). The
resultant product was recrystallized from a mixed
solvent consisting of dichloromethane and ethyl acetate
to obtain 88 mg (26.7%) of light yellow powders, (R)-2-
methyl-6-nitro-2'-4-[(4-(4-
trifluoromethylbenzyloxy)piperidin-1-yl)phenoxy)methyl]
2,3-dihydropyrimido[2,1-b]oxazole.
Melting point: 217.4°C-219.7°C

Example 1469
(R)-2-methyl-6-nitro-2'-4-{4-(4-
trifluoromethoxybenzyl)piperidin-1-yl)phenoxyethyl)-
2,3-dihydroimidazo[2,1-b]oxazole

8.41 g of 4-(4-(4-
trifluoromethoxybenzyl)piperidin-1-yl)phenol was
dissolved in DMF (84 ml), and 1.05 g of sodium hydride
was added thereto, followed by stirring at 70°C to 80°C
for 20 minutes. Thereafter, 7.29 g of (R)-2-chloro-1-
(2-methyl-2-cyramylimethyl)-4-nitro-1H-imidazole was
added to the reaction solution while cooled by ice,
followed by stirring at 70°C to 80°C for 20 minutes.
Thereafter, the reaction solution was cooled to room
temperature. Water was added to the reaction solution,
and repeated extraction was carried out with ethyl acetate. The combined organic layer was washed with
water and then with a saturated aqueous solution of
sodium chloride, and then dried over sodium sulfate.
The sodium sulfate was filtered off, and the filtrate
was concentrated under a reduced pressure. The residue
was purified by silica gel column chromatography
(dichloromethane : ethyl acetate = 9 : 1). The
resultant product was recrystallized from a mixed
solvent consisting of dichloromethane and ethyl acetate
to obtain 4.65 g (36.5%) of light yellow powders, (R)-
2-methyl-6-nitro-2-(4-(4-(4-
trifluoromethoxybenzyl)piperidin-1-yl)phenoxyethyl)-
2,3-dihydroimidazo[2,1-b]oxazole.

$^1$H-NMR (CDCl$_3$, ppm)
1.23-1.52 (2H, m), 1.52-1.66 (3H, m), 1.66-1.89 (3H,
804

m), 2.43-2.70 (4H, m), 3.50 (2H, d, \( J = 12.1 \) Hz), 3.91-
4.09 (2H, m), 4.16 [1H, d, \( J = 10.1 \) Hz], 4.48 (1H, d, \( J 
= 10.2 \) Hz), 6.66-6.81 (2H, m), 6.81-6.95 (2H, m), 7.05-
7.23 (4H, m), 7.54 (1H, s)

5 Melting point: 210.9°C-212.4°C
(\( \alpha \)$_b$ = -9.0 deg. (c = 1.0, CHCl$_3$)

Example 1470

(R)-2-(4-(4-chlorobenzyl)piperidin-1-
10-yl)phenoxyethyl)-2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole

1.036 g of 4-(4-(4-chlorobenzyl)piperidin-1-
-yl)phenol was dissolved in DMF (5 ml), and 151 mg of 
sodium hydride was added thereto, followed by stirring
15 at 70°C to 80°C for 20 minutes. Thereafter, 1.04 g of 
(R)-2-chloro-1-(2-methyl-2-oxyranyl)methyl]-4-nitro-1H-
imidazole was added to the reaction solution while 
cooled by ice, followed by stirring at 70°C to 80°C for 
20 minutes. Thereafter, the reaction solution was 
20 cooled to room temperature. Water was added to the 
reaction solution, and repeated extraction was carried 
out with ethyl acetate. The combined organic layer was 
washed with water and then with a saturated aqueous 
solution of sodium chloride, and then dried over sodium 
sulfate. The sodium sulfate was filtered off, and the 
filtrate was concentrated under a reduced pressure. 
The residue was purified by silica gel column 
chromatography (from hexane : ethyl acetate = 1 : 3 to
ethyl acetate). The resultant product was recrystallized from a mixed solvent consisting of dichloromethane and ethyl acetate to obtain 0.286 g (17.3%) of light yellow powdery crystals, (R)-2-(4-(4-
5 (4-chlorobenzyl)piperidin-1-yl)phenoxy)methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole.
Melting point: 207.1°C-211.2°C

Example 1471

(R)-2-methyl-6-nitro-2-(4-(4-(4-
trifluoromethoxy)cinnamyl)oxy)piperidin-1-
yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole

2.21 g of 4-(4-(4-
trifluoromethoxy)cinnamyl)oxy)piperidin-1-yl)phenol was dissolved in DMF (22 ml), and 0.247 g of sodium hydride was added thereto, followed by stirring at 70°C to 80°C for 20 minutes. Thereafter, 1.71 g of (R)-2-chloro-1-(2-methyl-2-oxiranylmethyl)-4-nitro-1H-imidazole was added to the reaction solution while cooled by ice, followed by stirring at 70°C to 80°C for 20 minutes. Thereafter, the reaction solution was cooled to room temperature. Water was added to the reaction solution, and repeated extraction was carried out with ethyl acetate. The combined organic layer was washed with water and then with a saturated aqueous solution of sodium chloride, and then dried over anhydrous magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under a reduced
pressure. The residue was purified by silica gel column chromatography (dichloromethane : ethyl acetate = 9 : 1). The resultant product was recrystallized from a mixed solvent consisting of dichloromethane and ethyl acetate to obtain 0.70 g (21.7%) of light yellow powdery crystals, (R)-2-methyl-6-nitro-2-(4-[(4-(4-
trifluoromethoxy)cinnamyoxy)piperidin-1-yl)phenoxy)methyl]-2,3-dihydroiminazo[2,1-b]oxazole.
Melting point: 213.7°C-217.4°C

Example 1472
(R)-6-nitro-2-(4-[(4-(4-
trifluoromethoxybenzyloxy)piperidin-1-yl)phenoxy)methyl]-2,3-dihydroiminazo[2,1-b]oxazole

4.60 g of 4-[(4-
trifluoromethoxybenzyloxy)piperidin-1-yl)phenol was dissolved in DMF (46 ml), and 0.55 g of sodium hydride was added thereto, followed by stirring at 70°C to 80°C for 20 minutes. Thereafter, 3.57 g of (R)-2-chloro-1-
oxoyranylmethyl-4-nitro-1H-imidazole was added to the reaction solution while cooled by ice, followed by stirring at 70°C to 80°C for 20 minutes. Thereafter, the reaction solution was cooled to room temperature. Water was added to the reaction solution, and repeated extraction was carried out with ethyl acetate. The combined organic layer was washed with water and then with a saturated aqueous solution of sodium chloride, and then dried over sodium sulfate. The sodium sulfate
was filtered off, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : ethyl acetate from 9 : 1 to 6 : 4). The resultant product was recrystallized from a mixed solvent consisting of dichloromethane and ethyl acetate to obtain 0.99 g (14.8%) of light yellow powdery crystals, (R)-6-nitro-2-(4-((4-(4-
trifluoromethoxybenzyloxy)piperidin-1-
yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole. Melting point: 188.3°C-189.4°C

Example 1473
(R)-2-methyl-6-nitro-2-(4-((4-(2-(4-
trifluoromethoxyphenyl)ethyl)piperidin-1-
yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole

1.01 g of (R)-2-chloro-1-(2-methyl-2-
oxyranyl)methyl)-4-nitro-1H-imidazole and 1.36 g of 4-
((4-(2-(4-trifluoromethoxyphenyl)ethyl)piperidin-1-
yl)phenol were dissolved in DMF (14 ml), and 0.18 g of sodium hydride was added thereto, followed by stirring at 50°C for 1 hour. Thereafter, the reaction solution was cooled to room temperature. Water was added to the reaction solution, and repeated extraction was carried out with ethyl acetate. The combined organic layer was washed with water and then with a saturated aqueous solution of sodium chloride, and then dried over sodium sulfate. The sodium sulfate was filtered off, and the
filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : ethyl acetate from 9 : 1 to 8 : 2). The resultant product was recrystallized from a mixed solvent consisting of dichloromethane, ethyl acetate, and diisopropyl ether to obtain 0.70 g (34.4%) of light yellow powdery crystals, (R)-2-methyl-6-nitro-2-(4-(4-(2-(4-trifluoromethoxyphenyl)ethyl)piperidin-1-yl)phenoxy)methyl)-2,3-dihydroimidazol[2,1-b]oxazole. Melting point: 239.4°C-241.3°C

Example 1474

(R)-2-methyl-6-nitro-2-(6-(4-(4-
trifluoromethoxyphenoxy)piperidin-1-yl)pyridin-3-yloxymethyl)-2,3-dihydroimidazo[2,1-b]oxazole 0.51 g of (R)-2-chloro-1-(2-methyl-2-oxynaphthylethyl)-4-nitro-1H-imidazole and 0.67 g of 3-hydroxy-6-(4-(4-trifluoromethoxyphenoxy)piperidin-1-yl)pyridine were dissolved in DMF (6.7 mL), and 91 mg of sodium hydride was added thereto, followed by stirring at 50°C for 1 hour. Thereafter, the reaction solution was cooled to room temperature. Water was added to the reaction solution, and repeated extraction was carried out with ethyl acetate. The combined organic layer was washed with water and then with a saturated aqueous solution of sodium chloride, and then dried over anhydrous magnesium sulfate. The magnesium
sulfate was filtered, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : ethyl acetate from 9 : 1 to 8 : 2). The resultant product was recrystallized from a mixed solvent consisting of dichloromethane, ethyl acetate, and diisopropyl ether to obtain 296 mg (29.1%) of light yellow powdery crystals, (R)-2-methyl-6-nitro-2-(6-(4-(4-trifluoromethoxyphenoxy)piperidin-1-yl)pyridin-3-yloxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole. Melting point: 185.9-186.7°C

Example 1475
(R)-6-nitro-2-(4-(4-(4-
trifluoromethoxybenzyl)piperidin-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole

0.72 g of (R)-2-chloro-1-oxynaphthylmethyl-4-nitro-1H-imidazole and 1.00 g of 4-(4-(4-trifluoromethoxybenzyl)piperidin-1-yl)phenol were dissolved in DMF (10 ml), and 0.14 g of sodium hydride was added thereto, followed by stirring at 50°C for 1 hour. Thereafter, the reaction solution was cooled to room temperature. Water was added to the reaction solution, and repeated extraction was carried out with ethyl acetate. The combined organic layer was washed with water and then with a saturated aqueous solution of sodium chloride, and then dried over anhydrous magnesium sulfate. The magnesium sulfate was filtered,
and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : ethyl acetate from 9 : 1 to 7 : 3). The resultant product was recrystallized from a mixed solvent consisting of dichloromethane, ethyl acetate, and diisopropyl ether to obtain 0.20 g (13.7%) of light yellow powdery crystals, (R)-6-nitro-2-{4-(4-(4-
trifluoromethoxybenzyl)piperidin-1-yl)phenoxyethyl}-2,3-dihydroimidazo[2,1-b]oxazole.
Melting point: 160.5°C-164.0°C

Example 1476
(R)-2-methyl-6-nitro-2-{4-(4-(4-
trifluoromethoxyphenyl)-1,4-diazepan-1-
yl)phenoxyethyl}-2,3-dihydroimidazo[2,1-b]oxazole

2.21 g of (R)-2-chloro-1-(2-methyl-2-
oxynanylmethyl)-4-nitro-1H-imidazole and 2.86 g of 4-
(4-(4-trifluoromethoxyphenyl)-1,4-diazepan-1-yl)phenol were dissolved in DMF (29 ml), and 0.39 g of sodium hydride was added thereto, followed by stirring at 50°C for 1 hour. Thereafter, the reaction solution was cooled to room temperature. Water was added to the reaction solution, and repeated extraction was carried out with dichloromethane. The combined organic layer was washed with water and then with a saturated aqueous solution of sodium chloride, and then concentrated. The residue was purified by silica gel column
chromatography (from hexane : ethyl acetate = 1 : 3 to ethyl acetate). The resultant product was then recrystallized from isopropyl alcohol to obtain 720 mg (16.6%) of red powders, \((R)-2\text{-methyl}-6\text{-nitro}-2-(4-(4-}
\text{(4-trifluoromethoxyphenyl)-1,4-diazepan-1-yl)phenoxyethyl})-2,3\text{-dihydroimidazo[2,1-b]oxazole.}

Melting point: 134.0°C-137.9°C

Example 1477

\((R)-2\text{-methyl}-2-(4-(4-(N\text{-methyl-N-(2-fluoro-4-trifluoromethylbenzyl)amino)piperidin-1-yl)phenoxyethyl})-6\text{-nitro-2,3-dihydroimidazo[2,1-b]oxazole}

0.80 g of \((R)-2\text{-methyl}-2-(4-(4-(N\text{-methyl-N-}
\text{tert-butoxycarbonylamino)piperidin-1-yl)phenoxyethyl})-6\text{-nitro-2,3-dihydroimidazo[2,1-b]oxazole was dissolved in 2 ml of trifluoroacetic acid and 2 ml of dichloromethane, followed by stirring at room temperature for 15 hours. Thereafter, the reaction solution was concentrated under a reduced pressure, and then, 2 ml of dichloromethane and 2 ml of triethylamine were added thereeto. The mixture was stirred at room temperature for 5 minutes, and it was then concentrated under a reduced pressure. The residue was dissolved in 8 ml of dichloroethane, and then, 0.63 g of 2-fluoro-4-trifluoromethylbenzaldehyde and 0.70 g of triacetoxy sodium borohydride were added thereeto while cooled by ice. The mixture was warmed to room temperature, and
the mixture was then stirred for 24 hours. Thereafter, an aqueous solution of potassium carbonate and dichloromethane were added to the reaction solution. The mixture was stirred, and then extracted with dichloromethane. The organic layer was dried over magnesium sulfate, and then filtered. The obtained filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : methanol = 9 : 1).

The resultant product was then crystallized from ethyl acetate to obtain 0.48 g (yield: 51.8%) of light yellow powders, (R)-2-methyl-2-(4-(4-(N-methyl-N-(2-fluoro-4-trifluoromethyl)benzyl)amino)piperidin-1-yl)phenoxy)methyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 197.5°C-199.2°C

Example 1478
(R)-2-methyl-2-(4-(4-(N-methyl-N-(2-trifluoromethyl)benzyl)amino)piperidin-1-yl)phenoxy)methyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

0.80 g of (R)-2-methyl-2-(4-(4-(N-methyl-N-tert-butoxycarbonylamino)piperidin-1-yl)phenoxy)methyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole was dissolved in 2 ml of trifluoracetic acid and 2 ml of dichloromethane, followed by stirring at room temperature for 15 hours. Thereafter, the reaction
solution was concentrated under a reduced pressure, and then, 2 ml of dichloromethane and 2 ml of triethylamine were added thereto. The mixture was stirred at room temperature for 5 minutes, and it was then concentrated under a reduced pressure. The residue was dissolved in 8 ml of dichloromethane, and then, 0.57 g of 2-trifluoromethylbenzaldehyde and 0.70 g of triacetoxy sodium borohydride were added thereto while cooled by ice. The mixture was warmed to room temperature, and the mixture was then stirred for 24 hours. Thereafter, an aqueous solution of potassium carbonate and dichloromethane were added to the reaction solution. The mixture was stirred, and then extracted with dichloromethane. The organic layer was dried over magnesium sulfate, and then filtered. The obtained filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : methanol = 9 : 1). The resultant product was then crystallized from ethyl acetate to obtain 0.47 g (yield: 52.4%) of light yellow powders, (R)-2-methyl-2-(4-(4-(N-methyl-N-(2-trifluoromethylbenzyl)amino)piperidin-1-yl)phenoxy)methyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 189.6°C-190.2°C

Example 1479
(R)-2-methyl-2-(4-(4-(N-methyl-N-(3,5-
bistrifluoromethylbenzyl)amino)piperidin-1-yl)(phenoxymethyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

0.80 g of (R)-2-methyl-2-(4-((N-methyl-N-tert-butoxy carbonylamino)piperidin-1-yl)(phenoxymethyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole was dissolved in 2 ml of trifluoroacetic acid and 2 ml of dichloromethane, followed by stirring at room temperature for 15 hours. Thereafter, the reaction solution was concentrated under a reduced pressure, and then, 2 ml of dichloromethane and 2 ml of triethylamine were added thereto. The mixture was stirred at room temperature for 5 minutes, and it was then concentrated under a reduced pressure. The residue was dissolved in 8 ml of dichloroethane, and then, 0.79 g of 3,5-bistrifluoromethylbenzaldehyde and 0.70 g of triacetoxy sodium borohydride were added thereto while cooled by ice. The mixture was warmed to room temperature, and the mixture was then stirred for 19 hours. Thereafter, an aqueous solution of potassium carbonate and dichloromethane were added to the reaction solution. The mixture was stirred, and then extracted with dichloromethane. The organic layer was dried over magnesium sulfate, and then filtered. The obtained filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : methanol = 9 : 1). The resultant product was then crystallized from ethyl
acetate to obtain 0.55 g (yield: 54.9%) of light yellow powders, \((R)-2\text{-methyl-2\text{-}}(4\text{-}(4\text{-}(N\text{-methyl-N\text{-}}(3,5\text{-bistrifluoromethylbenzyl)amino)piperidin-1\text{-}y})\text{phenoxymethyl}\text{-}6\text{-nitro-2,3\text{-dihydrorimidazo[2,1-b]oxazole}}\).

Melting point: 193.8°C-195.3°C

Example 1480

\((R)-2\text{-methyl-6\text{-nitro-2\text{-}(4\text{-}(4\text{-}(3\text{-trifluoromethoxybenzyl)piperidin-1\text{-}y})\text{phenoxymethyl}\text{-}2,3\text{-dihydrorimidazo[2,1-b]oxazole}}\)

1.21 g of \((R)-2\text{-chloro-1\text{-}(2\text{-methyl-2-oxyranymethyl})\text{-}4\text{-nitro-1H-imidazole}}\) and 1.56 g of \((4\text{-}(4\text{-}(3\text{-trifluoromethoxybenzyl)piperidin-1\text{-}y})\text{phenol}}\) were dissolved in DMF (16 ml), and 0.21 g of sodium hydride was then added thereto, followed by stirring at 50°C for 1 hour. Thereafter, the reaction solution was cooled to room temperature. Water was added to the reaction solution, and the mixture was then extracted repeatedly with dichloromethane. The combined organic layer was washed with water and then with a saturated aqueous solution of sodium chloride, and then dried over anhydrous sodium sulfate. The sodium sulfate was filtered off, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : ethyl acetate from 9 : 1 to 8 : 2). The resultant product was recrystallized from a mixed solvent consisting of
dichloromethane, ethyl acetate, and diisopropyl ether to obtain 0.80 g (33.8%) of light yellow powdery crystals, (R)-2-methyl-6-nitro-2-(4-(4-(3-
3-trifluoromethoxybenzyl)piperidin-1-yl)phenoxy)methyl)-
5 2,3-dihydroimidazo[2,1-b]oxazole.
Melting point: 187.4°C-189.8°C

Example 1481
(R)-2-methyl-2-(4-(4-(N-methyl-N-(5-chlorobenzofuran-2-
10 yl)methyl)amino)piperidin-1-yl)phenoxy)methyl)-6-nitro-
2,3-dihydroimidazo[2,1-b]oxazole

0.80 g of (R)-2-methyl-2-(4-(4-(N-methyl-N-
15 tert-butoxycarbonylamino)piperidin-1-yl)phenoxy)methyl)-
6-nitro-2,3-dihydroimidazo[2,1-b]oxazole was dissolved in 2 ml of trifluoroacetic acid and 2 ml of dichloromethane, followed by stirring at room temperature for 15 hours. Thereafter, the reaction solution was concentrated under a reduced pressure, and then, 2 ml of dichloromethane and 2 ml of triethylamine were added thereto. The mixture was stirred at room temperature for 5 minutes, and it was then concentrated under a reduced pressure. The residue was dissolved in 8 ml of dichloromethane, and then, 0.59 g of 5-
20 chlorobenzofuran-2-carbaldehyde and 0.70 g of triacetoxy sodium borohydride were added thereto while cooled by ice. The mixture was warmed to room temperature, and the mixture was then stirred for 22 hours. Thereafter, an aqueous solution of potassium
carbonate and dichloromethane were added to the reaction solution. The mixture was stirred, and then extracted with dichloromethane. The organic layer was dried over magnesium sulfate, and then filtered. The obtained filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : methanol = 9:1). The resultant product was then crystallized from acetone to obtain 0.65 g (yield: 66.5%) of yellow powders, (R)-2-methyl-2-(4-(4-(N-methyl-N-(5-chlorobenzofuran-2-ylmethyl)amino)piperidin-1-yl)phenoxy)methyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 207.4°C-210.0°C

Example 1482
(R)-2-methyl-6-nitro-2-(6-(4-(4-trifluoromethoxybenzyl)piperidin-1-yl)pyridin-3-yloxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole

2.63 g of (R)-2-chloro-1-(2-methyl-2-oxyranyl)methyl)-4-nitro-1H-imidazole and 3.41 g of 3-hydroxy-6-(4-(4-trifluoromethoxybenzyl)piperidin-1-yl)pyridine were dissolved in DMF (6.7 ml), and 0.46 g of sodium hydride was then added thereto, followed by stirring at 50°C for 1.5 hours. Thereafter, the reaction solution was cooled to room temperature. Water was added to the reaction solution, and the mixture was then extracted repeatedly with
dichloromethane. The combined organic layer was washed with water and then with a saturated aqueous solution of sodium chloride, and then dried over anhydrous magnesium sulfate. The magnesium sulfate was filtered, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : ethyl acetate from 9 : 1 to 6 : 4). The resultant product was recrystallized from a mixed solvent consisting of ethyl acetate and diisopropyl ether to obtain 1.46 g (28.3%) of light yellow powdery crystals, (R)-2-methyl-6-nitro-2-(6-{4-(4-trifluoromethoxybenzyl) piperidin-1-yl} pyridin-3-yloxy)methyl)-2,3-dihydroimidazo[2,1-b] oxazole.

Melting point: 200.1°C-202.9°C

Example 1483

(R)-6-nitro-2-(4-{4-{2-(4-
trifluoromethoxyphenyl)ethyl} piperidin-1-
yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole

0.75 g of (R)-2-chloro-1-oxyranylmethyl-4-nitro-1H-imidazole and 1.07 g of 4-{4-{2-(4-
trifluoromethoxyphenyl)ethyl} piperidin-1-yl)phenol were dissolved in DMF (11 mL), and 0.14 g of sodium hydride was then added thereto, followed by stirring at 50°C for 1 hour. Thereafter, the reaction solution was cooled to room temperature. Water was added to the reaction solution, and the mixture was then extracted repeatedly
with dichloromethane. The combined organic layer was washed with water and then with a saturated aqueous solution of sodium chloride, and then dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : ethyl acetate from 9 : 1 to 6 : 4). The resultant product was recrystallized from a mixed solvent consisting of dichloromethane and diisopropyl ether to obtain 0.31 g (19.8%) of light yellow powdery crystals, (R)-6-nitro-2-(4-(4-(2-(4 trifluoromethoxyphenyl)ethyl)piperidin-1-yl)phenoxyethyl)-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 208.9°C-211.7°C

Example 1484

(R)-2-methyl-2-(4-(4-(N-methyl-N-(4-trifluoromethoxycinnamyl)amino)piperidin-1-yl)phenoxyethyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

2.76 g of (R)-2-methyl-2-(4-(4-(N-methyl-N-tert-butoxycarbonylamino)piperidin-1-yl)phenoxyethyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole was dissolved in 5 ml of trifluoroacetic acid and 10 ml of dichloromethane, followed by stirring at room temperature for 0.5 hours. Thereafter, the reaction solution was concentrated under a reduced pressure, and then, 10 ml of dichloromethane and 10 ml of N,N-
dimethylethylamine were added thereto. The mixture was stirred at room temperature for 10 minutes, and it was then concentrated under a reduced pressure. The residue was dissolved in 30 mL of dichloroethane, and 1.43 g of 4-trifluoromethoxycinnamylaldehyde and 1.78 g of triacetoxy sodium borohydride were then added thereto while cooled by ice. The mixture was warmed to room temperature, followed by stirring overnight. Thereafter, an aqueous solution of potassium carbonate and dichloromethane were added to the reaction solution. The mixture was stirred, and then extracted with dichloromethane. The organic layer was dried over magnesium sulfate, and then filtered. The obtained filtrate was concentrated under a reduced pressure.

The residue was purified by silica gel column chromatography (dichloromethane : acetone from 5 : 1 to 1 : 1). The resultant product was then recrystallized from an aqueous acetone to obtain 1.976 g (yield: 58.9%) of light yellow powders, (R)-2-methyl-2-(4-(4-

(N-methyl-N-(4-

trifluoromethoxycinnamyl)amino)piperidin-1-

yl)phenoxyethyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 213.0°C-214.9°C

Example 1485

(R)-2-(4-(4-(3,4-dichlorocinnamyl)piperazin-1-

yl)phenoxyethyl)-2-methyl-6-nitro-2,3-

1482
dihydroimidazo[2,1-b]oxazole

2.76 g of (R)-2-methyl-2-(4-(4-tert-butoxycarbonylpiperazin-1-yl)phenoxy)methyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole was dissolved in 5 ml of trifluoroacetic acid and 10 ml of dichloromethane, followed by stirring at room temperature for 0.5 hours. Thereafter, the reaction solution was concentrated under a reduced pressure, and then, 10 ml of dichloromethane and 10 ml of N,N-dimethylethylamine were added thereto. The mixture was stirred at room temperature for 5 minutes, and it was then concentrated under a reduced pressure. The residue was dissolved in 30 ml of dichloroethane, and 1.33 g of 3,4-dichlorocinnamaldehyde and 1.78 g of triacetoxy sodium borohydride were then added thereto. The mixture was stirred at room temperature overnight. Thereafter, an aqueous solution of potassium carbonate and dichloromethane were added to the reaction solution. The mixture was stirred, and then extracted with dichloromethane. The organic layer was dried over magnesium sulfate, and then filtered. The obtained filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : acetone from 5 : 1 to 1 : 1). The resultant product was then crystallized from a mixed solvent consisting of dichloromethane and ethyl acetate to obtain 2.243 g (yield: 68.7%) of light yellow powders, (R)-2-4-(4-(3,4-
822
dichlorocinnamyl; piperazin-1-yl; phenoxymethyl)-2-
methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole.
Melting point: 204.7°C-206.4°C

Example 1486
(R)-2-methyl-2-(4-(N-methyl-N-(1-(4-
trifluoromethoxyphenyl)piperidin-4-
-ylmethyl)amino)phenoxymethyl)-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole

0.408 g of (R)-2-chloro-1-(2-methyl-2-
oxiranylethyl)-4-nitro-1H-imidazole and 0.57 g of 4-
(N-methyl-N-(1-(4-trifluoromethoxyphenyl)piperidin-4-
-ylmethyl)amino)phenol were dissolved in 6 ml of DMF,
and 72 mg of sodium hydride was then added thereto,
followed by stirring at 50°C to 60°C for 2 hours.
Thereafter, the reaction solution was cooled to room
temperature. Water was added to the reaction solution,
and the mixture was then extracted repeatedly with
ethyl acetate. The combined organic layer was washed
with water and then with a saturated aqueous solution
of sodium chloride, and then dried over magnesium
sulfate. The magnesium sulfate was filtered off, and
the filtrate was concentrated under a reduced pressure.
The residue was purified by silica gel column
chromatography (from hexane : ethyl acetate = 1 : 3 to
dichloromethane : ethyl acetate = 1 : 1). The
resultant product was recrystallized from an aqueous
acetone to obtain 0.130 g (yield: 15.4%) of orange
powdery crystals, (R)-2-methyl-2-(4-(N-methyl-N-(1-(4-
trifluoromethoxyphenyl)piperidin-4-
ylmethyl)amino)phenoxy)methyl)-6-nitro-2,3-

Melting point: 172.5°C-175.2°C

Example 1487
(R)-2-methyl-2-(4-(N-methyl-N-(1-(4-
trifluoromethoxyphenyl)piperidin-4-
ylmethyl)amino)phenoxy)methyl)-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole

0.131 g of (R)-2-chloro-1-(2-methyl-2-'
oxiranylumethyl)-4-nitro-1H-imidazole and 0.177 g of 4-
(N-methyl-N-(1-(4-trifluoromethoxyphenyl)piperidin-4-
yl)amino)phenol were dissolved in 4 ml of DMF, and 23
mg of sodium hydride was then added thereto, followed
by stirring at 50°C to 60°C for 2 hours. Thereafter,
the reaction solution was cooled to room temperature.
Water was added to the reaction solution, and the
mixture was then extracted repeatedly with ethyl
acetate. The combined organic layer was washed with
water and then with a saturated aqueous solution of
sodium chloride, and then dried over magnesium sulfate.
The magnesium sulfate was filtered off, and the
filtrate was concentrated under a reduced pressure.
The residue was purified by silica gel column
chromatography (from hexane : ethyl acetate = 1 : 3 to
dichloromethane : ethyl acetate = 1 : 1). The
resultant product was recrystallized from an aqueous acetone to obtain 93 mg (yield: 35%) of light yellow powdery crystals, (R)-2-methyl-2-(4-{N-methyl-N-(1-(4- 
trifluoromethoxyphenyl)piperidin-4-
yl)amino}phenoxy)methyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 137.9°C-139.2°C

Example 1489

10 (R)-2-methyl-6-nitro-2-(4-(1-(2-(4-
trifluoromethylphenyl)thiazol-4-ylmethyl)piperidin-4-
yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole

0.300 g of (R)-2-methyl-6-nitro-2-(4-(1-tert-
butyloxycarbonylpiperidin-4-yl)phenoxy)methyl)-2,3-
dihydroimidazo[2,1-b]oxazole was added to 1 ml of trifluoroacetic acid and 1 ml of dichloromethane,
followed by stirring at room temperature for 1 hour. Thereafter, the reaction solution was concentrated under a reduced pressure, the residue was then

dissolved in 1 ml of dichloromethane, and 1 ml of triethylamine was then added thereto. The mixture was stirred at room temperature for 5 minutes, and it was then concentrated under a reduced pressure. The residue was dissolved in 5 ml of methanol, and then,

25 0.219 g of 2-(4-trifluoromethylphenyl)thiazol-4-
carbonaldehyde, 82 mg of sodium cyanotrihydroborate, and 0.5 ml of acetic acid were added thereto while cooled by ice. The obtained mixture was stirred at room
temperature for 3 days. Thereafter, an aqueous saturated solution of sodium bicarbonate was added thereto. The mixture was stirred, extracted with ethyl acetate, and then washed with a saturated aqueous solution of sodium chloride. The organic layer was dried over magnesium sulfate, and then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (from dichloromethane : acetone = 3 : 1 to dichloromethane : methanol = 20 : 1). The resultant product was then recrystallized from an aqueous acetone to obtain 65 mg (yield: 16.6%) of white powders, \((R)-2\text{-methyl}-6\text{-nitro}-2\text{-}(4\text{-}(1\text{-}(2\text{-}(4\text{-trifluoromethylphenyl)thiazol-4-ylmethyl)piperidin-4-yl)phenoxy)methyl})-2,3\text{-dihydroimidazo}[2,1-b]oxazole.\)

Melting point: 194.6°C-196.4°C

Example 1489

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20 \((R)-2\text{-methyl}-6\text{-nitro}-2\text{-}(4\text{-}(1\text{-}(4\text{-trifluoromethylcinnamyl)piperidin-4-yl)phenoxy)methyl})-2,3\text{-dihydroimidazo}[2,1-b]oxazole\)

0.300 g of \((R)-2\text{-methyl}-6\text{-nitro}-2\text{-}(4\text{-}(1\text{-tert-butoxycarbonylpiperidin-4-yl)phenoxy)methyl})-2,3\text{-dihydroimidazo}[2,1-b]oxazole\) was added to 1 ml of trifluoroacetic acid and 1 ml of dichloromethane, followed by stirring at room temperature for 1 hour. Thereafter, the reaction solution was concentrated
under a reduced pressure, the residue was then
dissolved in 1 ml of dichloromethane, and 1 ml of
triethylamine was then added thereto. The mixture was
stirred at room temperature for 5 minutes, and it was
then concentrated under a reduced pressure. The
residue was dissolved in 5 ml of methanol, and then,
0.170 g of 4-trifluoromethylcinnamylaldehyde, 82 mg of
sodium cyanotrihydroborate, and 0.5 ml of acetic acid
were added thereto while cooled by ice. Thereafter,
the obtained mixture was stirred at room temperature
for 3 days. An aqueous saturated solution of sodium
bicarbonate was added thereto. The mixture was
stirred, extracted with ethyl acetate, and then washed
with a saturated aqueous solution of sodium chloride.
The organic layer was dried over magnesium sulfate, and
then concentrated under a reduced pressure. The
residue was purified by silica gel column
chromatography (from dichloromethane : acetone = 3 : 1
to dichloromethane : methanol = 20 : 1). The resultant
product was then recrystallized from an aqueous acetone
to obtain 66 mg (yield: 18.6%) of white powders, (R)-2-
methyl-6-nitro-2-(4-(1-(4-
trifluoromethylcinnamyl)piperidin-4-yl)phenoxy)methyl)-
2,3-dihydropyrimidazo[2,1-b]oxazole.

**Melting point:** 185.9°C-187.1°C

**Example 1490**

(R)-2-methyl-6-nitro-2-(4-(4-(2-(4-
trifluoromethoxyphenoxyl)piperazin-1-yl)phenoxyimethyl]-2,3-dihydroimidazo[2,1-b]oxazole

0.300 g of (R)-2-methyl-6-nitro-2-(4-(4-tert-butoxycarbonyl)piperazin-1-yl)phenoxyimethyl)-2,3-
dihydroimidazo[2,1-b]oxazole was added to 3 ml of trifluoroacetic acid and 3 ml of dichloromethane, followed by stirring at room temperature for 2 hours. Thereafter, the reaction solution was concentrated under a reduced pressure, the residue was then dissolved in 3 ml of dichloromethane, and 3 ml of triethylamine was then added thereto. The mixture was stirred at room temperature for 10 minutes, and it was then concentrated under a reduced pressure. The residue was dissolved in 5 ml of methanol, and then, 0.170 g of 4-trifluoromethoxyphenoxyacetaldehyde, 82 mg of sodium cyanotrihydroborate, and 0.1 ml of acetic acid were added thereto while cooled by ice. Thereafter, the obtained mixture was stirred at room temperature overnight. An aqueous saturated solution of sodium bicarbonate was added thereto. The mixture was stirred, extracted with ethyl acetate, and then washed with a saturated aqueous solution of sodium chloride. The organic layer was dried over magnesium sulfate, and then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (from dichloromethane : acetone = 3 : 1 to dichloromethane : methanol = 20 : 1). The resultant product was then recrystallized from an
aqueous acetone to obtain 157 mg (yield: 42.7%) of white powders, (R)-2-methyl-6-nitro-2-(4-(4-(2-(4-
trifluoromethoxyphenoxy)ethyl)piperazin-1-yl)phenoxymethyl)-2,3-dihydroimidazo[2,1-b]oxazole.

5 Melting point: 194.8°C-195.6°C

Example 1491

(R)-2-methyl-6-nitro-2-(4-(4-(4-
trifluoromethylcinnamyl)piperazin-1-yl)phenoxymethyl)-
2,3-dihydroimidazo[2,1-b]oxazole

0.300 g of (R)-2-methyl-6-nitro-2-(4-(4-tert-
butoxycarbonylpiperazin-1-yl)phenoxymethyl)-2,3-
dihydroimidazo[2,1-b]oxazole was added to 3 ml of trifluoroacetic acid and 3 ml of dichloromethane,
followed by stirring at room temperature for 1 hour.

Thereafter, the reaction solution was concentrated under a reduced pressure, the residue was then dissolved in 3 ml of dichloromethane, and 3 ml of triethylamine was then added thereto. The mixture was stirred at room temperature for 5 minutes, and it was then concentrated under a reduced pressure. The residue was dissolved in 5 ml of methanol, and then, 0.170 g of 4-trifluoromethylcinnamylaldehyde, 82 mg of sodium cyanotrihydroborate, and 0.1 ml of acetic acid were added thereto while cooled by ice. The obtained mixture was stirred at room temperature for 3 days.
Thereafter, an aqueous saturated solution of sodium bicarbonate was added thereto. The mixture was
stirred, extracted with ethyl acetate, and then washed with a saturated aqueous solution of sodium chloride. The organic layer was dried over magnesium sulfate, and then concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (from dichloromethane : acetone = 3 : 1 to dichloromethane : methanol = 20 : 1). The resultant product was then recrystallized from an aqueous acetone to obtain 66 mg (yield: 18.6%) of light yellow powders.

(R)-2-methyl-6-nitro-2-(4-(4-(trifluoromethyl)cinnamyl)piperazin-1-yl)phenoxymethyl)-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 199.7°C-202.0°C

Example 1492

(R)-2-methyl-6-nitro-2-(4-(4-(2-(4-(trifluoromethyl)phenyl)thiazol-4-ylmethyl)piperazin-1-yl)phenoxymethyl)-2,3-dihydroimidazo[2,1-b]oxazole 0.300 g of (R)-2-methyl-6-nitro-2-(4-(4-tert-butoxycarbonylpiperazin-1-yl)phenoxymethyl)-2,3-dihydroimidazo[2,1-b]oxazole was added to 3 ml of trifluoroacetic acid and 3 ml of dichloromethane, followed by stirring at room temperature for 2 hours. Thereafter, the reaction solution was concentrated under a reduced pressure. The residue was dissolved in 3 ml of dichloromethane, and 3 ml of triethylamine was then added thereto. The mixture was stirred at room temperature for 10 minutes, and then concentrated under
a reduced pressure. The residue was dissolved in 5 ml of methanol, and then, 0.218 g of 2-(4-
trifluoromethylphenyl)thiazol-4-carbaldehyde, 82 mg of sodium cyanotrihydroborate, and 0.5 ml of acetic acid
were added thereto while cooled by ice. The mixture
was stirred at room temperature overnight. Thereafter,
an aqueous saturated solution of sodium bicarbonate was
added thereto. The mixture was stirred, then extracted
with ethyl acetate, and then washed with a saturated
aqueous solution of sodium chloride. The organic layer
was dried over magnesium sulfate, and then concentrated
under a reduced pressure. The residue was purified by
silica gel column chromatography (from
dichloromethane : acetone = 3 : 1 to dichloromethane :
methanol = 20 : 1). The resultant product was then
crystallized from an aqueous acetone to obtain 0.167 g
(yield: 42.6%) of white powders, (R)-2-methyl-6-nitro-
2-(4-({2-({4-trifluoromethylphenyl)thiazol-4-
ylmethyl}piperazin-1-yl}phenoxy)methyl)-2,3-
Melting point: 210.0°C-212.1°C

Example 1493
(R)-2-((4-(4-(N-(4-chlorophenyl)-N-
methylamino)piperidin-1-yl)phenoxy)methyl)-2-methyl-6-
nitro-2,3-dihydropyrimidazo[2,1-b]oxazole

776 mg of 4-(4-(N-(4-chlorophenyl)-N-
methylamino)piperidin-1-yl)phenol was dissolved in 10
831
ml of DME, and 108 mg of sodium hydride was then added thereto, followed by stirring at 70°C to 80°C for 10 minutes. Thereafter, the reaction solution was cooled by ice, and 746 mg of (R)-2-chloro-1-(2-methyl-2-oxyanilinylmethyl)-4-nitro-1H-imidazole was then added thereto, followed by stirring at 70°C to 80°C for 20 minutes. Thereafter, the reaction solution was cooled to room temperature. Ice water was added to the reaction solution, the mixture was then stirred, and the insoluble precipitate was then removed by filtration. The filtrate was dissolved in dichloromethane, washed with a saturated aqueous solution of sodium chloride, and then dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : ethyl acetate = 10 : 1). The resultant product was then recrystallized from a mixed solvent consisting of dichloromethane and ethyl acetate to obtain 485 mg (yield: 39.8%) of white powdery crystals, (R)-2-((4-((N-(4-chlorophenyl)-N-methylamino)piperidin-1-yl)phenoxy)methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 173.7°C-175.1°C

Example 1494
(R)-2-methyl-6-nitro-2-(4-(4-(4-
trifluoromethylphenoxy)methyl)piperidin-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole

574 mg of (R)-2-chloro-1-(2-methyl-2-oxyranylmethyl)-4-nitro-1H-imidazole and 844 mg of 4-(4-(4-trifluoromethylphenoxy)methyl)piperidin-1-yl)phenol were heated to 140°C, followed by stirring for 4 hours. Thereafter, the mixture was cooled to room temperature, and the mixture was then purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 3). After completion of the concentration, the residue was dissolved in 10 ml of DMF. 174 mg of sodium tert-butoxide was added thereto while cooled by ice, and the mixture was then stirred at room temperature for 2 hours. Thereafter, the solvent was removed under a reduced pressure, and then, 100 ml of acetone and 10 ml of silica gel were added to the residue, followed by concentration. The residue was purified by silica gel column chromatography (dichloromethane : ethyl acetate from 10 : 1 to 1 : 1).

The resultant product was then recrystallized from a mixed solvent consisting of dichloromethane and ethyl acetate to obtain 1.15 g (yield: 38%) of white powders, (R)-2-methyl-6-nitro-2-[4-[4-(4-(4-trifluoromethylphenoxy)methyl)piperidin-1-yl)phenoxy)methyl]-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 223.2°C-225.2°C (decomposition)

Example 1495
(R)-2-methyl-6-nitro-2-(4-(4-(4-
trifluoromethylbenzyloxymethyl)piperidin-1-
yl)phenoxymethyl)-2,3-dihydroimidazo[2,1-b]oxazole
2.48 g of 4-(4-(4-
trifluoromethylbenzyloxymethyl)piperidin-1-yl)phenol
was dissolved in 30 ml of DMF, and 312 mg of sodium
hydride was then added thereto, followed by stirring at
70°C to 80°C for 10 minutes. Thereafter, the reaction
solution was cooled by ice, and 2.07 g of (R)-2-chloro-
1-(2-methyl-2-oxynaphthylmethyl)-4-nitro-1H-imidazole was
then added thereto, followed by stirring at 70°C to 80°C
for 20 minutes. Thereafter, the reaction solution was
cooled to room temperature. Ice water was added to the
reaction solution, the mixture was then stirred, and
the insoluble precipitate was then removed by
filtration. The filtrate was dissolved in
dichloromethane, washed with a saturated aqueous
solution of sodium chloride, and then dried over
magnesium sulfate. The magnesium sulfate was filtered
off, and the filtrate was concentrated under a reduced
pressure. The residue was purified by silica gel
column chromatography (dichloromethane : ethyl acetate
= 10 : 1). The resultant product was then
recrystallized from ethyl acetate to obtain 1.66 g
(yield: 44.7%) of white powdery crystals, (R)-2-methyl-
6-nitro-2-(4-(4-(4- 
trifluoromethylbenzyloxymethyl)piperidin-1-
yl)phenoxymethyl)-2,3-dihydroimidazo[2,1-b]oxazole.
Melting point: 172.3°C-172.9°C

Example 1496.

(R)-2-methyl-6-nitro-2-(4-(4-(4-
choloromethylphenoxy)methyl)piperidin-1-
yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole

1.09 g of 4-(4-(4-
choloromethylphenoxy)methyl)piperidin-1-yl)phenol was
dissolved in 20 ml of DMF, and 158 mg of sodium hydride
was then added thereto, followed by stirring at 70°C to
80°C for 20 minutes. Thereafter, the reaction solution
was cooled by ice, and 1.04 g of (R)-2-chloro-1-(2-
 methyl-2-oxiranymethyl)-4-nitro-1H-Imidazole was then
added thereto, followed by stirring at 60°C for 30
minutes. Thereafter, the reaction solution was cooled
to room temperature. Ice water was added to the
reaction solution, the mixture was then stirred, and
the insoluble precipitate was then removed by
filtration. The filtrate was dissolved in
dichloromethane, washed with a saturated aqueous
solution of sodium chloride, and then dried over
magnesium sulfate. The magnesium sulfate was filtered
off, and the filtrate was concentrated under a reduced
pressure. The residue was purified by silica gel
column chromatography (dichloromethane : methanol = 20 : 1). The resultant product was then recrystallized
from ethyl acetate to obtain 744 mg (yield: 43.5%) of
light yellow powdery crystals, (R)-2-methyl-6-nitro-2-
Example 149?

(R)-6-nitro-2-(4-(4-(4-
trifluoromethylphenoxy)methyl)piperidin-1-
yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole

1.22 g of 4-(4-(4-
trifluoromethylphenoxy)methyl)piperidin-1-yl)phenol was
dissolved in 15 ml of DMF, and 196 mg of sodium hydride
was then added thereto, followed by stirring at 70°C to
80°C for 30 minutes. Thereafter, the reaction solution
was cooled by ice, and 1.57 g of (R)-2-chloro-1-
oxynorinethyl-4-nitro-1H-imidazole was then added
thereto, followed by stirring at 80°C for 20 minutes.
Thereafter, the reaction solution was cooled to room
temperature. Ice water was added to the reaction
solution, the mixture was then stirred, and the
insoluble precipitate was then removed by filtration.
The filtrate was dissolved in dichloromethane, washed
with a saturated aqueous solution of sodium chloride,
and then dried over magnesium sulfate. The magnesium
sulfate was filtered, and the filtrate was concentrated
under a reduced pressure. The residue was purified by
silica gel column chromatography (dichloromethane :
methanol = 20 : 1). The resultant product was then
recrystallized from ethyl acetate to obtain 505 mg
(yield: 22.1%) of white powdery crystals, (R)-6-nitro-2-(4-(4-(4-trifluoromethyl)phenoxy)methyl)piperidin-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole. Melting point: 175.0°C-180°C

Example 1498

(R)-2-(4'-(4-(4-chlorobenzyl)piperazin-1-yl)biphenyl-4-yloxy)methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

850 mg of (R)-2-methyl-2-(4'-(4-tert-butoxycarbonylpiperazin-1-yl)biphenyl-4-yloxy)methyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole was dissolved in 10 ml of trifluoroacetic acid and 5 ml of dichloromethane, followed by stirring at room temperature overnight. Thereafter, the reaction solution was concentrated under a reduced pressure, and then, 6 ml of dichloromethane and 6 ml of triethylamine were added thereto. The mixture was stirred at room temperature for 5 minutes, and it was then concentrated under a reduced pressure. The residue was dissolved in 10 ml of DMF, and then, 444.2 mg of 4-(4-chlorobenzaldehyde and 672 mg of triacetoxy sodium borohydride were added thereto while cooled by ice, followed by stirring at room temperature overnight. Thereafter, an aqueous sodium bicarbonate solution and ethyl acetate were added to the reaction solution, the mixture was stirred, and the insoluble precipitate was removed by filtration. The filtrate was washed with
water and ethyl acetate, and was then dried to obtain 730 mg (yield: 51.8%) of light yellow powders, (R)-2-(4′-(4-chlorobenzyl)piperazin-1-yl)biphenyl-4-yloxy methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 247.8°C-248.5°C (decomposition)

Example 1499

(R)-2-methyl-6-nitro-2-(4′-(4-(

10 trifluoromethylbenzyl)piperazin-1-yl)biphenyl-4-yloxy methyl)-2,3-dihydroimidazo[2,1-b]oxazole

790 mg of (R)-2-methyl-2-(4′-(4-tert-

15 butoxycarbonylpiperazin-1-yl)biphenyl-4-yloxy methyl)-5-nitro-2,3-dihydroimidazo[2,1-b]oxazole was dissolved in 10 ml of trifluoroacetic acid and 5 ml of dichloromethane, followed by stirring at room temperature overnight. Thereafter, the reaction solution was concentrated under a reduced pressure, and then, 6 ml of dichloromethane and 6 ml of triethylamine were added thereto. The mixture was stirred at room temperature for 5 minutes, and it was then concentrated under a reduced pressure. The residue was dissolved in 15 ml of DMF, and then, 0.4 ml of 4-

25 trifluoromethylbenzaldehyde and 625 mg of triacetoxy sodium borohydride were added thereto while cooled by ice, followed by stirring at room temperature overnight. Thereafter, water was added to the reaction solution, the mixture was stirred, and the insoluble
precipitate was removed by filtration. The filtrate was washed with water and then dissolved in dichloromethane. The obtained solution was washed with a saturated aqueous solution of sodium chloride, and then dried over sodium sulfate. The sodium sulfate was filtered, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : methanol = 20 : 1). The resultant product was then recrystallized from a mixed solvent consisting of dichloromethane and ethyl acetate to obtain 585 mg (yield: 60.5%) of light yellow powders, \((R)-2\text{-methyl-6-nitro-2-(4'-(4-(4'-trifluoromethylbenzyl)piperazin-1-yl)biphenyl-4-yloxymethyl)-2,3-dihydroimidazo[2,1-b]oxazole}\). Melting point: 247.7°C-248.4°C (decomposition)

Example 1500

\((R)-2\text{-methyl-6-nitro-2-(4-(2-(4-trifluoromethoxybenzyl)oxy)ethyl)piperidin-1-yl)phenoxyethyl)-2,3-dihydroimidazo[2,1-b]oxazole\)

959 mg of \((R)-2\text{-chloro-1-(2-methyl-2-oxyranymethyl)-4-nitro-1H-imidazole}\) and 1.24 g of \(4-(4\text{-2-(4-trifluoromethoxybenzyl)oxy)ethyl)piperidin-1-yl)phenol\) were dissolved in 20 ml of DME, and 176 mg of sodium hydride was then added thereto, followed by stirring at 55°C for 1 hour. Thereafter, the temperature of the reaction solution was cooled to room temperature. Ice water was added to the reaction
solution, the mixture was then stirred, and the insoluble precipitate was then removed by filtration. The filtrate was dissolved in dichloromethane, washed with a saturated aqueous solution of sodium chloride, and then dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane: ethyl acetate = 10:1). The resultant product was then recrystallized from a mixed solvent consisting of dichloromethane and ethyl acetate to obtain 562 mg (yield: 28.8%) of white powdery crystals, (R)-2-methyl-6-nitro-2-(4-(4-(2-(4-trifluoromethoxybenzyl)oxy)ethyl)piperidin-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 204.8°C-206.7°C

Example 1501
(R)-2-methyl-6-nitro-2-(4-(4-(2-(4-
trifluoromethylbenzyl)oxy)ethyl)piperidin-1-
yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole 741 mg of (R)-2-chloro-1-(2-methyl-2-
oxoyranylumethyl)-4-nitro-1H-imidazole and 1.00 g of 4-(4-(2-(4-trifluoromethyl)benzyl)oxy)ethyl)piperidin-1-
yl)phenol were dissolved in 10 ml of DMF, and 136 mg of sodium hydride was then added thereto, followed by stirring at 55°C for 1 hour. Thereafter, the reaction solution was cooled to room temperature. Ice water was
added to the reaction solution, the mixture was then stirred, and the insoluble precipitate was then removed by filtration. The filtrate was dissolved in dichloromethane, washed with a saturated aqueous solution of sodium chloride, and then dried over magnesium sulfate. The magnesium sulfate was filtered, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : ethyl acetate 10:1). The resultant product was then recrystallized from a mixed solvent consisting of dichloromethane and ethyl acetate to obtain 548 mg (yield: 37.3%) of white powdery crystals, (R)-2-methyl-6-nitro-2-(4-(4-(2-(4-
trifluoromethyl)benzyloxy)ethyl)piperidin-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 198.0°C-199.2°C

Example 1502

(R)-2-(4-(4-(2-(4-chlorobenzyloxy)ethyl)piperidin-1-yl)phenoxy)methyl)-2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole

900 mg of (R)-2-chloro-1-(2-methyl-2-oxyranylmethyl)-4-nitro-1H-imidazole and 1.10 g of 4-(4-(2-(4-chlorobenzyloxy)ethyl)piperidin-1-yl)phenol were dissolved in 10 ml of DMF, and 165 mg of sodium hydride was then added thereto, followed by stirring at 55°C for 1 hour. Thereafter, the reaction solution was
cooled to room temperature. Ice water was added to the reaction solution, the mixture was then stirred, and the insoluble precipitate was then removed by filtration. The filtrate was dissolved in dichloromethane, washed with a saturated aqueous solution of sodium chloride, and then dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : ethyl acetate = 10 : 1). The resultant product was then recrystallized from a mixed solvent consisting of dichloromethane and ethyl acetate to obtain 549 mg (yield: 37.3%) of white powdery crystals, (R)-2-(4-(4-

(2-(4-chlorobenzyloxy)ethyl)piperidin-1-yl)phenoxy)methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 197.6°C-198.2°C

Example 1503

(R)-2-methyl-6-nitro-2-(4-(4-(4-(4-(4-(trifluoromethoxyphenoxy)piperidin-1-yl)benzyl)piperazin-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole

350 mg of (R)-2-methyl-2-(4-(4-tetrahydroxydecyl)piperazin-1-yl)phenoxy)methyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole was dissolved in 10 ml of trifluoroacetic acid, followed by stirring at room
temperature for 5 hours. Thereafter, the reaction solution was concentrated under a reduced pressure, and then, 2 mL of dichloromethane and 2 mL of triethylamine were added thereto. The mixture was stirred at room temperature for 5 minutes, and it was then concentrated under a reduced pressure. The residue was dissolved in 10 mL of dichloromethane, and then, 278 mg of 4-(4-(4-trifluoromethoxyphenoxy)piperidin-1-yl)benzaldehyde and 242 mg of triacetoxy sodium borohydride were added thereto while cooled by ice, followed by stirring at room temperature overnight. Thereafter, an aqueous sodium bicarbonate solution was added to the reaction solution, and then extracted with dichloromethane. The extract was washed with a saturated aqueous solution of sodium chloride, and then dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : ethyl acetate = 10 : 1). The resultant product was then recrystallized from a mixed solvent consisting of dichloromethane and diisopropyl ether to obtain 295 mg (yield: 55%) of light yellow powders, (R)-2-methyl-6-nitro-2-(4-4-4-(4-(4-trifluoromethoxyphenoxy)piperidin-1-yl)benzyl)piperazin-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole. Melting point: 198.2°C-201.4°C
Example 1504

(R)-2-(4′-(4-(3,4-dichlorobenzyl)piperazin-1-yl)biphenyl-4-yloxy-methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

350 mg of (R)-2-methyl-2-(4′-(4-tert-butoxycarbonylpiperazin-1-yl)biphenyl-4-yloxy-methyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole was dissolved in 10 ml of trifluoroacetic acid, followed by stirring at room temperature for 5 hours. Thereafter, the reaction solution was concentrated under a reduced pressure, and then, 2 ml of dichloromethane and 2 ml of triethylamine were added thereto. The mixture was stirred at room temperature for 5 minutes, and it was then concentrated under a reduced pressure. The residue was dissolved in 10 ml of dichloroethane, and then, 278 mg of 3,4-dichlorobenzaldehyde and 242 mg of triacetoxy sodium borohydride were added thereto while cooled by ice, followed by stirring at room temperature overnight. Thereafter, water was added to the reaction solution, the mixture was stirred, and the insoluble precipitate was removed by filtration. The filtrate was dissolved in dichloromethane. The solution was washed with a saturated aqueous solution of sodium chloride, and then dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : methanol = 20 : 1) to obtain 232 mg (yield: 41.1%) of
light yellow powders, (R)-2-\(4'-\)\((4-(3,4-
dichlorobenzyl)piperazin-1-yl)\)biphenyl-4-yloxy\)methyl\)\)-
2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole.
Melting point: 222.6°C-225.1°C (decomposition)

Example 1505

(R)-2-methyl-6-nitro-2-(4-(4-(4-(4-
trifluoromethoxyphenoxy)phenylamino)piperidin-1-
yl)phenoxy)methyl\)-2,3-dihydroimidazo[2,1-b]oxazole

376 mg of 4-(4-
trifluoromethoxyphenoxy)aniline and 453 mg of
triacetoxy sodium borohydride were added to a
dichloroethane solution (10 ml) containing 400 mg of
(R)-2-methyl-6-nitro-2-(4-(4-oxy)piperidin-1-
yl)phenoxy)methyl\)-2,3-dihydroimidazo[2,1-b]oxazole.
The mixture was stirred at room temperature overnight.
Thereafter, an aqueous saturated solution of sodium
bicarbonate was added to the reaction solution,
followed by repeated extraction with dichloromethane.
The organic layer was dried over magnesium sulfate, and
it was then filtered. The filtrate was concentrated
under a reduced pressure, and the residue was purified
by silica gel column chromatography (dichloromethane :
methanol = 20 : 1). The resultant product was
recrystallized from a mixed solvent consisting of
dichloromethane and diisopropyl ether to obtain 650 mg
(yield: 83.2%) of white powders, (R)-2-methyl-6-nitro-
2-\(4'-\)\((4-(4-(4-
trifluoromethoxyphenoxyl)phenylamino)piperidin-1-yl)phenoxyethyl)-2,3-dihydroimidazo[2,1-b]oxazole.
Melting point: 198.5°C-201.1°C (decomposition)

Example 1506

(R)-2-methyl-6-nitro-2-(4-(4-(N-methyl-N-(3-(4-trifluoromethoxyphenoxyl)propyl)amino)piperidin-1-yl)phenoxyethyl)-2,3-dihydroimidazo[2,1-b]oxazole

237 mg of (R)-2-methyl-6-nitro-2-(4-(4-(3-(4-trifluoromethoxyphenoxy)propyl)amino)piperidin-1-yl)phenoxyethyl)-2,3-dihydroimidazo[2,1-b]oxazole was dissolved in a mixed solvent consisting of 10 ml of dichloromethane and 10 ml of methanol. Thereafter, 0.15 ml of a 30% formaldehyde aqueous solution, 71.4 mg of sodium cyanotrithyborate, and 0.01 ml of acetic acid were added to the mixture, followed by stirring at room temperature overnight. Thereafter, an aqueous saturated solution of sodium bicarbonate was added to the reaction solution, followed by repeated extraction with dichloromethane. The organic layer was dried over magnesium sulfate, and it was then filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (dichloromethane : methanol = 20 : 1).

The resultant product was recrystallized from a mixed solvent consisting of dichloromethane and diisopropyl ether to obtain 215 mg (yield: 88.7%) of fine yellow powders, (R)-2-methyl-6-nitro-2-(4-(4-(N-methyl-N-(3-
(4-trifluoromethoxyphenoxy)propylamino)piperidin-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 167.4°C-170.2°C

Example 1507

(R)-2-(4-(4-(3,4-dichlorophenylamino)piperidin-1-yl)phenoxy)methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

628 mg of (R)-2-chloro-1-(2-methyl-2-oxoranyl)methyl)-4-nitro-1H-imidazole and 750 mg of 4-(4-(3,4-dichlorophenylamino)piperidin-1-yl)phenol were dissolved in 10 mL of DMF, and then, 117 mg of sodium hydride was then added thereto, followed by stirring at 60°C for 20 minutes. Thereafter, the reaction solution was cooled to room temperature. Water was added to the reaction solution, and the insoluble precipitate was then removed by filtration. The filtrate was dissolved in dichloromethane, washed with a saturated aqueous solution of sodium chloride, and then dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (from dichloromethane : ethyl acetate = 9 : 1 to 8 : 2). The resultant product was then recrystallized from a mixed solvent consisting of dichloromethane and diisopropyl ether to obtain 441 mg (yield: 39%) of light yellow powdery crystals, (R)-2-(4-(4-(3,4-dichlorophenylamino)piperidin-1-yl)phenoxy)methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole.
yl)phenoxyethyl)-2-methyl-6-nitro-2,3-

Melting point: 146°C-147.4°C

Example 1508

(R)-2-methyl-6-nitro-2-(4-(4-[(4-methyl-N-1-
trifluoromethoxyphenoxy)ethyl]amino)piperidin-1-
yl)phenoxyethyl)-2,3-dihydropyrimidazo[2,1-b]oxazole

200 mg of (R)-2-methyl-6-nitro-2-(4-(4-(2-(4-
trifluoromethoxyphenoxy)ethyl)amino)piperidin-1-
yl)phenoxyethyl)-2,3-dihydropyrimidazo[2,1-b]oxazole was

dissolved in a mixed solvent consisting of 2 ml of
dichloromethane and 2 ml of methanol. Thereafter, 0.13
ml of a 30% formaldehyde aqueous solution, 65 mg of
sodium cyanotrihydroborate, and 0.07 ml of acetic acid
were added to the mixture, followed by stirring at room
temperature overnight. Thereafter, an aqueous
saturated solution of sodium bicarbonate was added to
the reaction solution, followed by repeated extraction
with dichloromethane. The organic layer was dried over
magnesium sulfate, and it was then filtered. The
filtrate was concentrated under a reduced pressure, and
the residue was purified by silica gel column
chromatography (dichloromethane : methanol = 20 : 1).

The resultant product was recrystallized from a mixed
solvent consisting of dichloromethane and diisopropyl
ether to obtain 155 mg (yield: 75.7%) of white powders,
(R)-2-methyl-6-nitro-2-(4-(4-(4-methyl-N-1-(4-
trifluoromethoxyphenoxy)ethyl)amino)piperidin-1-yl)phenoxy)methyl]-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 185.7°C-187.7°C

Example 1509

(R)-2-methyl-6-nitro-2-(4-(4-{4-{4-
trifluoromethoxyphenyl)piperazin-1-yl)piperidin-1-
yl)phenoxy)methyl]-2,3-dihydroimidazo[2,1-b]oxazole

145 mg of 1-trifluoromethoxyphenylpiperazine,

273 mg of triacetoxy sodium borohydride, and 0.061 ml of acetic acid were added to an acetonitrile solution

(15 ml) containing 200 mg of (R)-2-methyl-6-nitro-2-(4-
(4-oxopiperidin-1-yl)phenoxy)methyl]-2,3-
dihydroimidazo[2,1-b]oxazole, followed by stirring at

room temperature for 11 days. Thereafter, an aqueous saturated solution of sodium bicarbonate was added to

the reaction solution, followed by repeated extraction with dichloromethane. The organic layer was dried over

magnesium sulfate, and it was then filtered. The

filtrate was concentrated under a reduced pressure, and

the residue was purified by silica gel column

chromatography (dichloromethane : methanol = 20 : 1). The resultant product was recrystallized from isopropyl

alcohol to obtain 143 mg (yield: 44.2%) of white

powders, (R)-2-methyl-6-nitro-2-(4-(4-{4-{4-
trifluoromethoxyphenyl)piperazin-1-yl)piperidin-1-
yl)phenoxy)methyl]-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 279°C-281°C
Example 1510

(R)-2-(4-(4-(3,5-dichlorophenylamino)piperidin-1-yl)phenoxy)methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

1.82 g of (R)-2-chloro-1-(2-methyl-2-oxyranylmethyl)-4-nitro-1H-imidazole and 2.02 g of 4-(4-(3,5-dichlorophenylamino)piperidin-1-yl)phenol were dissolved in 20 ml of DMF, and then, 264 mg of sodium hydride was added thereto, followed by stirring at 60°C for 20 minutes. Thereafter, the reaction solution was cooled to room temperature. Water and ethyl acetate were added to the reaction solution, the mixture was stirred, and the insoluble precipitate was then removed by filtration. The filtrate was dissolved in dichloromethane, washed with a saturated aqueous solution of sodium chloride, and then dried over magnesium sulfate. The magnesium sulfate was filtered off, and the filtrate was concentrated under a reduced pressure. The residue was purified by silica gel column chromatography (from dichloromethane : ethyl acetate = 9 : 1 to dichloromethane : methanol = 20 : 1). The resultant product was then recrystallized from a mixed solvent consisting of ethyl acetate and diethyl ether to obtain 1.19 g (yield: 38%) of light yellow powdery crystals, (R)-2-(4-(4-(3,5-dichlorophenylamino)piperidin-1-yl)phenoxy)methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole.
Melting point: 122°C - 124°C

**Example 1511**

(R)-2-\(4-(4-(4-(4-chlorophenyl)piperazin-1-yl)piperidin-1-yl)phenoxyethyl\)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

10 ml of an aqueous 20% sodium carbonate solution was added to an aqueous solution (10 ml) containing 290 mg of 1-(4-chlorophenyl)piperazine dihydrochloride, and thereafter, ultrasonic wave was applied to the mixture. The resultant product was extracted with dichloromethane, and dried over sodium sulfate. Thereafter, the solvent was removed under a reduced pressure. The residue was dissolved in 15 ml of dichloroethane. Thereafter, 200 mg of (R)-2-methyl-6-nitro-2-(4-(4-oxopiperidin-1-yl)phenoxyethyl)-2,3-dihydroimidazo[2,1-b]oxazole, 341 ml of triacetoxy sodium borohydride, and 0.092 ml of acetic acid were added to the mixture, followed by stirring at room temperature for 24 hours. Thereafter, an aqueous 20% sodium carbonate solution was added to the reaction solution, and the mixture was then concentrated under a reduced pressure. Water was added to the residue, and the insoluble precipitate was collected by filtration. The precipitate was washed with water and then dried. The resultant product was then recrystallized from isopropyl alcohol to obtain 232 mg (yield: 79.1%) of light yellow powders, (R)-2-(4-(4-(4-(4-}
chlorophenyl)piperazin-1-yl)piperidin-1-yl)phenoxy(methyl)-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 247°C-249°C

Example 1512

(R)-2-methyl-2-(4-(4-(N-methyl-N-(4-chlorophenyl)amino)piperidin-1-yl)piperidin-1-yl)phenoxy(methyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

241 mg of 4-(N-methyl-N-(4-chlorophenyl)amino)piperidine, 341 mg of triacetoxy sodium borohydride, and 0.092 ml of acetic acid were added to a dichloroethane solution (15 ml) containing 200 mg of (R)-2-methyl-6-nitro-2-(4-(4-oxopiperidin-1-yl)phenoxy)methyl]-2,3-dihydroimidazo[2,1-b]oxazole. The mixture was stirred at room temperature for 20 hours. Thereafter, an aqueous 20% sodium carbonate solution was added to the reaction solution, followed by repeated extraction with dichloromethane. The organic layer was dried over sodium sulfate, and it was then filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (dichloromethane : methanol = 20 : 1). The resultant product was then recrystallized from a mixed solvent consisting of dichloromethane and diethyl ether to obtain 105 mg (yield: 33.6%) of white powders, (R)-2-methyl-2-(4-(4-
(4-(N-methyl-N-(4-chlorophenyl)amino)piperidin-1-yl)piperidin-1-yl)phenoxy)methyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 230.8°C-232°C

Example 1513

(R)-2-methyl-2-(4-(4-(4-(N-methyl-N-(4-trifluoromethoxyphenyl)amino)piperidin-1-yl)piperidin-1-yl)phenoxy)methyl)-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole

283 mg of 4-(N-methyl-N-(4-trifluoromethoxyphenyl)amino)piperidine, 328 mg of triacetoxy sodium borohydride, and 0.089 ml of acetic acid were added to a dichloroethane solution (15 ml) containing 192 mg of (R)-2-methyl-6-nitro-2-(4-(4-oxopiperidin-1-yl)phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole, followed by stirring at room temperature for 14 hours. Thereafter, an aqueous 20% sodium carbonate solution was added to the reaction solution, followed by repeated extraction with dichloromethane. The organic layer was dried over sodium sulfate, and it was then filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (dichloromethane : methanol = 20 : 1).

The resultant product was recrystallized from a mixed solvent consisting of dichloromethane and diethyl ether to obtain 153 mg (yield: 47.1%) of yellow powders, (R)-
853
2-methyl-2-(4-(4-(4-(N-methyl-N-{4-
trifluoromethoxyphenyl)amino)piperidin-1-yl)piperidin-
1-yl)phenoxy)methyl)-6-nitro-2,3-dihydroimidazo[2,1-
b]oxazole.

5 Melting point: 196°C-197°C

Example 1514
(R)-2-(4-(4-(4-propylphenylamino)piperidin-1-
yl)phenoxy)methyl)-2-methyl-6-nitro-2,3-
dihydroimidazo[2,1-b]oxazole

1.86 g of (R)-2-chloro-1-(2-methyl-2-
oxyn-1(1H)-imidazole and 1.9 g of 4-(4-
(4-propylphenylamino)piperidin-1-yl)phenol were
dissolved in 20 ml of DMF, and then, 269 mg of sodium
15 hydride was then added thereto, followed by stirring at
50°C for 2 hours. Thereafter, the reaction solution was
cooled to room temperature. Water and ethyl acetate
were added thereto, the mixture was stirred, and the
insoluble precipitate was then removed by filtration.
20 The filtrate was dissolved in dichloromethane, washed
with a saturated aqueous solution of sodium chloride,
and then dried over magnesium sulfate. The magnesium
sulfate was filtered off, and the filtrate was
concentrated under a reduced pressure. The residue was
25 purified by silica gel column chromatography (from
dichloromethane : ethyl acetate = 9 : 1 to
dichloromethane : methanol = 20 : 1). The resultant
product was then recrystallized from a mixed solvent
consisting of ethyl acetate and diisopropyl ether to obtain 660 mg (yield: 21.9%) of light yellow powdery crystals, (R)-2-\((4-\text{propylphenylamino)piperidin-1-yl})\text{phenoxy}methyl\)-2-methyl-6-nitro-2,3-di\text{hydroimidazo}[2,1-b]oxazole.

Melting point: 222°C-223°C

Example 1515

\((R)-2-\(4-\text{(4-methyl-N-}\text{propylphenylamino)piperidin-1-yl})\text{phenoxy}methyl\)-2-methyl-6-nitro-2,3-di\text{hydroimidazo}[2,1-b]oxazole

300 mg of \((R)-2-\(4-\text{(4-\text{propylphenylamino)piperidin-1-yl})\text{phenoxy}methyl\)-2-methyl-6-nitro-2,3-di\text{hydroimidazo}[2,1-b]oxazole was dissolved in a mixed solvent consisting of 4 ml of dichloromethane and 4 ml of methanol. Thereafter, 0.14 ml of a 30% formaldehyde aqueous solution, 115 mg of sodium cyanotrihydroborate, and 0.1 ml of acetic acid were added to the mixture, followed by stirring at room temperature overnight. Thereafter, an aqueous 20% sodium carbonate solution was added to the reaction solution, followed by repeated extraction with dichloromethane. The organic layer was dried over magnesium sulfate, and it was then filtered. The filtrate was concentrated under a reduced pressure, and the residue was purified by silica gel column chromatography (dichloromethane : methanol = 40 : 1). The resultant product was recrystallized from a mixed
solvent consisting of ethyl acetate and diisopropyl ether to obtain 258 mg (yield: 83.6%) of fine yellow powders, (R)-2-(4-[(4-methyl-N-[(4-propylphenyl)amino]piperidin-1-yl)phenoxy)methyl]-2-methyl-6-nitro-2,3-dihydroimidazo[2,1-b]oxazole.

Melting point: 198°C-199°C

Test example 1

Antibacterial test (agar-plate dilution method)

The minimum inhibitory concentration of 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole obtained in sample 129 against M. tuberculosis H37Rv in 7H11 medium (BBL Co.) was determined. A bacterial suspension of the strain used was prepared beforehand by culturing the bacteria in 7H9 medium (BBL Co.) followed by calculation of the viable cell count and cryopreservation at -80°C. The final viable cell count of the preparation was approximately 10^8 CFU/ml. A 5-µL portion of the bacterial suspension was added to 7H11 agar medium containing the test compound, cultured at 37°C for 14 days, and then tested to measure the minimum inhibitory concentration.

The minimal inhibitory concentration against M. tuberculosis H37Rv was 0.0015 µg/mL.

Test Example 2

Antibacterial test (agar-plate dilution method)

For test compounds shown in the following table, the minimum inhibitory concentration against M.
Tuberculosis Kurono in 7H11 medium (BBL Co.) was determined. A bacterial suspension of the strain used was prepared beforehand by culturing the bacteria in 7H9 medium (BBL Co.) followed by calculation of the viable cell count and cryopreservation at -80°C. The final viable cell count of the preparation was approximately $10^6$ CFU/mL. A 5-μL portion of the bacterial suspension was added to 7H11 agar medium containing a test compound, cultured at 37°C for 14 days, and then tested to measure the minimum inhibitory concentration.

The results are shown in the Table 1 below.
### Table 183

<table>
<thead>
<tr>
<th>Test Compound</th>
<th>Minimum Inhibitory Concentration (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound of Example 1</td>
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(Cont'd)
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<th>Test Compound</th>
<th>Minimum Inhibitory Concentration (µg/ml)</th>
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<td>Compound of Example 346</td>
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<td>Compound of Example 349</td>
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<td>Compound of Example 498</td>
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<tr>
<th>Test Compound</th>
<th>Minimum Inhibitory Concentration (µg/ml)</th>
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<tr>
<td>Compound of Example 508</td>
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<td>Compound of Example 790</td>
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</table>
1. A 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound represented by the following general formula (1), an optically active form thereof, or a pharmacologically acceptable salt thereof:

![Chemical Structure](image)

wherein \( R^1 \) represents a hydrogen atom, or a C1-C6 alkyl group, 
\( n \) represents an integer between 0 and 6, 
\( R^1 \) and \(-\{(CH_2)_nR^2\} \) may bind to each other together with carbon atoms adjacent thereto, so as to form a spiro ring represented by the following general formula (30):

![Spiro Ring](image)

wherein RRR represents a piperidyl group [wherein, on the piperidine ring, at least one phenoxy group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)], and

\( R^2 \) represents a group described in any one of
the following (a) to (y):

(a) a phenyl group (wherein, on the phenyl ring, at least one piperidyl group may be substituted [wherein, on the piperidine ring, at least one phenoxy group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)];)

(b) a benzothiazolylloxy group (wherein, on the benzothiazole ring, at least one selected from the group consisting of the following (b-1) to (b-5) may be substituted:

(b-1) a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted),

(b-2) a piperazinyl group (wherein, on the piperazine ring, at least one selected from the group consisting of a phenyl C1-C6 alkyl group (wherein, on the phenyl group, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a phenyl C2-C6 alkenyl group (wherein, on
the phenyl group, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C₆ alkyl group, and a halogen substituted or unsubstituted Cl-C₆ alkoxy group, may be substituted), and a phenyl group (wherein, on the phenyl group, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C₆ alkyl group, and a halogen substituted or unsubstituted Cl-C₆ alkoxy group, may be substituted), may be substituted),

(b-3) a piperidyl group (wherein, on the piperidine ring, at least one selected from the group consisting of an amino group (wherein, on the amino group, at least one selected from the group consisting of a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C₆ alkyl group, and a halogen substituted or unsubstituted Cl-C₆ alkoxy group, may be substituted) and a Cl-C₆ alkyl group may be substituted), a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C₆ alkyl group, and a halogen substituted or unsubstituted Cl-C₆ alkoxy group, may be substituted), and a phenyl Cl-C₆ alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C₆ alkyl group, and a halogen substituted or unsubstituted Cl-C₆ alkoxy group, may be substituted),
and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted), may be substituted],
(b-4) a pyrrolyl group [wherein, on the pyrrole ring, at least one selected from the group consisting of a Cl-C6 alkyl group and a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted) may be substituted], and
(b-5) a phenylthio group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted];
(c) a quinolyloxy group [wherein, on the quinoline ring, at least one selected from the group consisting of the following (c-1) to (c-4) may be substituted:
(c-1) a halogen atom,
(c-2) a phenoxy group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted],
(c-3) a piperazinyl group [wherein, on the
piperazine ring, at least one selected from the group consisting of a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a phenyl group (wherein, on the phenyl ring, at least one group selected from the group consisting of a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), and a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), may be substituted], and

(c-4) a piperidyl group (wherein, on the piperidine ring, at least one selected from the following group may be substituted: an amino group (wherein, on the amino group, at least one selected from the group consisting of a phenyl group (wherein, on the phenyl ring, at least one selected from the
group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted) and a C1-C6 alkyl group may be substituted); a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a C1-C4 alkylenedioxy group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a phenyl C1-C6 alkoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a naphthyl C1-C6 alkyl group; and a phenyl C1-C6 alkyldiene group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or
unsubstituted Cl-C6 alkyl group, and a halogen
substituted or unsubstituted Cl-C6 alkoxy group, may be
substituted)]};

(d) a pyridyloxy group (wherein, on the
pyridine ring, at least one selected from the group
consisting of the following (d-1) and (d-2) may be
substituted:

(d-1) a piperidyl group (wherein, on the
piperidine ring, at least one selected from the group
consisting of a phenoxy group (wherein, on the phenyl
ring, at least one selected from the group consisting
of a halogen atom, a halogen substituted or
unsubstituted Cl-C6 alkyl group, and a halogen
substituted or unsubstituted Cl-C6 alkoxy group, may be
substituted), a phenyl Cl-C6 alkoxy substituted Cl-C6
alkyl group (wherein, on the phenyl ring, at least one
selected from the group consisting of a halogen atom, a
halogen substituted or unsubstituted Cl-C6 alkyl group,
and a halogen substituted or unsubstituted Cl-C6 alkoxy
group, may be substituted), a phenoxy Cl-C6 alkyl group
(wherein, on the phenyl ring, at least one selected
from the group consisting of a halogen atom, a halogen
substituted or unsubstituted Cl-C6 alkyl group, and a
halogen substituted or unsubstituted Cl-C6 alkoxy
group, may be substituted), and a phenyl Cl-C6 alkyl
group (wherein, on the phenyl ring, at least one
selected from the group consisting of a halogen atom, a
halogen substituted or unsubstituted Cl-C6 alkyl group,
and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted; and

d) a piperazinyl group (wherein, on the piperazine ring, at least one selected from the group consisting of a C1-C6 alkoxy carbonyl group, a furyl C1-C6 alkyl group [wherein, on the furan ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)], a pyridyl C1-C6 alkyl group [wherein, on the pyridine ring, at least one selected from the group consisting of a furyl group and a phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)], a benzothiienyl C1-C6 alkyl group (wherein, on the benzothiophene ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted
C1-C6 alkoxy group, may be substituted), a benzofuryl C1-C6 alkyl group [wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], a benzofuryl C2-C6 alkenyl group [wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], a thiazolyl C1-C6 alkyl group [wherein, on the thiazole ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)], a phenoxy C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), an indolyl C1-C6 alkyl group (wherein, on the indole ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), and a phenyl C1-C6 alkyl
group (wherein, on the phenyl ring, at least one selected from the group consisting of a benzofuryl group, a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted) may be substituted]);

(e) a 1,2,3,4-tetrahydroquinolylxy group (wherein, on the 1,2,3,4-tetrahydroquinoline ring, at least one selected from the group consisting of an oxo group, a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted], and a phenyl Cl-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted], may be substituted);

(f) a 1,2,3,4-tetrahydronaphthoxy group (wherein, on the 1,2,3,4-tetrahydronaphthalene ring, at least one oxo group may be substituted);

(g) a 2H-chromenyxyol group (wherein, on the 2H-chromene ring, at least one oxo group may be substituted);

(h) a naphtoxy group (wherein, on the naphthalene ring, at least one piperidyl group may be
substituted (wherein, on the piperidine ring, at least one phenoxy group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted)));

(i) a 1,2,3,4-tetrahydroisoquinolyloxy group (wherein, on the 1,2,3,4-tetrahydroisoquinoline ring, at least one selected from the group consisting of a Cl-C6 alkoxy carbonyl group, a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted), and a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]), may be substituted);

(j) a group -NR^{22}R^{23} (wherein R^{22} represents a hydrogen atom or Cl-C6 alkyl group, and R^{23} represents at least one selected from the following (j-1) to (j-5):

(j-1) a phenyl group (wherein, on the phenyl ring, at least one piperidyl group is substituted (wherein, on the piperidine ring, at least one phenoxy
group may be substituted [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]),

(j-2) a phenyl Cl-C6 alkyl group [wherein, on the phenyl ring, at least one group selected from the group consisting of a piperidyl group [wherein, on the piperidine ring, a phenoxy group is substituted [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]) and a group \(-NR^2R^3\) (wherein \(R^2\) represents a hydrogen atom or Cl-C6 alkyl group, and \(R^3\) represents a phenyl C2-C6 alkenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]), is substituted],

(j-3) a piperidyl Cl-C6 alkyl group [wherein, on the piperidine ring, at least one phenyl group is substituted [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy
group, may be substituted),

(j-4) a thiazolyl group [wherein, on the thiazole ring, at least one group selected from the group consisting of a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], a piperazinyl C1-C6 alkyl group [wherein, on the piperazine ring, at least one phenyl group may be substituted [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]], and a piperidyl C1-C6 alkyl group [wherein, on the piperidine ring, at least one phenoxyl group may be substituted [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]], may be substituted], and

(j-5) a phenyl C2-C6 alkenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]);
(k) a benzoazolyl group (wherein, on the benzoazole ring, at least one selected from the group consisting of a piperazinyl group (wherein, on the piperazine ring, at least one selected from the group consisting of a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), and a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a piperidyl group (wherein, on the piperidine ring, at least one selected from the group consisting of a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted) and an amino group (wherein, on the amino group, at least one selected from the group consisting of a C1-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group, may be substituted) may be substituted), and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)

(1) a benzoimidazolyl group (wherein, on the benzoimidazole ring, at least one selected from the group consisting of a C1-C6 alkyl group, a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], a piperidyl group [wherein, on the piperidine ring, at least one phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted), a piperazinyl group [wherein, on the piperazine ring, at least one phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group and a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted)
may be substituted) and a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted);

(m) a 1,2,3,4-tetrahydroisoquinolyl group (wherein, on the 1,2,3,4-tetrahydroisoquinoline ring, at least one selected from the group consisting of the following (m-1) and (m-2) may be substituted:

(m-1) an amino group (wherein, on the amino group, at least one selected from the group consisting of a C1-C6 alkyl group, a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), and a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), may be substituted) and

(m-2) a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be
substituted]);

(n) a piperidyl group (wherein, on the piperidine ring, at least one selected from the group consisting of the following (n-1) to (n-4) may be substituted:

(n-1) a phenyl group (wherein, on the phenyl ring, at least one group -NR²³R²⁷ is substituted (wherein R²⁶ represents a hydrogen atom or Cl-C₆ alkyl group, and R²⁷ represents a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C₆ alkyl group, and a halogen substituted or unsubstituted Cl-C₆ alkoxy group, may be substituted)));

(n-2) a group W₁NR²³R²⁷ wherein W₁ represents a Cl-C₆ alkyiene group, R²⁶ represents a hydrogen atom or Cl-C₆ alkyl group, and R²⁷ represents a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C₆ alkyl group, and a halogen substituted or unsubstituted Cl-C₆ alkoxy group, may be substituted));

(n-3) a Cl-C₆ alkoxy group wherein two phenyl groups are substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C₆ alkyl group, and a halogen substituted or unsubstituted Cl-C₆ alkoxy group, may be substituted),
and

(n-6) a phenyl Cl-C6 alkyl group (wherein, on the phenyl group ring, at least one phenyl group is substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted));

(o) a piperazinyl group (wherein, on the piperazine ring, at least one selected from the following group is substituted: a Cl-C6 alkyl group wherein two phenyl groups are substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted), a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one phenoxy group is substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, is substituted)), a thiazolyl group (wherein, on the thiazole ring, at least one phenyl group may be substituted), a phenoxy Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a phenyl group (wherein, on the phenyl ring, halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, is substituted), and an imidazolyl group (wherein, on the imidazole ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)));

(p) a thiazolyl C1-C6 alkoxy group (wherein, on the thiazole ring, at least one type selected from the group consisting of the following (p-1) to (p-5) may be substituted:

(p-1) a phenoxy C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted),

(p-2) an anilino C1-C6 alkyl group (wherein,
on the phenyl ring, at least one selected from the
group consisting of a halogen atom, a halogen
substituted or unsubstituted Cl-C6 alkyl group, and a
halogen substituted or unsubstituted Cl-C6 alkoxy
group, may be substituted],

(p-3) a phenyl Cl-C6 alkyl group [wherein, on
the phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted Cl-C6 alkyl group, and a halogen
substituted or unsubstituted Cl-C6 alkoxy group, may be
substituted],

(p-4) a piperazinyl Cl-C6 alkyl group [wherein, on
the piperazine ring, at least one phenyl
group may be substituted (wherein, on the phenyl ring,
at least one selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted
Cl-C6 alkyl group, and a halogen substituted or
unsubstituted Cl-C6 alkoxy group, may be substituted)],
and

(p-5) a piperidyl Cl-C6 alkyl group [wherein,
on the piperidine ring, at least one phenoxy group may
be substituted (wherein, on the phenyl ring, at least
one selected from the group consisting of a halogen
atom, a halogen substituted or unsubstituted Cl-C6
alkyl group, and a halogen substituted or unsubstituted
Cl-C6 alkoxy group, may be substituted)];

(q) an 8-azabicyclo[3.2.1]octyl group
(wherein, on the 8-azabicyclo[3,2,1]octane ring, at
least one phenoxy group may be substituted \{wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted\};

\{r\} a group represented by the following chemical formula (31):

\[
\begin{array}{c}
\text{(31)}
\end{array}
\]

[wherein X represents a halogen atom, or an amide substituted C1-C6 alkyl group which may have a C1-C6 alkyl group as a substituent, m represents an integer between 0 and 3, and R\textsuperscript{3} represents a group described in any one of the following (i) to (xxii):

(i) a group -(W)\textsuperscript{2} o-NR\textsuperscript{3}R\textsuperscript{3} (wherein W represents a group -CO- or a C1-C6 alkylene group, o represents 0 or 1, R\textsuperscript{3} represents a hydrogen atom, C1-C6 alkyl group, or phenylcarbamoyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], and R\textsuperscript{3} represents: a phenyl C1-C6 alkoxy carbonyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a]
halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]; a phenyl C2-C6 alkenylcarbonyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]; a phenyl C2-C6 alkenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]; a piperidyl Cl-C6 alkyl group [wherein, on the piperidine ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]); a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one phenyl group is substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted)); a benzofuryl Cl-C6 alkyl group (wherein, on the benzofuran ring, at least one halogen substituted or unsubstituted Cl-C6 alkyl group may be
substituted); a piperidinyldicarbonyl C1-C6 alkyl group (wherein, on the piperidine ring, at least one phenoxy group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); or a group represented by the following chemical formula (32):

![Chemical formula](image)

(32)

wherein R* represents: a C1-C6 alkyl group; a phenyl group (wherein, on the phenyl ring, at least one selected from the following group may be substituted: a C1-C4 alkylenedioxy group, a cyano group, a nitro group, an amino group that may have a C1-C6 alkyl group as a substituent, an amino substituted sulfonyl group that may have a C1-C6 alkyl group as a substituent, a C1-C6 alkoxy carbonyl group, a C1-C6 alkylthio group, a phenoxy group, a phenyl C1-C6 alkoxy group, a pyrrolidinyl group (wherein, on the pyrrolidine ring, at least one oxo group may be substituted), an imidazolyl group, an isoxazolyl group, an oxazolyl group, a phenyl C1-C6 alkyl group, a phenyl group, an amino C1-C6 alkyl group that may have a C1-C6 alkyl group as a substituent, a pyrrolidinyl C1-C6 alkoxy group, a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group); a
phenyl C1-C6 alkoxy carbonyl group (wherein, on the
phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group, may be
substituted); a benzofuryl C1-C6 alkyl group (wherein,
on the benzofuran ring, at least one selected from the
group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a
halogen substituted or unsubstituted C1-C6 alkoxy
group, may be substituted); a benzofuryl C2-C6 alkenyl
group (wherein, on the benzofuran ring, at least one
selected from the group consisting of a halogen atom, a
halogen substituted or unsubstituted C1-C6 alkyl group,
and a halogen substituted or unsubstituted C1-C6 alkoxy
group, may be substituted); a phenoxy C1-C6 alkyl group
(wherein, on the phenyl ring, at least one selected
from the group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a
halogen substituted or unsubstituted C1-C6 alkoxy
group, may be substituted); a thiazoyl C1-C6 alkyl
group (wherein, on the thiazole ring, at least one
phenyl group may be substituted (wherein, on the phenyl
ring, at least one selected from the group consisting
of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group, may be substituted]; a phenyl C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a phenyl group (wherein, on the phenyl ring, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]; a pyridyl C1-C6 alkyl group [wherein, on the pyridine ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)]; a C1-C6 alkoxy carbonyl group; a benzoyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a phenylcarbamoyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a benzothienyl C1-C6 alkyl group (wherein, on the
benzothiophene ring, at least one halogen atom may be substituted; an indolyl C1-C6 alkyl group (wherein, on the indole ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a 4H-1,3-benzodioxinyl group (wherein, on the 4H-1,3-benzodioxine ring, at least one halogen atom may be substituted); benzothienyl group; a naphthyl group; a quinolyl group; a benzothiazolyl group (wherein, on the benzothiazole ring, at least one C1-C6 alkyl group may be substituted); a 2,3-dihydro-1H-indenyl group (wherein, on the 2,3-dihydro-1H-indan ring, at least one oxo group may be substituted); or a 9H-fluoren-yl group or phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted));

(ii) a group represented by the following chemical formula (33):

\[
\begin{align*}
&\text{(35)} \\
&\text{(Wherein } W \text{ and } o \text{ are the same as above, a dotted line represents that the bond may be a double bond, and when the dotted line represents a double bond, it means that)}
\end{align*}
\]
only R^k is substituted; R' represents a hydrogen atom, hydroxyl group, C1-C6 alkoxy group, or phenyl group [wherein, on the phenyl ring, halogen may be substituted]; and R^g represents a group described in any one of the following (1) to (63):

(1) a phenyl C1-C6 alkoxy substituted C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a C1-C4 alkylenedioxy group, a halogen atom, a cyano group, a phenyl group, a phenyl C1-C6 alkoxy group, a phenyl C2-C6 alkenyl group, a phenoxy group, a C1-C6 alkylthio group, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted);

(2) a phenyl C1-C6 alkoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a cyano group, a phenyl group, a C1-C6 alkoxy carbonyl group, a phenoxy group, a C1-C6 alkylthio group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted);

(3) a phenyl C2-C6 alkenyloxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted);
(4) a group \(-(W)\omega-\text{RR}^8\text{R}^8\)

(wherein \(W\) and \(\omega\) are the same as above, and \(R^8\) and \(R^{10}\) each identically or differently represent a hydrogen atom; a Cl-C6 alkyl group that may have a hydroxyl group as a substituent; a Cl-C6 alkanoyl group; a Cl-C6 alkoxy carbonyl group; a phenyl Cl-C6 alkoxy carbonyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]; a phenyl group [on the phenyl ring, at least one selected from the following group may be substituted as a substituent: a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, a halogen substituted or unsubstituted Cl-C6 alkoxy group, an amino group that may have, as a substituent, a group selected from the group consisting of a Cl-C6 alkanoyl group and a Cl-C6 alkyl group, a Cl-C6 alkoxy carbonyl group, a phenyl group, a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted), an aminosulfonyl group, a 1,2,3,4-tetrahydroquinolyl group (wherein, on the 1,2,3,4-tetrahydroquinoline ring, at least one oxo group may be substituted as a substituent), a Cl-C6 alkyl sulfonyl
group, a C3-C8 cycloalkyl group, a nitro group, a cyano group, a C1-C6 alkylthio group, a phenylsulfonyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a hydroxyl group substituted C1-C6 alkyl group, and a group represented by the following chemical formula (34):

\[
\begin{align*}
W_1^- & \begin{array}{c}
O \\
R^{11} \\
R^{12}
\end{array} \\
\end{align*}
\]

(34)

(wherien W₁ represents a C1-C6 alkylene group, and \(R^{11}\) and \(R^{12}\) each identically or differently represent a C1-C6 alkoxy group); a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a C1-C4 alkylenedioxy group, a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a group \(-N(R^{11a})_2R^{12a}\) (wherein \(R^{11a}\) and \(R^{12a}\) each identically or differently represent a hydrogen atom, C1-C6 alkyl group, or phenyl group, and \(R^{11a}\) and \(R^{12a}\) may bind to each other together with nitrogen atoms adjacent thereto directly or through
nitr**ogen, oxygen or sulfur atoms, so as to form a 5-7 membered saturated heterocyclic ring), a phenox**y group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a phenyl C1-C6 alkoxy group, an amino group substituted C1-C6 alkoxy group that may have a C1-C6 alkyl group as a substituent, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C10 alkoxy group, may be substituted as a substituent); a benzofuryl C1-C6 alkyl group (wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a phenylsulfon**yl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, and a C1-C4 alkylenedioxy may be substituted); a phenoxy**carbonyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted);
a phenyl C2-C6 alkenyl group; wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a C1-C6 alkoxy substituted C1-C6 alkyl group; a C2-C6 alkenyl group; a C1-C6 alkoxy substituted C2-C6 alkanoyl group; a C3-C8 cycloalkyl substituted C1-C6 alkyl group; a phenoxy C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]; a benzoxy group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]; a phenylcarbamoyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]; a pyridyl group; a pyridyl C1-C6 alkyl group; an imidazolyl C1-C6 alkyl group; a 1,2,3,4-tetrahydroquinolyl group [wherein, on the 1,2,3,4-tetrahydroquinoline ring, at least one selected from the group consisting of an oxo group and a C1-C6
alkyl group may be substituted as a substituent); a quinolyl group; an indolyl group; an amino group that may have a C1-C6 alkyl group as a substituent; an indazolyl group; a naphthyl group; a C3-C8 cycloalkyl group; an amino substituted C1-C6 alkyl group that may have a C1-C6 alkyl group as a substituent; a cyano substituted C1-C6 alkyl group; a furyl substituted C1-C6 alkyl group; a group of the formula (35)

\[
\begin{align*}
\text{N-RR} \\
\end{align*}
\]

(35)

(Wherein RR represents a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)); or a piperazinyl substituted C1-C6 alkyl group (wherein, on the piperazine ring, at least one phenyl group may be substituted as a substituent (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)), further, \(R^9\) and \(R^{10}\) may bind to each other together with nitrogen atoms adjacent thereto directly or through nitrogen, oxygen or sulfur atoms, so as to form a 1,2,3,4-tetrahydroisoquinolyl group, isoindolyl group,
or 5-7 membered saturated heterocyclic ring, wherein, on the heterocyclic ring, at least one selected from the following group may be substituted: a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, a halogen substituted or unsubstituted C1-C6 alkoxy group, a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a phenyl group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], a benzoyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], a pyridyl C1-C6 alkyl group, a C3-C8 cycloalkyl group, a phenyl C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a C1-C4 alkylenedioxy group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted], a piperidyl C1-C6 alkyl group, a piperidyl group, a phenyl C1-C6 alkoxy group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted].
group, may be substituted), a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted), an amino group wherein at least one selected from the group consisting of a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted), a Cl-C6 alkyl group, and a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted), may be substituted as a substituent, a benzoazazolyl group, a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted), and a benzoimidazolyl group);

(S) a phenyl Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a phenyl group (wherein, on the phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); (5) a carbamoyloxy group (wherein, on the amino group, at least one selected from the group consisting of a C1-C6 alkyl group and a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted] may be substituted); (7) a carbamoyloxy substituted C1-C6 alkyl group (wherein, on the amino group, at least one selected from the group consisting of a C2-C6 alkyl group, a phenyl C1-C6 alkyl group, a C3-C8 cycloalkyl group, a naphthyl group, a 2,3-dihydro-1H-indenyl group, a 2,3-dihydrobenzofuryl group, and a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a C1-C4 alkylenedioxy group, a cyano group, a phenoxy group, a C1-C6 alkylthio group, a C1-C6 alkanoyl group, a phenyl group, a phenyl C1-C6 alkyl group, a halogen atom, a halogen substituted or unsubstituted C1-C10 alkyl group, and a halogen substituted or unsubstituted C1-C10 alkoxy group, may be substituted], may be substituted);
(8) a phenoxy C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the following group may be substituted: a halogen atom; a C1-C4 alkylenedioxy group; a C1-C6 alkoxy carbonyl group; a phenyl group; a phenoxy group; a pyrrolyl group; a benzothiazolyl group; a 1,2,4-triazolyl group; an imidazolyl group; an isoxazolyl group; a benzoxazolyl group; a benzotriazolyl group; a cyano group; a nitro group; a C2-C6 alkenyl group; a C1-C6 alkanoyl group; a C1-C6 alkoxy carbonyl substituted C1-C6 alkyl group; a C1-C6 alkanoyl substituted C1-C6 alkyl group; a group \(-N(R^{13b})R^{12b}\) (wherein \(R^{13b}\) and \(R^{12b}\) each identically or differently represent a hydrogen atom, C1-C6 alkyl group, Cl-C6 alkanoyl group, or phenyl group, and \(R^{13b}\) and \(R^{12b}\) may bind to each other together with nitrogen atoms adjacent thereto directly or through nitrogen, oxygen or sulfur atoms, so as to form a 5-7 membered saturated heterocyclic ring, wherein, on the heterocyclic ring, at least one selected from the group consisting of a C1-C6 alkoxy carbonyl group and an amino group (wherein, on the amino group, at least one selected from a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted) and a C1-C6 alkyl group may be substituted) may be substituted); a phenyl C1-C6 alkoxy
group; a phenyl C1-C6 alkyl group; a C1-C6 alkylthio
group; a C3-C8 cycloalkyl group; a halogen substituted
or unsubstituted C1-C6 alkyl group; and a halogen
substituted or unsubstituted C1-C10 alkoxy group);

(9) a tetrahydropranoxy C1-C6 alkyl group;
(10) a hydroxyl substituted C1-C6 alkyl group;
(11) a furyl C1-C6 alkoxy substituted C1-C6 alkyl group
(wherein, on the furan ring, at least one C1-C6
alkoxycarbonyl group may be substituted);

(12) a tetrazolyl C1-C6 alkoxy substituted C1-C6 alkyl
group (wherein, on the tetrazole ring, at least one
selected from the group consisting of a phenyl group
(wherein, on the phenyl ring, at least one selected
from the group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a
halogen substituted or unsubstituted C1-C6 alkoxy
group, may be substituted), a phenyl C1-C6 alkyl group,
and a C3-C8 cycloalkyl C1-C6 alkyl group, may be
substituted);

(13) an isoxazolyl C1-C6 alkoxy substituted C1-C6 alkyl
group (wherein, on the isoxazole ring, at least one C1-
C6 alkyl group may be substituted);

(14) a benzothiophenyl C1-C6 alkoxy substituted C1-C6
alkyl group (wherein, on the benzothiophene ring, at
least one selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted
C1-C6 alkyl group, and a halogen substituted or
unsubstituted C1-C6 alkoxy group, may be substituted);
(15) a 1,3,4-oxadiazolyl C1-C6 alkoxy substituted C1-C6 alkyl group (wherein, on the 1,3,4-oxadiazole ring, a phenyl group may be substituted [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]);

(16) a C2-C6 alkynlyloxy substituted C1-C6 alkyl group;
(17) a naphthyl C1-C6 alkoxy substituted C1-C6 alkyl group;

(18) a 1,2,4-oxadiazolyl C1-C6 alkoxy substituted C1-C6 alkyl group [wherein, on the 1,2,4-oxadiazole ring, a phenyl group may be substituted];

(19) a pyridyl C1-C6 alkoxy substituted C1-C6 alkyl group [wherein, on the pyridine ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted];

(20) a thiazolyl C1-C6 alkoxy substituted C1-C6 alkyl group [wherein, on the thiazole ring, at least one selected from the group consisting of a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted) and a C1-C6 alkyl group may
be substituted];

(21) a 1,2,3,4-tetrahydronaphthyl Cl-C6 alkoxy substituted Cl-C6 alkyl group [wherein, on the 1,2,3,4-tetrahydronaphthalene ring, at least one Cl-C6 alkyl group may be substituted];

(22) a carbamoyl Cl-C6 alkoxy substituted Cl-C6 alkyl group [wherein, on the amino group, at least one selected from the group consisting of a C3-C8 cycloalkyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted) may be substituted];

(23) a benzofuryl Cl-C6 alkoxy substituted Cl-C6 alkyl group [wherein, on the benzofuran ring, at least one cyano group may be substituted];

(24) a benzofuryl Cl-C6 alkyl group [wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted];

(25) a phenoxy group [wherein, on the phenyl ring, at least one selected from the group consisting of a phenyl Cl-C6 alkoxy group, a C3-C8 cycloalkyl group, a C7-C10 alkoxy group, and a phenoxy group, is substituted];
(26) a naphthyloxy group;
(27) a 2,3-dihydrobenzofuryloxy group [wherein, on the 2,3-dihydrobenzofuran ring, at least one oxo group may be substituted];
(28) a benzothiazolylloxy group [wherein, on the benzothiazole ring, at least one C1-C6 alkyl group may be substituted];
(29) a 1,2,3,4-tetrahydronaphthyloxy group [wherein, on the 1,2,3,4-tetrahydronaphthalene ring, at least one oxo group may be substituted];
(30) a dibenzofuryloxy group;
(31) a quinolylloxy group;
(32) a furyl C1-C6 alkoxy group [wherein, on the furan ring, at least one C1-C6 alkoxy carbonyl group may be substituted];
(33) a tetrazolyl C1-C6 alkoxy group [wherein, on the tetrazole ring, at least one selected from the group consisting of a phenyl C1-C6 alkyl group and a C3-C8 cycloalkyl C1-C6 alkyl group may be substituted];
(34) a 1,2,4-oxadiazoaryl C1-C6 alkoxy group [wherein, on the 1,2,4-oxadiazole ring, a phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)];
(35) a benzothiophenyl C1-C6 alkoxy group [wherein, on the benzothiophene ring, at least one halogen atom may be
(36) an isoxazolyl C1-C6 alkoxy group (wherein, on the isoxazole ring, at least one C1-C6 alkyl group may be substituted); 

(37) a 1,3,4-oxadiazolyl C1-C6 alkoxy group (wherein, on the 1,3,4-oxadiazole ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, at least one C1-C6 alkyl group may be substituted)); 

(38) a naphthyl C1-C6 alkoxy group; 

(39) a pyridyl C1-C6 alkoxy group (wherein, on the pyridine ring, at least one halogen substituted or unsubstituted C1-C6 alkyl group may be substituted); 

(40) a thiazolyl C1-C6 alkoxy group (wherein, on the thiazole ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)); 

(41) a 1,2,3,4-tetrahydronaphthyl C1-C6 alkoxy group (wherein, on the 1,2,3,4-tetrahydronaphthalene ring, at least one C1-C6 alkyl group may be substituted); 

(42) a phenoxy C1-C6 alkoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted);
(43) a carbamoyl C1-C6 alkoxy group (wherein, on the amino group, at least one selected from the group consisting of a C3-C8 cycloalkyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted) may be substituted);

(44) a benzofuryl C1-C6 alkoxy group (wherein, on the benzofuran ring, at least one cyano group may be substituted);

(45) a naphthoxy C1-C6 alkyl group (wherein, on the naphthalene ring, at least one C1-C6 alkoxy group may be substituted);

(46) a benzothiazoxylxyloxy C1-C6 alkyl group (wherein, on the benzothiazole ring, at least one C1-C6 alkyl group may be substituted);

(47) a quinolyloxy C1-C6 alkyl group (wherein, on the quinoline ring, at least one C1-C6 alkyl group may be substituted);

(48) a 2,3-dihydrobenzofuryloxy C1-C6 alkyl group (wherein, on the 2,3-dihydrobenzofuran ring, at least one selected from the group consisting of a C1-C6 alkyl group and an oxo group may be substituted);

(49) a 1,2,3,4-tetrahydronaphthoxy C1-C6 alkyl group (wherein, on the 1,2,3,4-tetrahydronaphthalene ring, at least one oxo group may be substituted);

(50) a 2,3-dihydro-1H-indenylxyloxy C1-C6 alkyl group
(wherein, on the 2,3-dihydro-1H-indene ring, at least one oxo group may be substituted);

(51) a benzoxathiocarbonyloxy Cl-C6 alkyl group (wherein, on the benzoxathiolute ring, at least one oxo group may be substituted);

(52) an isoquinolyl oxy Cl-C6 alkyl group;

(53) a pyridyl oxy Cl-C6 alkyl group;

(54) a dibenzofuryloxy Cl-C6 alkyl group;

(55) a 2H-l-benzopyranloxy Cl-C6 alkyl group (wherein, on the 2H-l-benzopyran ring, at least one oxo group may be substituted);

(56) a benzoisoxazolyl oxy Cl-C6 alkyl group;

(57) a benzofurazanloxy Cl-C6 alkyl group;

(58) a quinoxalyl oxy Cl-C6 alkyl group;

(59) a Cl-C6 alkoxy Cl-C6 alkoxy substituted Cl-C6 alkyl group;

(60) a thienyl Cl-C6 alkoxy substituted Cl-C6 alkyl group (wherein, on the thiophene ring, at least one halogen atom may be substituted);

(61) a phenyl C2-C6 alkenyloxy substituted Cl-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted);

(62) a quinolyl Cl-C6 alkoxy substituted Cl-C6 alkyl group; and

(63) a piperidylcarbonyl Cl-C6 alkoxy substituted Cl-C6
alkyl group,
and further, R^7 and R^8 together may form a group
=C(R^{29})(R^{30}), wherein R^{29} and R^{30} each identically or
differently represent a hydrogen atom, C1-C6 alkyl
group, or phenyl group [wherein, on the phenyl ring, at
least one selected from the group consisting of a
halogen atom, a halogen substituted or unsubstituted
C1-C6 alkyl group, and a halogen substituted or
unsubstituted C1-C6 alkoxy group, may be substituted]);
(iii) a group represented by the following chemical
formula (36):

```
(W_0)_{\alpha} -N---H--R^{13}
```

(wherin W, and \( \alpha \) are the same as above, and R^{13}
represents: a 2,3-dihydro-1H-indenyl group; a
benzothienyl group; a phenyl C2-C10 alkenyl group
[wherein, on the phenyl ring, at least one selected
from the group consisting of a halogen atom, a C1-C4
alkylenedioxy group, a C1-C6 alkylthio group, a benzoyl
group, a cyano group, a nitro group, a C2-C6
alkanoyloxy group, an amino group that may have a C1-C6
alkyl group as a substituent, a hydroxyl group, a
phenyl C1-C6 alkoxy group, a phenoxy group, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a
halogen substituted or unsubstituted C1-C6 alkoxy
group, may be substituted]; a naphthyl C2-C6 alkenyl
group; a benzofuryl C1-C6 alkyl group [wherein, on the
benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted; a benzothienyl C2-C6 alkenyl group; a benzothiazolyl C2-C6 alkenyl group (wherein, on the benzothiazole ring, at least one C1-C6 alkyl group may be substituted); a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the following group is substituted: a piperidinyl group (on the piperidine ring, at least one phenoxy group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)), a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, is substituted), and a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)); a diphenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a
halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]; a benzoyl C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]; an amino group wherein at least one selected from the following group may be substituted: a C1-C6 alkyl group, a C1-C6 alkoxy carbonyl group, and a phenyl C1-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]; an amino C1-C6 alkyl group wherein at least one selected from the group consisting of a C1-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted) may be substituted; a benzofuryl C2-C6
alkenyl group [wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted]; a piperidyl group [wherein, on the piperidine ring, at least one phenyl C2-C6 alkenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)]; a ferrocene substituted C1-C6 alkyl group; an indolyl C1-C6 alkyl group (wherein, on the indole ring, at least one halogen atom may be substituted); a phenyl C2-C6 alkynyl group; a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a C1-C4 alkylenedioxy group, a phenyl group, a C1-C6 alkoxy carbonyl group, a hydroxyl group, and a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), is substituted]; a benzofuryl group [wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom and a C1-C6 alkyl group may be substituted]; a benzothiazolinyl group [wherein, on
the benzothiazoline ring, at least one oxo group may be substituted); a benzothienyl group [wherein, on the benzothiophene ring, at least one halogen atom may be substituted]; a naphthyl group; a 1,2,3,4-tetrahydroquinolyl group [wherein, on the 1,2,3,4-tetrahydroquinoline ring, at least one selected from the group consisting of an oxo group and a Cl-C6 alkyl group may be substituted]; a benzoisoxazolyl group; a 2,3-dihydrobenzofuryl group; a 1,2-dihydroquinolyl group [wherein, on the 1,2-dihydroquinoline ring, at least one oxo group may be substituted]; a 1,2,3,4-tetrahydroquinazolyl group [wherein, on the 1,2,3,4-tetrahydroquinazoline ring, at least one selected from the group consisting of an oxo group and a Cl-C6 alkyl group may be substituted]; a benzocycloheptyl group; a phenoxyl Cl-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]; a benzothienyl substituted Cl-C6 alkyl group [wherein, on the benzothiophene ring, at least one halogen atom may be substituted]; a naphthyl substituted Cl-C6 alkyl group [wherein, on the naphthalene ring, at least one Cl-C6 alkoxy group may be substituted]; a pyridyl substituted Cl-C6 alkyl group [wherein, on the pyridine ring, at least one halogen atom may be substituted]; a furyl substituted Cl-C6 alkyl group [wherein, on the
furan ring, at least one nitro group may be substituted; a thienyl substituted C1-C6 alkyl group [wherein, on the thiophene ring, at least one halogen atom may be substituted]; a thiazolyl substituted C1-C6 alkyl group [wherein, on the thiazole ring, at least one selected from the group consisting of a C1-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom and a halogen substituted or unsubstituted C1-C6 alkyl group may be substituted); a tetrazolyl substituted C1-C6 alkyl group [wherein, on the tetrazole ring, at least one C1-C6 alkyl group may be substituted]; an isoxazolyl substituted C1-C6 alkyl group [wherein, on the isoxazole ring, at least one C1-C6 alkyl group may be substituted]; a 1,2,4-oxadiazolyl substituted C1-C5 alkyl group [wherein, on the 1,2,4-oxadiazole ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, a C1-C6 alkyl group may be substituted)]; or a benzofurazanyl substituted C1-C6 alkyl group);

(iv) a group represented by the following chemical formula (37):

\[
\begin{align*}
\text{R}^{14} \\
\end{align*}
\]

(37)

(wherein \( \text{R}^{14} \) represents: a phenylamino group [wherein, at the N-position of the phenylamino group, a C1-C6").
alkyl group may be substituted, and on the phenyl ring of the phenylamino group, at least one halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted; a piperidyl group [wherein, on the piperidine ring, at least one selected from the group consisting of a phenoxy group (wherein, on the phenyl ring, a halogen substituted or unsubstituted C1-C6 alkoxy group may be substituted) and an amino group (wherein, on the amino group, at least one selected from the group consisting of a C1-C6 alkyl group and a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted] may be substituted as a substituent) may be substituted]; a piperazinyl group [wherein, on the piperazine ring, at least one selected from the following group may be substituted: a C1-C6 alkoxy carbonyl group, a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)].
910
group, may be substituted), and a benzoyl group
(wherein, on the phenyl ring, at least one selected
from the group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a
halogen substituted or unsubstituted C1-C6 alkoxy
group, may be substituted); a phenyl group (wherein,
on the phenyl ring, at least one selected from the
group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a
halogen substituted or unsubstituted C1-C6 alkoxy
group, may be substituted); a homopiperazinyl group
(wherein, on the homopiperazine ring, at least one
selected from the group consisting of a C1-C6
alkoxycarbonyl group and a phenyl C1-C6 alkyl group
(wherein, on the phenyl ring, at least one selected
from the group consisting of a halogen atom, a halogen
substituted or unsubstituted C1-C6 alkyl group, and a
halogen substituted or unsubstituted C1-C6 alkoxy
group, may be substituted) may be substituted); or a
phenoxy group (wherein, on the phenyl ring, at least
one selected from the group consisting of a halogen
substituted or unsubstituted C1-C6 alkoxy group and a
phenoxy substituted phenyl group (wherein, on the
phenyl ring, at least one halogen substituted or
unsubstituted C1-C6 alkoxy group may be substituted),
may be substituted));
(v) a group represented by the following chemical
formula (38):
(wherein R^{13} is the same as above, and a dotted line represents that the bond may be a double bond);
(vi) a homopiperazinyl group (wherein, on the homopiperazine ring, at least one selected from the following group may be substituted: a Cl-C6 alkoxy carbonyl group; a phenyl Cl-C6 alkyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]; a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]; a phenyl Cl-C6 alkoxy carbonyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]; a phenylcarbamoyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted].

(38)
group, may be substituted]; a phenyl C2-C6 alkenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]; and a benzoyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]);

(vii) a group represented by the following chemical formula (39):

\[
\begin{array}{c}
\text{N} \\
\text{R}^{19} \\
\text{R}^{20}
\end{array}
\]

(39)

(wherein \( R^{19} \) represents a Cl-C6 alkoxy group, and \( R^{20} \) represents a phenyl group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted Cl-C6 alkyl group, and a halogen substituted or unsubstituted Cl-C6 alkoxy group, may be substituted]);

(viii) a group \(-\text{CHR}^{20}\text{R}^{21}\)

(wherein \( R^{20} \) is the same as above, and \( R^{21} \) represents an amino group that may have a Cl-C6 alkyl group as a substituent);

(ix) a 1,2,3,4-tetrahydroisoquinolyl group [wherein, on the 1,2,3,4-tetrahydroisoquinoline ring, at least one
amino group may be substituted [wherein, on the amino
group, at least one selected from the group consisting
of a phenyl C1-C6 alkyl group (wherein, on the phenyl
ring, at least one selected from the group consisting
of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group, may be
substituted) and a C1-C6 alkyl group may be
substituted]);
(x) an oxazoly1 group (wherein, on the oxazolo ring, at
least one selected from the following group may be
substituted: a phenyl group (wherein, on the phenyl
ring, at least one selected from the group consisting
of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group, may be
substituted), a C1-C6 alkyl group, and a piperidyl
group (wherein, on the piperidine ring, at least one
phenoxy group may be substituted (wherein, on the
phenyl ring, at least one selected from the group
consisting of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group, may be
substituted));
(xi) an isoindolinyl group (wherein, on the isoindoline
ring, at least one selected from the group consisting
of a halogen atom, a halogen substituted or
unsubstituted C1-C6 alkyl group, and a halogen
substituted or unsubstituted C1-C6 alkoxy group, may be substituted);
(xii) a thiazolyl group (wherein, on the thiazole ring, at least one selected from the following group may be substituted: a phenoxy C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a group -(W₁)OR⁻¹⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻AppBar
ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a piperazinyl group (wherein, on the piperazine ring, at least one phenyl group may be substituted; wherein, on the phenyl ring, at least one member of the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); a piperidyl group (wherein, on the piperidine ring, at least one selected from the group consisting of a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted) and a phenyl C1-C6 alkyl group may be substituted); and a phenoxy group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)); (xiii) a hydroxyl group substituted C1-C6 alkyl group; (xiv) an oxazolyl C1-C6 alkyl group (wherein, on the oxazole ring, at least one phenyl group may be substituted; wherein, on the phenyl ring, at least one
selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted});
(xv) an isoxazolyl group [wherein, on the isoxazoline ring, at least one phenyl ring may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)];
(xvi) a benzoisoxazolyl group [wherein, on the benzoisoxazole ring, at least one halogen atom may be substituted];
(xvii) a phenylthio group [wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted];
(xviii) a benzoimidazolyl group [wherein, on the benzoimidazole ring, at least one selected from the group consisting of a halogen atom and a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted) may be substituted];
(xiv) a pyrrolidinyl group [wherein, on the pyrrolidine ring, at least one amino group is substituted (wherein,
on the amino group, at least one selected from the group consisting of a C1-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); 

(xx) a phenylsulfonyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted); 

(xxii) an imidazolyl group (wherein, on the imidazole ring, at least one phenyl group is substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)); and 

(xxii) a phenylsulfinyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted));

(s) an imidazolyl group (wherein, on the imidazole ring, at least one selected from the group
consisting of a halogen atom and a nitro group may be substituted);

(t) an isoindolinyloxy group (wherein, on the isoindoline ring, at least one selected from the following group may be substituted: a C1-C6 alkoxy carbonyl group, a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a benzofuryl group, a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a phenyl C2-C6 alkenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a furyl C1-C6 alkyl group (wherein, on the furan ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a pyridyl C1-C6 alkyl group (wherein, on the pyridine ring, at least one selected from the group consisting of a furyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6
alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted). A benzofuryl C1-C6 alkyl group (wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a benzothienyl C1-C6 alkyl group (wherein, on the benzothiophene ring, at least one halogen atom may be substituted), a benzofuryl C2-C6 alkenyl group (wherein, on the benzofuran ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), a thiazolyl group (wherein, on the thiazole ring, at least one phenyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)), and a phenoxy C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)).

{u) a benzothiazolidinyloxy group (wherein,
on the benzothiazolidine ring, at least one selected from the group consisting of an oxo group and a phenyl C1-C6 alkyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted), may be substituted); 

(v) an indolyloxy group (wherein, on the indole ring, at least one phenyl C1-C6 alkyl group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)); 

(w) a pyrrolidinyl group (wherein, on the pyrrolidine ring, at least one amino group is substituted (wherein, on the amino group, at least one selected from the group consisting of a C1-C6 alkyl group and a phenyl group (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)); 

(x) an indolinyl group (wherein, on the indoline ring, at least one halogen atom may be substituted); and
(y) an indolinyloxy group [wherein, or the indoline ring, at least one selected from the group consisting of a phenyl C1-C6 alkyl group [wherein, or the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted; and an oxo group may be substituted].

2. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 1, wherein R² represents a group described in any one of (a) to (c), (e) to (h), (j) to (q), and (s) to (y).

3. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 1, wherein R² represents the group described in (d).

4. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 1, wherein R² represents the group described in (i).

5. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 1, wherein R² represents the group described in
6. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 1, wherein R² represents a hydrogen atom.

7. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 1, wherein R² represents a C1-C6 alkyl group.

8. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 1, wherein R² and -(CH₂)₅R³ may bind to each other to form a spiro ring together with the carbon atom adjacent thereto, represented by the following formula (30):

```
     RRR
   /\   \
  /   \  /
R   R   R

(30)
```

wherein RRR represents a piperidyl group [wherein, on the piperidine ring, at least one phenoxy group may be substituted (wherein, on the phenyl ring, at least one selected from the group consisting of a halogen atom, a halogen substituted or unsubstituted C1-C6 alkyl group, and a halogen substituted or unsubstituted C1-C6 alkoxy group, may be substituted)].

9. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a
pharmacologically acceptable salt thereof according to claim 6 or 7, wherein R³ represents the group described in (i).

10. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein R³ represents the group described in (ii).

11. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein R³ represents the group described in (iii).

12. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein R³ represents the group described in (iv).

13. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein R³ represents the group described in (v).

14. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein R³ represents the group described in (vi).
15. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein \( R^3 \) represents the group described in (vii).

16. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein \( R^3 \) represents the group described in (viii).

17. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein \( R^3 \) represents the group described in (ix).

18. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein \( R^3 \) represents the group described in (x).

19. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein \( R^3 \) represents the group described in (xi).

20. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to
claim 6 or 7, wherein \( R' \) represents the group described in (xii).

21. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein \( R' \) represents the group described in (xiii).

22. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein \( R' \) represents the group described in (xiv).

23. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein \( R' \) represents the group described in (xv).

24. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein \( R' \) represents the group described in (xvi).

25. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein \( R' \) represents the group described in (xvii).

26. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole
compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein R represents the group described in (xviii).

27. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein R represents the group described in (xix).

28. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein R represents the group described in (xx).

29. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein R represents the group described in (xxi).

30. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 6 or 7, wherein R represents the group described in (xxii).

31. The 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, or a pharmacologically acceptable salt thereof according to claim 1, which is selected from the group consisting of:
2-methyl-6-nitro-2-(4-{4-(4-
trifluoromethylbenzyloxymethyl)piperidin-1-
yl]phenoxy)ethyl}-2,3-dihydropyrimidazo[2,1-b]oxazole,
(R)-2-methyl-6-nitro-2-(4-{4-(4-
trifluoromethylbenzyloxymethyl)piperidin-1-
yl]phenoxy)ethyl}-2,3-dihydropyrimidazo[2,1-b]oxazole,
(S)-2-methyl-6-nitro-2-(4-{4-(4-
trifluoromethylbenzyloxymethyl)piperidin-1-
yl]phenoxy)ethyl}-2,3-dihydropyrimidazo[2,1-b]oxazole,
2-methyl-6-nitro-2-(4-{4-{4-
chlorophenoxy)ethyl)piperidin-1-yl]phenoxy)ethyl}-2,3-
dihydropyrimidazo[2,1-b]oxazole,
(R)-2-methyl-6-nitro-2-(4-{4-{4-
chlorophenoxy)ethyl)piperidin-1-yl]phenoxy)ethyl}-2,3-
dihydropyrimidazo[2,1-b]oxazole,
(S)-2-methyl-6-nitro-2-(4-{4-{4-
chlorophenoxy)ethyl)piperidin-1-yl]phenoxy)ethyl}-2,3-
dihydropyrimidazo[2,1-b]oxazole,
2-methyl-6-nitro-2-(4-{4-(4-
trifluoromethylicinnamyl)piperazin-1-yl]phenoxy)ethyl}-
2,3-dihydropyrimidazo[2,1-b]oxazole,
(R)-2-methyl-6-nitro-2-(4-{4-(4-
trifluoromethylicinnamyl)piperazin-1-yl]phenoxy)ethyl}-
2,3-dihydropyrimidazo[2,1-b]oxazole,
(S)-2-methyl-6-nitro-2-(4-{4-(4-
trifluoromethylicinnamyl)piperazin-1-yl]phenoxy)ethyl}-
2,3-dihydropyrimidazo[2,1-b]oxazole,
2-methyl-6-nitro-2-(4-{4-{4-
trifluoromethoxybenzyloxy)piperidin-1-yl]phenoxy)methyl}-2,3-dihydroimidazo[2,1-b]oxazole,
(R)-6-nitro-2-(4-(4-trifluoromethoxybenzyloxy)piperidin-1-yl]phenoxy)methyl]-2,3-dihydroimidazo[2,1-b]oxazole,
(S)-6-nitro-2-(4-(4-trifluoromethoxybenzyloxy)piperidin-1-yl]phenoxy)methyl]-2,3-dihydroimidazo[2,1-b]oxazole,
(R)-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxymethyl)piperidin-1-yl)phenoxymethyl]2,3-dihydroimidazo[2,1-b]oxazole,

(S)-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxymethyl)piperidin-1-yl)phenoxymethyl]2,3-dihydroimidazo[2,1-b]oxazole,
(R)-2-methyl-6-nitro-2-[4-\{4-[4-(4-
 trifluoromethylphenyl)piperazin-1-yl]piperidin-1-
yl)phenoxymethyl\}-2,3-dihydroimidazo[2,1-b]oxazole,

(S)-2-methyl-6-nitro-2-[4-\{4-[4-(4-
 trifluoromethylphenyl)piperazin-1-yl]piperidin-1-
yl)phenoxymethyl\}-2,3-dihydroimidazo[2,1-b]oxazole,

2-methyl-6-nitro-2-[4-\{4-[4-(4-
 trifluoromethoxyphenoxy)benzyl]piperazin-1-
yl)phenoxymethyl\}-2,3-dihydroimidazo[2,1-b]oxazole,

(R)-2-methyl-6-nitro-2-[4-\{4-[4-(4-
 trifluoromethoxyphenoxy)benzyl]piperazin-1-
yl)phenoxymethyl\}-2,3-dihydroimidazo[2,1-b]oxazole,

(S)-2-methyl-6-nitro-2-[4-\{4-[4-(4-
 trifluoromethoxyphenoxy)benzyl]piperazin-1-
yl)phenoxymethyl\}-2,3-dihydroimidazo[2,1-b]oxazole,

6-nitro-2-[4-\{4-[3-(4-
 trifluoromethoxyphenyl)propyl]piperidin-1-
yl)phenoxymethyl\}-2,3-dihydroimidazo[2,1-b]oxazole,

(R)-6-nitro-2-[4-\{4-[3-(4-
 trifluoromethoxyphenyl)propyl]piperidin-1-
yl)phenoxymethyl\}-2,3-dihydroimidazo[2,1-b]oxazole,

(3)-6-nitro-2-[4-\{4-[3-(4-
 trifluoromethoxyphenyl)propyl]piperidin-1-
yl)phenoxymethyl\}-2,3-dihydroimidazo[2,1-b]oxazole,

2-methyl-6-nitro-2-[4-[2-(4-
 trifluoromethoxyphenyl)oxazol-4-yl]phenoxymethyl\}-2,3-
dihydroimidazo[2,1-b]oxazole,

(R)-2-methyl-6-nitro-2-[4-[2-(4-
trifluoromethoxyphenyl)oxazol-4-yl)phenoxy methyl)-2,3-dihydroimidazo[2,1-b]oxazole,
(S)-2-methyl-6-nitro-2-(4-(2-(4-
trifluoromethoxyphenyl)oxazol-4-yl)phenoxy methyl)-2,3-dihydroimidazo[2,1-b]oxazole,
6-nitro-2-(4-(4-(4-
chlorophenoxy methyl)piperidin-1-yl)phenoxy methyl)-2,3-
dihydroimidazo[2,1-b]oxazole,
(R)-6-nitro-2-(4-(4-(4-
chlorophenoxy methyl)piperidin-1-yl)phenoxy methyl)-2,3-
dihydroimidazo[2,1-b]oxazole,
(S)-6-nitro-2-(4-(4-(4-
chlorophenoxy methyl)piperidin-1-yl)phenoxy methyl)-2,3-
dihydroimidazo[2,1-b]oxazole,
2-methyl-6-nitro-2-(4-(4-(5-
trifluoromethylbenzofuran-2-yl)methylpiperidin-1-
yl)phenoxy methyl)-2,3-dihydroimidazo[2,1-b]oxazole,
(R)-2-methyl-6-nitro-2-(4-(4-(5-
trifluoromethylbenzofuran-2-yl) methylpiperidin-1-
yl)phenoxy methyl)-2,3-dihydroimidazo[2,1-b]oxazole,
(S)-2-methyl-6-nitro-2-(4-(4-(5-
trifluoromethylbenzofuran-2-yl) methylpiperidin-1-
yl)phenoxy methyl)-2,3-dihydroimidazo[2,1-b]oxazole,
2-methyl-6-nitro-2-(4-(2-(4-
chlorophenyl)oxazol-4-yl)phenoxy methyl)-2,3-
dihydroimidazo[2,1-b]oxazole,
(R)-2-methyl-6-nitro-2-(4-(2-(4-
chlorophenyl)oxazol-4-yl)phenoxy methyl)-2,3-
dihydroimidazo[2,1-b]oxazole,
(S)-2-methyl-6-nitro-2-(4-[2-(4-chlorophenyl)oxazol-4-yl]phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole,
6-nitro-2-[4-(4-trifluoromethylphenoxy)methyl]piperidin-1-yl]phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole,
(R)-6-nitro-2-(4-[4-(4-trifluoromethylphenoxy)methyl]piperidin-1-yl]phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole,
(S)-6-nitro-2-(4-[4-(4-trifluoromethylphenoxy)methyl]piperidin-1-yl]phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole,
2-methyl-6-nitro-2-(4-[4-(4-bromocinnamyl)piperazin-1-yl]phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole,
(R)-2-methyl-6-nitro-2-(4-[4-(4-bromocinnamyl)piperazin-1-yl]phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole,
(S)-2-methyl-6-nitro-2-(4-[4-(4-bromocinnamyl)piperazin-1-yl]phenoxy)methyl)-2,3-dihydroimidazo[2,1-b]oxazole,
2-methyl-6-nitro-2-(2-[4-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yloxymethyl)-2,3-dihydroimidazo[2,1-b]oxazole,
(R)-2-methyl-6-nitro-2-[2-(4-trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-yloxymethyl)-2,3-dihydroimidazo[2,1-b]oxazole, and
(S)-2-methyl-6-nitro-2-{2-[(4-trifluoromethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-6-yloxymethyl]-2,3-dihydroimidazo[2,1-b]oxazole.

32. An antituberculous agent, characterized in that said agent comprises the 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound, an optically active form thereof, or a pharmacologically acceptable salt thereof according to claim 1.

33. A method for producing a compound represented by general formula (1):

\[
\text{(1)}
\]

(wherein \(R^1, R^2,\) and \(n\) have the same definitions as described in claim 1), said method comprising:

a reaction of a 4-nitroimidazole compound represented by the following general formula (2):

\[
\text{(2)}
\]

(wherein \(X\) represents a halogen atom or a nitro group), with an epoxy compound represented by the following general formula (3a):
(wherein \( R^1, R^2 \) and \( n \) have the same definitions as described in claim 1), to obtain a compound represented by the following general formula (4a):

\[
\begin{align*}
\text{(3a)}
\end{align*}
\]

(wherein \( R^3, R^2 \) and \( n \) have the same definitions as described in claim 1, and \( X^1 \) represents a halogen atom or a nitro group); and a subsequent ring closure of the obtained compound represented by the above general formula (4a).

34. A method for producing a compound represented by the following general formula (1w):

\[
\begin{align*}
\text{(1w)}
\end{align*}
\]

(wherein \( R^{1a} \) represents a hydrogen atom, or C1-C6 alkyl group, \( R^{2a} \) represents a group described in any one of (a) to (y) according to claim 1, and \( n \) represents an integer between 0 and 5).

said method comprising:
a reaction of a compound represented by the following general formula (3b):

![Chemical Structure Image]

(3b)

(wherein $R^{3a}$ is the same as described above, and $X^1$ represents a halogen atom or nitro group), with a compound $R^{2b}H(5)$ or a salt thereof (wherein $R^{3a}$ represents a group described in any one of (a) to (y) according to claim 1), to obtain a compound represented by the following general formula (4c):

![Chemical Structure Image]

(4c)

(wherein $R^1$ has the same definition as described in claim 1, $R^{2b}$ represents a group described in any one of (a) to (y) according to claim 1, and $X^1$ represents a halogen atom or a nitro group); and a subsequent ring closure of the obtained compound represented by the above general formula (4c).

35. A method for producing a compound represented by the following general formula (1w):
(wherein R\textsuperscript{1A}, R\textsuperscript{2A}, and n have the same definitions as described in claim 34;)

said method comprising:

a reaction of a compound represented by the following general formula (6):

\[
\begin{align*}
\text{R}\textsuperscript{1A} & \quad \text{R}\textsuperscript{1A} \\
\text{O}_2\text{N} & \quad \text{O}_2\text{N} \\
\end{align*}
\]

(6)

(wherin R\textsuperscript{1A} and n have the same definitions as described in claim 34, and R\textsuperscript{15} represents a C1-C6 alkylsulfonyl group or a benzenesulfonyl group wherein a C1-C6 alkyl group may be substituted),

with a compound R\textsuperscript{2A}H(S) or a salt thereof (wherein R\textsuperscript{2A} represents a group described in any one of (a) to (y) according to claim 1).
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D499/04 A61K31/41 A61P31/00
//(C07D499/04, 263:00, 235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbol)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claims No.</th>
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<tbody>
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<td>A</td>
<td>STOVER ET AL.: &quot;A small molecule nitroimidazopyran drug candidate for the treatment of tuberculosis&quot; NATURE, vol. 405, 2000, pages 962-966, XP002319277 Fig. 1, cpd. C61-17341</td>
<td>1-35</td>
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</table>

X Further documents are listed in the continuation of box C.

X Patent family members are listed in Annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document not published on or after the international filing date

"L" later document which may throw a different light on the invention or otherwise difficult to establish the publication date of another document in any other language (IPA symbol)

"O" document relating to an oral disclosure of invention, the content of which can be treated in the same way as information from written or oral documents

"LP" document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search

3 March 2005

Date of mailing of the international search report

17/03/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5816, 38120, Munich, DE

Authorized officer

Fritz, M

Form PCT/ISA/210 (second sheet) (January 2004)
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(57) Abstract: The invention relates to novel, antibacterial active piperidine derivatives of the formula (I), wherein one of U and V represents N, the other represents O or CH. M represents CH₂CH₂, CH₂CH₂, CH₂CH₂CH₂, or CH₂CO₂; R₁ represents alkyl, haloalkyl, alkoxy, haloalkoxy, haloalkoxy, halogen or amines. R₂ represents hydrogen, hydrogen or halogen; R³ represents carboxyl, carboxamide, alkylamino carbonyl, hydroxy, amino carbonyl, 2-nitroaryl or 3-methyl-1,2,4-triazol-5-yl. R₄ represents alkyl, (CH₂)ₙ, haloalkyl, haloalkoxy, haloalkoxy, haloalkoxy, halogen or amines. R₅ represents hydrogen, hydrogen or halogen; R₆ represents carboxyl, carboxamide, alkylamino carbonyl, hydroxy, amino carbonyl, 2-nitroaryl or 3-methyl-1,2,4-triazol-5-yl.
Actelion 65A/T12

New piperidine antibiotics

The present invention concerns novel antibiotics, pharmaceutical antibacterial compositions containing them and the use thereof in the manufacture of a medicament for the treatment of infections (e.g. a bacterial infection). These compounds are useful antimicrobial agents effective against a variety of human and veterinary pathogens including among others Gram positive and Gram negative aerobic and anaerobic bacteria and mycobacteria.

The intensive use of antibiotics has exerted a selective evolutionary pressure on microorganisms to produce genetically based resistance mechanisms. Modern medicine and socioeconomic behaviour exacerbates the problem of resistance development by creating slow growth situations for pathogenic microbes, e.g. artificial joints-related infections, and by supporting long-term host reservoirs, e.g. in immuno-compromised patients.

In hospital settings, an increasing number of strains of Staphylococcus aureus, Streptococcus pneumoniae, Enterococcus spp., and Pseudomonas aeruginosa, major sources of infections, are becoming multi-drug resistant and therefore difficult if not impossible to treat:
- S. aureus is resistant to β-lactam, quinolone and now even to vancomycin;
- S. pneumoniae is becoming resistant to penicillin, quinolone and even to new macrolides;
- Enterococci are quinolone and vancomycin resistant and β-lactams are inefficacious against these strains;
- Enterobacteriaceae are cephalosporin and quinolone resistant;
- P. aeruginosa are β-lactam and quinolone resistant.

Further new emerging organisms like Acinetobacter which have been selected during therapy with the currently used antibiotics are becoming a real problem in hospital settings.

In addition, microorganisms that are causing persistent infections are increasingly being recognized as causative agents or cofactors of severe chronic diseases like peptic ulcers or heart diseases.

A new type of quinoline or naphthridine derivatives having antibacterial activity and therefore useful for treating infections in mammals, particularly in humans have been reported.
WO 99/37635, WO 00/21948, WO 00/21952, WO 00/43383 and WO 03/101138 disclose quinoline, naphthyridine and quinoxaline derivatives containing a 4-methylpiperidinyl spacer.

WO 00/78748, WO 02/50040 and WO 02/050061 disclose quinoline and naphthyridine derivatives containing a piperazinyl spacer.


WO 2004/035569 discloses quinoline and naphthyridine derivatives containing a 3-aminomethylpiperidinyl spacer.


It has now been found that certain novel bicyclic derivatives are useful antimicrobial agents and effective against a variety of multi-drug resistant bacteria. Thus, the present invention relates to novel piperidine derivatives of the general formula

![Chemical Structure](image)

wherein

one of U and V represents N, the other represents N or CH:
M represents CH₂CH₂, CH=CH, CH(OH)CH(OH), CH(OH)CH₂, CH(NH₂)CH₂, COCH₂ or OCH₂;
R¹ represents alkyl, haloalkyl, alkoxy, haloalkoxy, halogen or cyano;
R² represents hydrogen or halogen;
R³ represents carboxy, carboxamido, alkylaminocarbonyl, hydroxy, aminocarbonyloxy, 2-tetrazolyl or 3-methyl-1,2,4-oxadiazol-5-yl;
R⁴ represents alkyl, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, haloalkyl, alkenyl, arylalkyl, aryl-S(O)₅-alkyl, heteroarylalkyl, heteroarylamino carbonylalkyl, heteroaryl-S(O)₅-alkyl, CH₂-CH=CH-aryl or cycloalkyl-S(O)₅-alkyl;

n is an integer from 0 to 3; and
m is 0 or 2 (and preferably 0).

In particular, the compounds of formula I may be compounds of formula I₇₃

\[ \text{I₇₃} \]

wherein
U represents CH and V represents N or U and V are each N;
M represents CH₂CH₂, CH(OH)CH(OH), CH(OH)CH₂ or OCH₂;
R¹ represents alkoxy;
R² represents hydrogen;
R³ represents carboxy, hydroxy or aminocarbonyloxy;
R⁴ represents arylalkyl, aryl-S(O)₅-alkyl, heteroarylalkyl, heteroarylamino carbonylalkyl, heteroaryl-S(O)₅-alkyl or CH₂-C=C-aryl;
n is an integer between 0 and 3; and
m is 0.
Another aspect of this invention relates to compounds of formula I

![Chemical structure](image)

wherein

one of U and V represents N, the other represents N or CH;

M represents CH₂CH₂, CH=CH, CH(OH)CH(OH), CH(OH)CH₂, CH(NH₂)CH₂, COCH₂ or OCH₂;

R¹ represents alkyl, alkoxy, halogen or cyano;

R² represents hydrogen or halogen;

R³ represents carboxy, carboxamido, alkylationcarboxyl, hydroxy, aminocarboxyloxyl, 2-tetrazoyl or 3-methyl-1,2,4-oxadiazol-5-yl;

R⁴ represents C₁-C₅-alkyl, C₂-C₅-alkenyl, arylalkyl, aryl-S(O)₉₅-alkyl, heteroarylalkyl, heteroaryl-S(O)₉₅-alkyl, CH₂-C=O-aryl or cycloalkyl-S(O)₉₅-alkyl;

n is an integer between 0 and 3; and

m is 0 or 2.

A further embodiment of the bicyclic derivatives of the above formula I, I₁ₑ or Iₚ₁ relates to their prodrugs, their tautomers, their optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, meso forms, pharmaceutically acceptable salts, solvent complexes and morphological forms thereof. Particularly preferred are the optically pure enantiomers, optically pure diastereoisomers, meso forms, pharmaceutically acceptable salts, solvent complexes and morphological forms.
The following paragraphs provide definitions of the various chemical moieties for the compounds of formula I and are intended to apply to these compounds unless an otherwise expressly set out definition provides a broader definition:

- The term “alkyl” refers to a saturated straight or branched chain alkyl group, containing from one to nine, preferably one to six, in particular one to four carbon atoms, for example methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl n-hexyl, 2,2-dimethylbutyl, n-octyl. Any alkyl group as defined herein may be substituted with one, two or more substituents, for example F, Cl, Br, I, NH₂, OH, SH, COOH or NO₂. Examples for substituted alkyl groups are trifluoromethyl, trifluoroethyl, hydroxymethyl, hydroxyethyl, carboxymethyl and carboxyethyl.

- The term “cycloalkyl” refers to a saturated, monocyclic or bicyclic group with three to ten carbon ring-atoms, optionally containing one double bond, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, decahydronaphthalenyl, octahydroindenyl or cyclohex-2-ynyl. Any cycloalkyl group as defined herein may be substituted with one, two or more halogen substituents in particular fluorine. Any cycloalkyl group as defined herein may be substituted with one, two or more substituents, for example F, Cl, Br, I, NH₂, OH, SH, COOH or NO₂. An example for substituted cycloalkyl groups is 4-fluorocyclohexyl. The term “cycloalkyl” preferably refers to cyclopentyl and cyclohexyl.

- The term “alkenyl” refers to a straight or branched chain olefinic group with one or two double bonds containing from two to nine, preferably two to six, in particular two to four carbon atoms, for example vinyl, allyl, 2-butene, 3-butenyl, 4-butenyl and 2,4-butadienyl.

- The term “alkoxy” is an “alkyl-O” group, where “alkyl” has the above significance. Examples for substituted alkoxy groups are trifluoromethoxy and trifluoroethoxy.

- The term “halogen” refers to fluorine, chlorine, bromine or iodine, preferably to fluorine or chlorine.

- The term “aryl” refers to an aromatic cyclic group with one, two or three rings, having five to 14 carbon ring-atoms preferably from five or six to ten carbon ring-atoms, for example phenyl or naphthyl groups. Any aryl group as defined herein may be substituted with one, two or more substituents, for example F, Cl, Br, I, OH, NH₂, SH, N₃, NO₂,
carboxy, carbamoyl (CONH$_2$), alkylaminocarbonyl such as methylaminocarbonyl or dimethylaminocarbonyl, alkoxy carbonyl groups such as methoxy or ethoxycarbonyl, alkylsulfonyl groups such as methylsulfonyl or ethylsulfonyl, alkyl groups such as methyl or ethyl, perfluoroalkyl groups such as trifluoromethyl or trifluoroethyl, alkoxy groups such as methoxy, amino groups such as methylamino or dimethylamino, or cyano. Specific examples are 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 4-methylphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-trifluoromethoxy-phenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2,4-dimethoxyphenyl and 2,4-dimethylphenyl.

The term "heteroaryl" refers to an aryl group as defined herein where one, two or more ring-carbon atoms are replaced by an oxygen, nitrogen or sulphur atom, for example thophenyl, furyl, pyridyl, imidazolyl, pyrazolyl, quinolinyl, isoquinolinyl, pyrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, thiadiazolyl, indolyl, indazolyl, tetrazolyl, pyrazinyl, pyrimidinyl and pyridazinyl groups.

The term "heteroaryl" also covers bicyclic structures such as benzofuran-2-yl, benzimidazol-2-yl, benzo[1,3]dioxol-5-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, 4H-benzo[1,4]oxazin-3-one-6-yl, 4H-benzo[1,4]thiazin-3-one-6-yl, 3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl, 1H-pyrido[2,3-b][1,4]thiazin-2-one-7-yl, 2,3-dihydro-[1,4]dioxinopyridin-7-yl, 2,3-dihydro-[1,4]dioxinopyridin-7-yl, 4H-pyrido[3,2-b][1,4]oxazin-3-one-6-yl, 3,4-dihydro-2H-pyrido[3,2-b]thiazin-6-yl, 3-oxo-3,4-dihydro-2H-pyrido[3,2-b]thiazin-6-yl, 3,4-dihydro-1H-quinolin-2-one-7-yl, 3,4-dihydro-1H-quinolin-2-one-7-yl, 2-oxo-3,4-dihydro-1H-[1,8]naphthyridin-6-yl, 6,7-dihydro-[1,4]dioxinopyrimidin-2-yl, 2-oxo-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yl, 2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-7-yl, benzo[1,2,3]thiadiazol-5-yl, benzofuran-3-yl and 7-fluoro-4H-benzo[1,4]thiazin-3-one-6-yl. Any heteroaryl group as defined herein may be substituted with one, two or more substituents, for example F, Cl, Br, I, OH, NH$_2$, SH, N$_3$, NO$_2$, carboxyl, carbamoyl (CONH$_2$), alkylaminocarbonyl such as methylaminocarbonyl or dimethylaminocarbonyl, alkoxy carbonyl groups such as methoxy or ethoxycarbonyl, alkylsulfonyl groups such as methylsulfonyl or ethylsulfonyl, alkyl groups such as methyl or ethyl, perfluoroalkyl groups such as trifluoromethyl or trifluoroethyl, alkoxy groups such as methoxy, amino groups such as methylamino or dimethylamino, or cyano. Specific examples are thiophen-
2-yl, thiazol-2-yl, 4-methyl-thiazol-2-yl, 5-trifluoromethyl-pyridin-2-yl and benzofuran-2-yl.

The aforesaid groups "alkyl", "aryl" and "heteroaryl" when combined to form the groups "arylalkyl", "aryl-S(O)m-alkyl", "heteroarylalkyl" and "heteroaryl-S(O)m-alkyl" have the same exemplary meaning as their constituents discussed above. As brief examples only, the combinations can mean:

- "alkylaminocarbonyl": methylaminocarbonyl, ethylaminocarbonyl;
- "arylalkyl": benzyl, phenethyl, napthethylmethyl, 4-fluorobenzyl,
  2,4-dimethoxybenzyl, 2,4-di-trifluoromethyl-phenethyl;
- "aryl-S(O)m-alkyl": phenylsulfonylthethyl, 2-trifluoromethyl-phenylsulfonylthethyl,
  3-trifluoromethyl-phenylsulfonylthethyl, 4-trifluoromethyl-phenylsulfonylthethyl,
  4-fluoro-phenylsulfonylthethyl, 2,5-difluoro-phenylsulfonylthethyl;
- "heteroarylalkyl": thiophen-2-yl-propyl, pyrrol-2-yl-propyl, pyrid-2-yl-propyl,
  thiazol-2-yl-propyl, 5-fluoro-pyridin-2-yl-propyl or benzofuran-2-yl-propyl;
- "heteroaryl-S(O)m-alkyl": thiophen-2-yl-sulfonylthethyl, thiazol-2-yl-sulfonylthethyl,
  pyrrol-2-yl-sulfonylthethyl, pyridin-2-yl-sulfonylthethyl, pyridin-2-yl-sulfonylethyl,
  4-fluoro-thiazol-2-yl-sulfonylethyl, 3-trifluoromethyl-pyrrol-2-yl-sulfonylethyl;
- "CH3-C=CH-alkyl": 3-phenyl-propargyl, 3-(4-fluoro-phenyl)-propargyl,
  3-(2-trifluoromethyl-phenyl)-propargyl;
- "cycloalkyl-S(O)m-alkyl": cyclohex-2-yl-sulfonylthethyl, cyclopent-2-yl-sulfonylethyl.

The following paragraphs provide definitions of the various chemical moieties for the compounds according to the invention and are intended to apply uniformly throughout the specification and claims (except for the compounds of formula I, that have their own definitions), unless an otherwise expressly set out definition provides a broader or narrower definition:

The term "alkyl" refers to a saturated straight or branched chain alkyl group, containing from one to nine, preferably one to six, in particular one to four carbon atoms, for example methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, n-hexyl, 2,2-dimethylbutyl, n-octyl. The term "(C1-C9)alkyl" (x being an integer) refers to an alkyl group containing 1 to x carbon atoms.
The term "haloalkyl" refers to a saturated straight or branched chain alkyl group, containing from one to six and preferably one to four carbon atoms, in which at least one hydrogen atom (and possibly all) has been replaced by a halogen atom. Representative examples of haloalkoxy groups include, but are not limited to, trifluoromethyl or 2,2,2-trifluoroethyl. The term "(C<sub>1</sub>-C<sub>x</sub>)haloalkyl" (x being an integer) refers to a straight or branched chain haloalkyl group containing 1 to x carbon atoms.

The term "cycloalkyl", alone or in combination, refers to a saturated, monocyclic or bicyclic group with three to ten carbon ring-atoms, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cycloheptenyl, cyclooctenyl, decahydronaphthalenyl or octahydroindenyl. The term "cycloalkyl" preferably refers to cyclopentyl or cyclohexyl.

The term "alkoxy" refers to a saturated straight or branched chain alkoxy group, containing from one to nine, preferably one to six, and in particular one to four carbon atoms. Representative examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, iso-propanoy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy or n-hexyloxyl. The term "(C<sub>1</sub>-C<sub>x</sub>)alkoxy" refers to a straight or branched chain alkoxy group containing 1 to x carbon atoms.

The term "haloalkoxy" refers to a saturated straight or branched chain alkoxy group, containing from one to six and preferably one to four carbon atoms, in which at least one hydrogen atom (and possibly all) has been replaced by a halogen atom. Representative examples of haloalkoxy groups include, but are not limited to, trifluoromethoxy or difluoromethoxy. The term "(C<sub>1</sub>-C<sub>x</sub>)haloalkoxy" (x being an integer) refers to a straight or branched chain haloalkoxy group containing 1 to x carbon atoms.

The term "halogen" refers to fluorine, chlorine, bromine or iodine, and preferably to fluorine or chlorine.

The term "alkylaminocarbonyl" means an alkylaminocarbonyl group wherein the alkyl group is a (C<sub>1</sub>-C<sub>x</sub>)alkyl group.

The term (C<sub>1</sub>-C<sub>x</sub>)alkoxy-(C<sub>1</sub>-C<sub>y</sub>)alkyl refers to a (C<sub>1</sub>-C<sub>y</sub>)alkyl group as previously defined itself substituted with a (C<sub>1</sub>-C<sub>x</sub>)alkoxy group as previously defined.

The term "alkenyl" refers to a straight or branched chain olefinic group with one or two double bonds containing from two to nine, preferably two to six, in particular two to four.
carbon atoms, for example vinyl, allyl, 2-buteryl, 3-butearyl, 4-butenyl and 2,4-butadienyl. The term “(C_2-C_x)alkenyl” (x being an integer) refers to an alkyl group containing 2 to x carbon atoms.

The term “aryl”, alone or in combination, refers to an aromatic cyclic group with one, two or three rings, having five to 14 carbon ring-atoms preferably from five or six to ten carbon ring-atoms, for example phenyl or naphthyl groups. Any aryl group as defined herein may be substituted with one to three substituents each independently selected from the group consisting of halogen, OH, NH_2, carboxyl, carbamoyl (CONH_2), methylaminocarbonyl, dimethylaminocarbonyl, methoxy carbonyl, ethoxy carbonyl, (C_1-C_4)alkyl, trifluoromethyl, (C_1-C_4)alkoxy, trifluoromethoxy and cyano (preferably, an aryl group will be optionally substituted with one to three substituents independently selected from the group consisting of halogen, (C_1-C_4)alkyl and (C_1-C_4)alkoxy). Specific examples of aryl are 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 4-methylphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 3,4-difluorophenyl, 2,4-dimethoxyphenyl and 2,4-dimethylphenyl.

The term “heteroaryl”, alone or in combination, refers to an aryl group as defined herein where one, two or more ring-carbon atoms are replaced by an oxygen, nitrogen or sulphur atom, for example thiophenyl, furyl, pyridyl, imidazolyl, pyrazolyl, benzofuran-2-yl, benzimidazol-2-yl, benzothiazol-2-yl, quinolinyl, isoquinolinyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, thiadiazolyl, indolyl, indazolyl, tetrazolyl, pyrazinyl, pyrimidinyl and pyridazinyl groups. Any heteroaryl group as defined herein may be substituted with one or two substituents each independently selected from the group consisting of halogen, OH, NH_2, carboxyl, carbamoyl (CONH_2), methylaminocarbonyl, dimethylaminocarbonyl, methoxy carbonyl, ethoxy carbonyl, (C_1-C_4)alkyl, trifluoromethyl, (C_1-C_4)alkoxy, trifluoromethoxy and cyano (preferably, a heteroaryl group will be optionally substituted with one or two substituents each independently selected from the group consisting of halogen, (C_1-C_4)alkyl and (C_1-C_4)alkoxy). Specific examples are thiophen-2-yl, thiazol-2-yl, 4-methyl-thiazol-2-yl, 5-trifluoromethyl-pyrimid-2-yl and benzofuran-2-yl.
The term "arylalkyl" refers to an arylalkyl group wherein the aryl group is an aryl group as defined previously and the alkyl group is a \((C_1-C_4) alkyl\) group.

The term "aryl-S(O)_m-alkyl" refers to an aryl-S(O)_m-alkyl group wherein the aryl group is an aryl group as defined previously and the alkyl group is a \((C_1-C_4) alkyl\) group.

The term "heteroarylalkyl" refers to a heteroarylalkyl group wherein the heteroaryl group is a heteroaryl group as defined previously and the alkyl group is a \((C_1-C_4) alkyl\) group.

The term "heteroarylaminocarbonylalkyl" refers to a heteroarylaminocarbonylalkyl group wherein the heteroaryl group is a heteroaryl group as defined previously and the alkyl group is a \((C_1-C_4) alkyl\) group.

The term "heteroaryl-S(O)_m-alkyl" refers to a heteroaryl-S(O)_m-alkyl group wherein the heteroaryl group is a heteroaryl group as defined previously and the alkyl group is a \((C_1-C_4) alkyl\) group.

The term "CH₂-CH=CH-aryl" refers to a CH₂-CH=CH-aryl group wherein the aryl group is an aryl group as defined previously.

The term "cycloalkyl-S(O)_m-alkyl" refers to a cycloalkyl-S(O)_m-alkyl group wherein the cycloalkyl group is a cycloalkyl group as defined previously and the alkyl group is a \((C_1-C_4) alkyl\) group.

When in the formula
M represents the radical OCH$_2$, this means specifically that the oxygen atom of the OCH$_2$ radical is attached to the group whereas CH$_3$ part of the OCH$_3$ radical is attached to the group. The same is applicable mutatis mutandis to the other asymmetric meanings of the group M.

As brief examples only, the combinations "alkylaminocarbonyl", "aryllalkyl", "aryl-S(O)$_m$-alkyl", "heteroarylalkyl", "heteroaryl-S(O)$_m$-alkyl", "CH$_2$-CH=CH-aryl" and "cycloalkyl-S(O)$_m$-alkyl" can mean:

- "alkylaminocarbonyl": methylaminocarbonyl or ethylaminocarbonyl;
- "aryllalkyl": benzy1, phenethyl, naphthylmethyl, 4-fluorobenzyl, 2,4-dimethoxybenzyl or 2,4-di-trifluoromethyl-phenethyl;
- "aryl-S(O)$_m$-alkyl": phenylsulfanylthyl, 2-trifluoromethyl-phenylsulfanylthyl, 3-trifluoromethyl-phenylsulfanylthyl, 4-trifluoromethyl-phenylsulfanylthyl, 4-fluoro-phenylsulfanylthyl or 2,5-difluoro-phenylsulfanylthyl;
- "heteroarylalkyl": thiophen-2-yl-propyl, pyrrol-2-yl-propyl, pyrid-2-yl-propyl, thiazol-2-yl-propyl, 5-fluoro-pyridin-2-yl-propyl, benzofuran-2-yl-propyl or benzofuran-2-yl-methyl;
- "heterocaryl-S(O)ₘ-alkyl": thiophen-2-ylsulfanyethyl, thiazol-2-ylsulfanyethyl, pyrrol-2-yl-sulfanyethyl, pyridin-2-yl-sulfanyethyl, pyridin-2-yl-sulfonyl-ethyl, 4-fluoro-thiazol-2-ylsulfanyethyl or 3-trifluoromethyl-pyrrol-2-yl-sulfanyethyl;
- "CH₂=CH-aryl": (2,5-difluoro-phenyl)-allyl;
- "cycloalkyl-S(O)ₘ-alkyl": cyclohexylsulfanyethyl or cyclopentylsulfanyethyl.

Compounds of formula I carrying a double bond in M are present as Z/E (cis/trans) isomer mixtures or as Z (cis) or E (trans) isomers. Preferred are the E (trans) isomers.

The combinations for the symbols U and V are evident from the following particular structures:

According to a first variant of the invention, the compounds of formula I, Iₑₑ or Iₚₚ will be such that U is CH and V is N.

According to a second variant of the invention, the compounds of formula I, Iₑₑ or Iₚₚ will be such that both U and V are N.

According to a third variant of the invention, the compounds of formula I, Iₑₑ or Iₚₚ will be such that both U is N and V is CH.

Compounds of formula I wherein M is CH₂CH₂, CH(OH)CH₂, OCH₂ or CH(OH)CH(OH) (and notably CH₂CH₂, CH(OH)CH₂ or OCH₂) will be preferred.

Also preferred will be compounds of formula I wherein R¹ is C₄-C₃ alkyl, methoxy, ethoxy, trifluoromethyl, trifluoromethoxy or cyano, in particular methyl, methoxy or cyano (and notably methoxy).

Preferably also, R² will be hydrogen or fluorine (and notably hydrogen).

R³ will preferably be carboxy.
R is preferably be phenylsulfanyethyl, 2,5-difluorophenylsulfonyl, cyclopentylsulfanyethyl, cyclohexylsulfanyethyl or thien-2-ylsulfanyethyl. (2,5-difluoro-phenyl)-allyl or benzo[5]. More preferably, R is preferably be phenylsulfanyethyl, 2,5-difluorophenylsulfonyl, cyclopentylsulfanyethyl, cyclohexylsulfanyethyl or thien-2-ylsulfanyethyl (particularly thien-2-ylsulfanyethyl, (2,5-difluoro-phenyl)-allyl or benzo[5]-ylmethyl and more particularly thien-2-ylsulfanyethyl).

n will preferably be 0, 1 or 2 when R is carboxy, carboxamido or alkylaminocarbonyl. n will preferably be 1, 2 or 3 when R is hydroxy or aminocarbonyl.

m is preferably 0.

Besides, preferred compounds of formula I are those wherein at least one of the following characteristics is present:

- U is CH and V is N;
- R is \((C_1-C_2)\)alkyl, \((C_1-C_2)\)haloalkyl, \((C_1-C_2)\)alkoxy, \((C_1-C_2)\)haloalkoxy, halogen or cyano;
- R represents hydrogen or fluorine;
- R represents carboxy, carboxamido, alkylaminocarbonyl, hydroxy or aminocarbonyl;
- M is \(CH_2CH_2\), \(CH=CH\), \(CH(OH)CH(OH)\), \(CH(OH)CH_2\), \(COCH_2\) or \(OCH_2\);
- R is arylalkyl, aryl-S(O)alkyl, heteroarylalkyl, heteroarylaminoalkylalkyl, heteroaryl-S(O)alkyl or \(CH_2=CH\)aryl, n representing each time 0.

More preferred compounds of formula I are those wherein at least one of the following characteristics is present:

- U is CH and V is N;
- R is methoxy or cyano (and in particular methoxy);
- R represents hydrogen;
- R represents carboxy and n is 0 or 1 (and in particular 0);
- M is \(CH_2CH_2\), \(CH(OH)CH(OH)\), \(CH(OH)CH_2\) or \(OCH_2\) (and notably \(CH(OH)CH_2\));
- R is selected from the group consisting of:
- 1a -

- heteroaryloalkyl wherein the heteroaryl is benzofuran-2-yl and the alky group is a (C1-C3)alkyl group (in particular methyl);

- heteroaryl-\text{SO}_{3}\text{H}-alkyl wherein \( m \) is 0, the heteroaryl is 2-thienyl and the alky group is a (C1-C3)alkyl group (in particular ethyl); and

- \( \text{CH}_2-\text{CH} = \text{CH-aryl} \) wherein the aryl is phenyl or 2,5-difluorophenyl.

The stereochemistry of the piperidine ring derives from the degradation product of quinine and is the following \textit{(Tetrahedron Letters} (2001), 42, 3235-38):

\[
\begin{array}{c}
\text{CH}_2 \text{CH} = \text{CH} \text{CH}_2 \text{CH}_2 \text{N} \text{R}^4 \\
\text{R}^4
\end{array}
\]

Preferred compounds of the formula I are the following:

- \((3R,4S)-4-[2-(3\text{-methoxy-quinolin-5-yl}-\text{oxy})\text{-ethyl}]1-[2-(\text{thiophen-2-ylsulfanyl})\text{-ethyl}]\text{-piperidin-3-carboxylic acid}

- \((3R,4R)-4-[3-(3\text{-methoxy-quinolin-5-yl})\text{-propyl}]1-[2-(\text{thiophen-2-ylsulfanyl})\text{-ethyl}]\text{-piperidin-3-carboxylic acid}

- \((3R,4R)-4-[3-(3\text{-methoxy-quinolin-5-yl})\text{-propyl}]1-[2-(\text{thiophen-2-ylsulfanyl})\text{-ethyl}]\text{-piperidin-3-propionic acid}

- \((3R,4S)-3\text{-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl}]1-[2-(\text{thiophen-2-ylsulfanyl})\text{-ethyl}]\text{-piperidin-3-carboxylic acid}

- \((3R,4R)-4-[3\text{RS}-3\text{-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl}]1-[2-(\text{thiophen-2-ylsulfanyl})\text{-ethyl}]\text{-piperidin-3-propionic acid}

- \((3R,4R)-4-[3\text{RS}-3\text{-fluoro-3-methoxy-quinolin-5-yl}-3\text{-hydroxy-propyl}]1-[2-(\text{thiophen-2-ylsulfanyl})\text{-ethyl}]\text{-piperidin-3-carboxylic acid}

- \((3R,4R)-4-[3\text{RS}-3\text{-fluoro-3-methoxy-quinolin-5-yl}-3\text{-hydroxy-propyl}]1-[2-(\text{thiophen-2-ylsulfanyl})\text{-ethyl}]\text{-piperidin-3-propionic acid}
• (3R,4S)-4-[(2-(6-fluoro-3-methoxy-quinolin-5-yloxy)-ethyl)-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidine-3-carboxylic acid
• 3-{(3R,4S)-4-[2-(6-fluoro-3-methoxy-quinolin-5-yloxy)-ethyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl]-propionic acid
5 • (3R,4R)-4-[(3RS)-3-hydroxy-3-(2-methoxy-quinolin-8-yl)-propyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidine-3-carboxylic acid
• 3-{(3R,4S)-4-[(3RS)-3-hydroxy-3-(2-methoxy-quinolin-8-yl)-propyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl]-propionic acid
• (3R,4S)-4-[2-(2-methoxy-quinolin-8-yloxy)-ethyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidine-3-carboxylic acid
10 • 3-{(3R,4S)-4-[2-(2-methoxy-quinolin-8-yloxy)-ethyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl]-propionic acid
• (3R,4R)-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-1-(3-phenyl-propyl)-piperidine-3-carboxylic acid
15 • (3R,4R)-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-1-(2-phenylsulfanyl-ethyl)-piperidine-3-carboxylic acid
• (1R,2R)-3-{(3R,4S)-3-(2-hydroxy-ethyl)-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-4-yl]-1-(3-methoxy-quinoxalin-5-yl)-propane-1,2-diol

and in particular the 14 last compounds mentioned in the list hereabove.

20 Also preferred are the following compounds.
• 3-{(3R,4S)-4-[2-(3-methoxy-quinolin-5-yloxy)-ethyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl]-propionic acid;
• 3-{(3R,4S)-4-[2-(3-methoxy-quinolin-5-yloxy)-ethyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl]-propionic acid;
25 • (3R,4R)-4-[(3-methoxy-quinolin-5-yl)-propyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidine-3-carboxylic acid;
• (3R,4S)-1-benzofuran-2-ylmethyl-4-[3-(3-methoxy-quinolin-5-yl)-propyl]-piperidine-3-carboxylic acid;
• (3R,4R)-[(4-[(3-methoxy-quinolin-5-yl)-propyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl]-acetic acid;
30 • 2-[(3R,4S)-4-[(3-methoxy-quinolin-5-yl)-propyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl]-ethanol;
The following compounds contain carbamic acid: 2-[(3R,4R)-4-{3-(3-methoxy-quinolin-5-yl)-propyl}-1-{2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl]-ethyl ester; 4-{3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl}-1-{2-(thiophen-2-ylsulfanyl)-ethyl]-piperidine-3-carboxylic acid; 1-benzofuran-2-ylmethyl-(3R,4R)-4-{(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-piperidine-3-carboxylic acid; (3R,4R)-4-{(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl}-1-trans-(3-phenylallyl)-piperidine-3-carboxylic acid; (3R,4R)-1-[3-(2,5-difluoro-phenyl)-allyl]-4-{(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-piperidine-3-carboxylic acid; (3R,4R)-4-{(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl}-1-(thiazol-2-ylcarbamoylmethyl)-piperidine-3-carboxylic acid; (3R,4S)-4-{(2R,5R)-2,3-dihydroxy-3-(3-methoxy-quinolin-5-yl)-propyl}-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl]-acetic acid; (1R,2R)-{(3R,4S)-3-[(3-(2-hydroxy-ethyl)-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-4-yl)]}-1-(3-methoxy-quinolin-5-yl)-propane-1,2-diol; (1R,2R)-{(3R,4S)-3-[1-trans-(2,5-difluoro-phenyl)-allyl]-3-(2-hydroxy-ethyl)-piperidin-4-yl]}-1-(3-methoxy-quinolin-5-yl)-propane-1,2-diol; and the pharmaceutically acceptable salts of the latter.

In particular, the following compounds:
- 3-((3R,4S)-4-[2-(3-methoxy-quinolin-5-yl)-oxyethyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl]-propanoic acid;
- 3-((3R,4S)-4-[2-(3-methoxy-quinolin-5-yl)-oxyethyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl]-prop-1-ol;
- (3R,4R)-4-[3-(3-methoxy-quinolin-5-yl)-propyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidine-3-carboxylic acid;

and their pharmaceutically acceptable salts will be preferred.

Compounds of formula I are suitable for the use as chemotherapeutic active compounds in human and veterinary medicine and as substances for preserving inorganic and organic materials in particular all types of organic materials for example polymers, lubricants, paints, fibres, leather, paper and wood.
These compounds according to the invention are particularly active against bacteria and bacteria-like organisms. They are therefore particularly suitable in human and veterinary medicine for the prophylaxis and chemotherapy of local and systemic infections caused by these pathogens as well as disorders related to bacterial infections comprising pneumonia, otitis media, sinusitis, bronchitis, tonsillitis, and mastoiditis related to infection by Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Enterococcus faecalis, E. faecium, E. cassestlatus, S. epidermidis, S. haemolyticus, or Peptostreptococcus spp.; pharyngitis, rheumatic fever, and glomerulonephritis related to infection by Streptococcus pyogenes. Groups C and G streptococci, Corynebacterium diphteriae, or Actinobacillus haemolyticus; respiratory tract infections related to infection by Mycoplasma pneumoniae, Legionella pneumophila, Streptococcus pneumoniae, Haemophilus influenzae, or Chlamydia pneumoniae; blood and tissue infections, including endocarditis and osteomyelitis, caused by S. aureus, S. haemolyticus, E. faecalis, E. faecium, E. durans, including strains resistant to known antibacterials such as, but not limited to, beta-lactams, vancomycin, aminoglycosides, quinolones, chloramphenicol, tetracyclines and macrolides; uncomplicated skin and soft tissue infections and abscesses, and puerperal fever related to infection by Staphylococcus aureus, coagulase-negative staphylococci (i.e., S. epidermidis, S. haemolyticus, etc.), Streptococcus pyogenes, Streptococcus agalactiae, Streptococcal groups C-F (minute colony streptococci), viridans streptococci, Corynebacterium minutissimum, Clostridium spp., or Bartonella henselae; uncomplicated acute urinary tract infections related to infection by Staphylococcus aureus, coagulase-negative staphylococcal species, or Enterococcus spp.; urethritis and cervicitis; sexually transmitted diseases related to infection by Chlamydia trachomatis, Haemophilus ducreyi, Treponema pallidum, Ureaplasma urealyticum, or Neisseria gonorrhoeae: toxin diseases related to infection by S. aureus (food poisoning and toxic shock syndrome), or Groups A, B, and C streptococci; ulcers related to infection by Helicobacter pylori; systemic febrile syndromes related to infection by Borrelia recurrentis: Lyme disease related to infection by Borrelia burgdorferi; conjunctivitis, keratitis, and dacrocystitis related to infection by Chlamydia trachomatis, Neisseria gonorrhoeae, S. aureus, S. pneumoniae, S. pyogenes, H. influenzae, or Listeria spp.; disseminated Mycobacterium avium complex (MAC) disease related to infection by Mycobacterium avium, or Mycobacterium intracellulare; infections caused by Mycobacterium tuberculosis, M. leprae, M. paratuberculosis, M. kansuri, or M. chelonei; gastroenteritis related to infection by Campylobacter jejuni; intestinal protozoa
related to infection by *Cryprocystispora* spp.; odontogenic infection related to infection by *viridans streptococci*; persistent cough related to infection by *Bordetella pertussis*; gas gangrene related to infection by *Clostridium perfringens* or *Bacteroides* spp.; and atherosclerosis or cardiovascular disease related to infection by *Helicobacter pylori* or *Chlamydia pneumoniae*.

Compounds of Formula (1) according to the present invention are further useful for the preparation of a medicament for the treatment of infections that are mediated by bacteria such as *E. coli*, *Klebsiella pneumoniae* and other *enterobacteriaceae*, *Actinobacter* spp., *Stenothrophomonas maltophilia*, *Neisseria meningitidis*, *Bacillus cereus*, *Bacillus anthracis*, *Corynebacterium* spp., *Propionibacterium* *acnes* and *bacteroides* spp.

Compounds of Formula (1) according to the present invention are further useful to treat protozoal infections caused by *Plasmodium malariae*, *Plasmodium falciparum*, *Toxoplasma gondii*, *Pneumocystis carinii*, *Trypanosoma brucei* and *Leishmania* spp.

The present list of pathogens is to be interpreted merely as examples and in no way as limiting.

As well as in humans, bacterial infections can also be treated in other species like pigs, ruminants, horses, dogs, cats and poultry.

The present invention also relates to pharmaceutically acceptable salts, or solvates and hydrates, respectively, and to compositions and formulations of compounds of formula I.

Examples of pharmaceutically acceptable salts of sufficiently basic compounds of formula I are selected from the group consisting of salts of physiologically acceptable mineral acids like hydrochloric, hydrobromic, sulfuric and phosphoric acid; or salts of organic acids like methylsulfonyl, p-toluensulfonic, lactic, acetic, trifluoroacetic, citric, ascorbic, fumaric, maleic and salicylic acid. Further, a sufficiently acidic compound of formula I may form alkali or earth alkaline metal salts, for example sodium, potassium, lithium, calcium or magnesium salts; ammonium salts; or organic base salts, for example methylamine, dimethylamine, trimethylamine, triethylamine, ethylenediamine, ethanolamine, choline hydroxide, eglumine, piperidine, morpholine, tris-(2-hydroxyethyl)amine, lysine or arginine salts. Compounds of Formula I may be solvated, especially hydrated. The hydration can occur during the process of production or as a consequence of the hygroscopic nature of the
initially water free compounds of Formula I. The compounds of Formula I contain asymmetric C-atoms and may be present either as achiral compounds, mixtures of diastereomers, mixtures of enantiomers or as optically pure compounds.

The pharmaceutical composition according to the present invention contains at least one compound of formula I as the active agent and optionally carriers and/or diluents and/or adjuvants, and may also contain additional known antibiotics.

The present invention also relates to pro-drugs that are composed of a compound of formula I or I too having at least one pharmaceutically acceptable protective group that will be cleaved off under physiological conditions. Such prodrugs have been reviewed by Beaumont, Kevin; Webster, Robert; Gardner, Iain; Dack, Kevin in Current Drug Metabolism (2003), 4(6), 461-485. Examples of such prodrugs are, in case the compound of formula I or I too contains a free carboxylic acid, alkoxyl (e.g. ethoxy), phenacylxyloxy (e.g. benzylxyloxy), OCH(R*)OCOR* (e.g. pivaloyloxy methylloxy), OCH(R*)OCO2R* (e.g. [[(1-methylethoxy)carbonyl]oxy]ethyl ester; proxetil), OCH(R*)OR*, 2-alkyl-, 2-cycloalkyl-, or 2-cycloalkylalkyl-oxycarbonyl-2-alkylidenemethoxy groups, 5-alkyl[1,3]dioxol-2-one-4-ylmethoxy, dialkylamino-alkoxy or acyloxy wherein R* is hydrogen or (C1-C6)alkyl and R* is hydrogen, (C1-C6)alkyl, (C2-C6)alkenyl, (C1-C6)alkoxy-(C1-C6)alkyl, (C1-C6)haloalkoxy-(C1-C6)alkyl, (C3-C6)cycloalkyl or (C3-C6)cycloalkylmethyl. Furthermore, if a free hydroxy group is present on a compound of formula I or I too, it can be protected as a prodrug of the type sulfate (OSO3H), phosphate (OP03H), oxymethylene phosphate (OCH2PO3H2), succinate (OCOCH2CH2COOH), ester of dimethylaminoglycine or of a naturally occurring amino acid, or as an inorganic salt of one of the latter.

As mentioned above, therapeutically useful agents that contain compounds of Formula I, their solvates, salts or formulations are also comprised in the scope of the present invention.

In general, compounds of Formula I will be administered by using the known and acceptable modes known in the art, eitheralone or in combination with any other therapeutic agent. Such therapeutically useful agents can be administered by one of the following routes: oral, e.g. as tablets, dragee, coated tablets, pills, semisolids, soft or hard capsules, for example soft and hard gelatine capsules, aqueous or oily solutions, emulsions, suspensions or syrups, parenteral including intravenous, intramuscular and subcutaneous injection, e.g. as an injectable solution or suspension, rectal as suppositories, by inhalation or insufflation, e.g. as a powder formulation, as microcrystal or as a spray (e.g. liquid aerosol), transdermal, for example via
an transdermal delivery system (TDS) such as a plaster containing the active ingredient, topical or intranasal. The substance of the present invention can also be used to impregnate or coated devices that are foreseen for implantation like catheters or artificial joints. The pharmaceutically useful agents may also contain additives for conservation, stabilisation, e.g. UV stabilizers, emulsifiers, sweetener, aromatisers, salts to change the osmotic pressure, buffers, coating additives and antioxidants.

Another aspect of the invention concerns a method for the treatment of disease comprising the administration to the patient of a pharmaceutically active amount of a derivative of formula 1

**PREPARATION OF COMPOUNDS OF FORMULA 1**

**Abbreviations:**

The following abbreviations are used throughout the specification and the examples:

- **AcOH** - Acetic acid
- **AD-mix α** - 1,4-bis(dihydroquinine)phthalazine, K₃Fe(CN)₆, K₂CO₃ and K₃OsO₄·2H₂O
- **AD-mix β** - 1,4-bis(dihydroquinidine)phthalazine, K₃Fe(CN)₆, K₂CO₃ and K₃OsO₄·2H₂O
- **aq.** - aqueous
- **atm** - atmosphere
- **9-BBN** - 9-borabicyclo[3.3.1]nonane
- **d** - day(s)
- **1,2-DCE** - 1,2-dichloroethane
- **DCM** - dichloromethane
- **DIAD** - diisopropyl azodicarboxylate
- **DIBAH** - diisobutyl aluminium hydride
- **DIPEA** - N,N-diisopropylethylamine
- **DMAP** - 4-dimethylaminopyridine
- **1,2-DME** - 1,2-dimethoxyethane
- **DMF** - N,N-dimethylformamide
<table>
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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
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<tr>
<td>DMPO</td>
<td>1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone</td>
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<td>EA</td>
<td>ethyl acetate</td>
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<td>MsCl</td>
<td>mesyl chloride</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-butyllithium</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NMO</td>
<td>N-methylmorpholine-N-oxide</td>
</tr>
<tr>
<td>organ.</td>
<td>organic</td>
</tr>
<tr>
<td>PPh3</td>
<td>triphenylphosphine</td>
</tr>
<tr>
<td>PTSA</td>
<td>p-toluenesulfonic acid</td>
</tr>
<tr>
<td>RF</td>
<td>retention factor</td>
</tr>
<tr>
<td>SiO₂</td>
<td>silica gel</td>
</tr>
<tr>
<td>TBAF</td>
<td>N-tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBDMS-Cl</td>
<td>tert-butyldimethylsilyl chloride</td>
</tr>
<tr>
<td>TBA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
</tbody>
</table>
The novel compounds of formula I can be manufactured in accordance with the present invention by

a) reacting a compound of the general formula II

\[
\begin{align*}
\text{II} & \quad R^1 \\
& \quad R^2 \\
& \quad L^1
\end{align*}
\]

with a compound of the general formula III

\[
\begin{align*}
\text{III} & \quad R^3 \\
& \quad \text{ICH}_{3}\text{Ph} \\
& \quad \text{L}^2 \text{M} \text{CH} = \text{C} \text{H} \text{H} \\
& \quad \text{H} \quad R^{49}
\end{align*}
\]

wherein L\(^1\) and L\(^2\) are reactive atoms or groups functionally modified to connect the moieties of formulas II and III, R\(^{49}\) is as R\(^4\) or is a nitrogen protecting group such as benzylloxycarbonyl, allyloxycarbonyl or t-butyloxycarbonyl, carboxy and/or hydroxy groups present are protected, and the other symbols are as before.
and, where required, deprotecting such carboxy and/or hydroxy groups and subjecting any nitrogen protecting group $R^{40}$ to the process under b); or

b) $N$-deprotecting a compound of the general formula IV:

![Diagram of IV]

wherein $PG$ is a nitrogen protecting group such as benzzyloxycarbonyl, allyloxycarbonyl or tert-buzyloxycarbonyl, carboxy and/or hydroxy groups present are protected, and the other symbols are as before;

and, where required, deprotecting such carboxy and/or hydroxy groups and treating the $N$-deprotected product with compounds yielding the group $R^4$; or

c) transforming the group $R^{30}$ of a compound of the general formula V:

![Diagram of V]

wherein $R^{30}$ is COOR or OR$^0$, $R$ and $R^9$ are carboxy and hydroxy protecting groups, respectively, and the other symbols are as before,
into the group $R^3$; or

d) converting a compound of formula I into a pharmaceutically acceptable salt thereof.

The starting piperidine derivatives of formula III, wherein $R^{10}$ is a nitrogen protecting group, such as benzzyloxy carbonyl, allyloxy carbonyl or t-butyloxy carbonyl, are manufactured as follows:

Compounds of formula III-1 (Scheme 1) are obtained from the corresponding silyl ethers III-a like for example t-butyldimethylsilyl ethers (compounds of formula III wherein $L^2M$ is TBDMOSOCH$_2$) by treatment with fluoride ions like TBAF, aq. hydrofluoric acid or NaF. These ethers III-a are prepared starting from compound III-b (formula III wherein $R^4$ is COOC(CH$_3$)$_3$, $R^1 = CH\cdot CH_2$, $L^1M = HOCH_2$ and $n = 0$) obtained according to Tetrahedron Letters (2001), 42, 3235-3238 after protection of the primary alcohol as t-butyldimethylsilyl ether (TBDMS) by reaction with t-butyldimethylsilyl chloride in DMF in presence of imidazole between 0°C and 20°C (see J. Am. Chem. Soc. (1972), 94, 6190).


In a further step, compound III-b is oxidized into the corresponding aldehyde III-c wherein $R^4$ is COOC(CH$_3$)$_3$, $R^2 = CHO$, $L^2M =$ TBDMOSOCH$_2$ and $n = 1$ using the Molfat-Swern (see Synthesis (1981), 165), or the Dess-Martin periodinane (see J. Am. Chem. Soc. (1991), 113, 7277) oxidation protocols.

In a further step compound III-c is oxidized into the corresponding acid III-d wherein $R^4$ is COOC(CH$_3$)$_3$, $R^2 = COOH$, $L^2M =$ TBDMOSOCH$_2$ and $n = 1$ using potassium permanganate in an acetone-water mixture (see Synthesis (1987), 85) or sodium chlorite in 2-methyl-2-propanol in presence of 2-methyl-2-butene (see Tetrahedron (1981), 37, 2091-2096).
Compound III-a can also be transformed into the corresponding aldehyde III-e wherein \( R^a \) is COOC(CH\(_2\))\(_3\), \( R^b = \text{CHO} \), \( L^2M \) = TBDMSOCH\(_2\) and \( n = 0 \) by ozonolysis in DCM between -40°C and 40°C.

The corresponding aldehyde III-e is reduced into the corresponding alcohol III-f wherein \( R^a \) is COOC(CH\(_3\))\(_2\), \( R^b = \text{OH} \), \( L^2M \) = TBDMSOCH\(_2\) and \( n = 1 \) using NaBH\(_4\) in methanol or THF between -30°C and 30°C.

Aldehyde III-e is oxidised into the corresponding acid III-g using potassium permanganate in acetic acid or the above-mentioned protocol for the preparation of III-d.

Aldehyde III-e is subjected to Wittig olefination using carbomethoxy triphenylphosphorane in THF, DCM or toluene between -30°C and 110°C or to Wittig Horner olefination using diethylphosphonoacetic acid methyl ester in THF or DCM between -30°C and 60°C in the presence of an alkali base such as potassium methoxide or NaH affording compound III-h wherein \( R^d = \text{COOC(CH\(_3\))\(_2\)}, \ R^f = \text{CH=CHCOOMe}, \ L^2M = \text{TBDMSOCH}\(_2\) \) and \( n = 0 \) (see Org. Synth. Coll. (1973), 5, 509, 547). Compound III-h is further hydrogenated over palladium on charcoal in EA or MeOH at rt affording compound III-i wherein \( R^d = \text{COOC(CH\(_3\))\(_2\)}, \ R^f = \text{COOMe}, \ L^2M = \text{TBDMSOCH}\(_2\) \) and \( n = 2 \).

The ester III-i is transformed into the corresponding acid III-j wherein \( R^d = \text{COOC(CH\(_3\))\(_2\)}, \ R^f = \text{COOH}, \ L^2M = \text{TBDMSOCH}\(_2\) \) and \( n = 2 \) using NaOH or KOH in dioxane/water between 0°C and 100°C.

The ester III-i is reduced into the corresponding alcohol III-k wherein \( R^d = \text{COOC(CH\(_3\))\(_2\)}, \ R^f = \text{OH}, \ L^2M = \text{TBDMSOCH}\(_2\) \) and \( n = 3 \) using LiBH\(_4\) or DIBAH in THF or DCM between -30°C and 30°C.

For compound of formula III wherein \( R^a = 2,2\text{-dimethyl-[1,3]dioxolan-4-yl, and } n = 0, \) compound III-a is transformed into the corresponding dial derivative by treatment either with a catalytic amount of osmium tetroxide in the presence of a co-oxidant such as NMO in aqueous solvent such as acetic or DCM (Chen, J.K., Chem. Rev. (1995), 95, 1761-1795) or with AD mixtures in a water/2-methyl-2-propanol mixture as described in Chem. Rev. (1994), 94, 2483. The dial is then reacted with acetone, acetonemethyl acetate, or 2-methoxypropene in presence of a catalytic amount of acid like PTSA in a solvent like DCM or ether to yield a compound of formula III wherein \( R^a = 2,2\text{-dimethyl-[1,3]dioxolan-4-yl, and } n = 0 \).
dimethyl[1,3]dioxolan-4-yl group represents a masked acid function which can be transformed into the corresponding acid in a later stage by sequential treatment for example with PTSA or HCl in a solvent like THF/water or MeOH and followed by sodium periodi
todate oxidation (see Synthesis, 1974, 229). The resulting aldehyde is further oxidized into the
5 corresponding acid of formula III, i.e. where R^3 = COOH and n = 0, using methods mentioned
above.

Compounds of the general formula III-2 are obtained from the corresponding compounds
III-1 using the Moffat-Swern oxidation protocol (cf. above) The resulting aldehyde is further
converted to the corresponding alkenes using the phosphorane generated from
10 methyltriphenylphosphonium bromide and a base like n-BuLi or potassium tert-butoxide in a
solvent such as THF at a temperature between −80°C and 0°C (see Org. Synth. Coll. (1973),
5, 751). The terminal alkenes is hydroborated using methods mentioned above. The resulting
alcohol is oxidized using said Moffat-Swern oxidation protocol.

The sulfones of the general formula III-3 are generated in two steps from the corresponding
15 alcohols. Indeed, a Mitsunobu reaction between the alcohols III-1 and an appropriate thiol
such as 1-phenyl-1H-tetrazole-5-thiol in conditions previously described affords the
intermediate thiols that can be oxidized to the corresponding sulfones III-3 using aq.
hydrogen peroxide in presence of ammonium heptamolybdate tetrahydrate (see J. Org.
Chem. (1963), 28, 1140).

20 The alkynes of formula III-4 are obtained from compounds of formula III-1 in two steps.
After oxidation of the free alcohol moiety into an aldehyde using a Moffat-Swern oxidation
(see Synthesis (1981), 165), or the Dess-Martin periodinane oxidation (see J. Am. Chem.
Soc. (1991), 113, 7277), the resulting aldehyde is transformed to the corresponding alkyne
using either the protocol developed by Corey and Fuchs (see Tetrahedron Letters (1972),
3769) or more preferably, the method developed by Bestmann using
dimethylidiazomethylphosphonate in presence of K₂CO₃ in MeOH (see Synlett (1996), 521).

The required quinoline and quinazoline derivatives of formula II are either commercially
available or prepared following literature procedures. For example 3-substituted quinazalin-
5-ol (L = OH, U = V = N) are prepared as described by Y. Abe et al. in J. Med. Chem. (1998),
25 41, 4062.
Substituted 5-formylquinoline, 8-formylquinoline, or 5-formylquinoxaline derivatives of formula II are prepared following literature procedures or from the corresponding 5-bromoquinoline, 8-bromoquinoline, or 5-bromoquinoxaline derivatives II (L' = Br) are after treatment with an alkyl lithium such as n-BuLi at a temperature ranging between -80°C and -30°C and subsequent quenching of the lithio specie with DMF as described in J. Org. Chem. 1980, 45, 1514.

\[
\begin{align*}
\text{II-1} & \quad \text{III-1} \\
\text{IV-1} & \quad \text{V-1}
\end{align*}
\]

Scheme 1

In Scheme 1, III-1 is the compound of formula III, wherein L^2M is HOClH, R^4 is a nitrogen protecting group PG and carboxy and/or hydroxy groups are protected; the other symbols have their above meanings.

As shown in Scheme 1, compounds of formula I can be obtained by coupling, for example, a 3-substituted 5-hydroxy quinoline, a 2-substituted 8-hydroxy quinoline, or a 3-substituted 5-hydroxy quinoxaline II-1 with an alcohol derivative III-1. The coupling reaction between II-1 and III-1 may be achieved under Mitsunobu conditions (as reviewed in O. Mitsunobu Synthesis (1981), 1). For example, an alcohol III-1 and a derivative II-1 are reacted to form the ether IV-1 in the presence of diethyl or diisopropyl azodicarboxylate and triphenylphosphine. The reaction may be performed in a wide range of solvents such as DMF, THF, DCM and at a wide range of temperatures (between -78°C and 50°C). An alternate route to IV-1 may require the activation of the alcohol III-1 as for example a tosylate, a
triflate or a mesylate by treatment with TSCI, trifluoromethanesulphonanhydride or MeSCI respectively in the presence of an organic base such as TEA between -40°C and 60°C in a dry aprotic solvent like DCM, MeCN or THF. Once activated, alcohol III-1 reacts with the anion of the hydroxy derivative II-1, generated with a mineral base such as NaH or K₂CO₃ or an organic base such as lithium hexamethyldisilazide, to generate IV-1 between -20°C and 60°C.

Removal of protecting groups (PG) such as t-butoxycarbonyl or benzyloxycarbonyl on the pipidine nitrogen atom in IV-1 is carried out under standard acidic conditions to give the corresponding free amine. Alternatively the benzyloxycarbonyl group can be removed under catalytic hydrogenation over palladium on charcoal. The allyloxycarbonyl protecting group is removed by palladium acetate in presence of an allyl scavenger. The use of protecting groups to mask reactive functionality is well known to those of skill in the art, and other protecting groups are listed in reference book such as P.J. Kocienski ‘Protecting Groups’, Thieme (1994).

The so PG-deprotected amine is then reacted with compounds yielding the group R₃, e.g. an aldehyde and a suitable reducing agent to provide the homologue V-1. The intermediate imine may be formed in a variety of protic or aprotic solvents such as DMF, N,N-dimethylacetamide, DCM, 1,2-DCE, MeOH, MeCN, in presence or not of a drying agent such as molecular sieves. The imine is reduced subsequently or simultaneously with a suitable reagent such as NaBH₄, sodium triacetoxycoborohydride or sodium cyanoborohydride (R.O. and M.K. Hutchins Comprehensive Organic Synthesis, B.M. Trost, I. Fleming, Eds; Pergamon Press: New York (1991). vol. 8, p. 25-78). Alternatively, the PG-deprotected amine may also be alkylated to give product V-1 by nucleophilic displacement of a suitable alkyl halide, mesylate or tosylate between -20°C and 100°C in a dry aprotic solvent like DCM, MeCN, DMF or THF in presence of a base such as K₂CO₃ or DIPEA.

The introduction of group R₄ can also be effected before coupling of compounds II-1 and III-1.

Carboxy- and hydroxy-protecting groups present are removed under standard conditions well known to those of skill in the art to yield e.g. a product V-1 where R₃ is carboxy or hydroxy.
In Scheme 2, III-2 is the compound of formula III, wherein $L^2M$ is $HC(O)CH_2$, $R^4$ is a nitrogen protecting group $PG$ and carboxy and/or hydroxy groups are protected; the other symbols have their above meanings.

Compounds of formula (I) can also be obtained by reacting for example a substituted quinolin-5-yl lithium, quinolin-8-yl lithium, or quinoxalin-5-yl lithium derivative II-2 with an aldehyde derivative III-2 (Scheme 2). Thus the corresponding 5-bromoquinoline, 8-bromoquinoline, or 5-bromoquinoxaline derivatives III (L$^1$=Br) are treated with an alkyl lithium such as $n$-BuLi in an inert solvent like THF or ether at a temperature between $-100^\circ C$ and $0^\circ C$, preferably between $-80^\circ C$ and $-40^\circ C$. The resulting organolithium derivative II-2 is treated with the corresponding aldehydes III-2 at a temperature between $-100^\circ C$ and $0^\circ C$, preferably between $-80^\circ C$ and $-10^\circ C$. In a subsequent step the nitrogen protecting group is removed and the free amine is reacted with an alkyl halide, mesylate or
tosylate or with an aldehyde under reductive condition as previously described. Finally when appropriate, the ester is deprotected and/or further processed as previously described. The introduction of group R^3 can also be effected before coupling of compounds II-2 and III-2.


\[
\begin{align*}
R^1 & \quad \text{V-3} \\
R^2 & \quad \text{VI-3}
\end{align*}
\]

\[
\begin{align*}
R^3 & \quad \text{VII-3}
\end{align*}
\]

In Scheme 3, all the symbols have their above meanings and carboxy and/or hydroxy groups are protected.

Compounds of formula (I) can also be obtained by reacting for example a substituted 5-formylquinoline, 8-formylquinoline, or 5-formylquinoline derivative II-3 with a sulfone
derivative III-3 in presence of a base such as potassium- or lithium-hexamethyldisilazide in a solvent such as 1,2-DME, DMF or toluene as reviewed by Blakemore, P.R. in J. Chem. Soc., Perkin Trans. 1 (2002), 2563-2585 (Scheme 3). The resulting alkene IV-3 can be further transformed into the diol derivative V-3 by treatment with a catalytic amount of osmium tetroxide in presence of a co-oxidant such as NMO in aqueous solvent such as acetone or DCM (Cha, J.K. Chem. Rev. (1995), 95, 1761-1795). Compounds IV-3 and V-3 are further transformed as described above. The introduction of group R° can also be effected before coupling of compounds II-3 and III-3.

\[
\begin{align*}
\text{II-4} & \quad + \quad \text{III-4} \quad \rightarrow \quad \text{IV-4} \\
\text{V-4} & \quad \rightarrow \quad \text{VI-4}
\end{align*}
\]

Scheme 4

In Scheme 4, all the symbols have their above meanings and carboxy and/or hydroxy groups are protected.

Compounds of formula I can also be obtained by reacting for example a triflate derivative II-4 with an alkyne derivative III-4 under Sonogashira conditions using catalytic amount of a palladium salt, a base such as triethylamine and a catalytic amount of a copper derivative (usually copper iodide) in a solvent such a DMF between 20°C to 100°C (see Sonogashira, K. in Metal-Catalyzed Reactions, Diedrich, P., Stang, P.J., Eds; Wiley-VCH: New York (1998)) (Scheme 4). These trifluoromethanesulphonyloxy derivatives are obtained from the phenol II-1 with trifluoromethanesulphonic anhydride, in the presence of an organic base such as...
triethylamine, N-ethyl-N,N-disopropylamine or pyridine between -40°C and 80°C in an aprotic solvent like DCM or THF (K. Ritter, *Synthesis* (1993), 735). The resulting alkyne IV-4 is hydrogenated to the alkane V-4 using catalytic system such as platinum oxide in a solvent like EtOH or EA or palladium on charcoal in presence of hydrogen. Other methods may also be suitable as reviewed by Siegel, S.; Takaya, H.; Noyori, R.; Pasto, D. J. G. in *Comprehensive Organic Synthesis*, B. M. Trost, I. Fleming, Eds.; Pergamon Press: New York 1991, vol. 8, p. 417-488. The alkane V-4 is further transformed into the compounds VI-4 using procedures previously described. Alternatively, the alkyne IV-3 can also hydrogenated into the alkane V-4 by hydrogenation over palladium on charcoal. Introduction of group R³ is effected, before or after coupling of compounds II-4 and III-4, as previously described.

The transformation of group R³ in compounds V into groups R³ starts with hydrolysis of group COOR or OR³ into carboxy or hydroxy, respectively:

**Hydrolysis of carboxy protecting groups**

Representative carboxy protecting groups are alkyl e.g. methyl, ethyl or t-butyl, heteroalkyl, e.g. trichloroethyl, arylalkyl e.g. benzyl or para nitrobenzyl, alkenyl, e.g. allyl, trialkylsilyl e.g. trimethylsilyl, t-butyldimethylsilyl or di t-butydimethylsilyl, alkylthioalkyl e.g. methylthiomethyl (MTM), alkoxyalkoxyalkyl, e.g. methoxyethoxymethyl (MEM), arylalkoxyalkyl, e.g. benzyloxyalkoxyalkyl (BOM), trialkylsilylalkoxyalkyl, e.g. 2-(trimethylsilyloxy)methyl (SEM), trialkylsilylalkyl, e.g. 2-(trimethylsilyl)ethyl (TMSE).

Further examples of protecting groups to mask acids and the conditions to regenerate them are well known to those of skill in the art, and are listed in reference book such as P.J. Kocienski ‘Protecting Groups’, Thieme, 1994.

**Hydrolysis of hydroxy protecting groups**

Representative hydroxy protecting groups to form ethers are alkyl, e.g. methyl or ethyl, alkoxyalkyl e.g. methoxymethyl (MOM), alkoxyalkoxyalkyl e.g. 2-methoxyethoxymethyl (MEM), trialkylsilylalkoxyalkyl e.g. 2-trimethylsilyloxyalkoxyalkyl (SEM), tetrahydroprpyran-2-yl, allyl, trimethylsilyl (trityl), alkyl or arylsilyl ether e.g. triisopropylsilyl (TIPS), t-butyldiphenylsilyl (TBDPS), t-butyldimethylsilyl (TBDMS), or esters like acetate, trichloroacetate or pivalate or carbonates like trichloroethylcarbonate (TROC). Further examples of protecting groups to mask alcohols and the conditions to regenerate them are well known to those of skill in the art, and are listed in reference book such as P.J. Kocienski ‘Protecting Groups’, Thieme, 1994.
The so obtained compounds of formula I where \( R^1 \) is carboxy or hydroxy, can be further transformed to introduce other groups \( R^1 \) as per process step e) as follows:

For compounds of formula I wherein \( R^3 = \) aminocarboxyloxy, the corresponding alcohols (\( R^3 = \) OH) is first treated with trichloroacetyl isocyanate in an aprotic solvent such as DCM or THF between –20°C to 40°C, and subsequently hydrolysed with an aqueous solution of an inorganic base such as potassium carbonate in an alcoholic solvent such as 2-methyl-2-propanol or methanol, usually under refluxing conditions (see J. Am. Chem. Soc. (1982), 104, 1109). Chlorosulfonyl isocyanate may also be used to accomplish this transformation (see J. Org. Chem. (1987), 52, 3342).

For compounds of formula I wherein \( R^1 = \) alkylaminocarbonyl or carbamoyl, the corresponding acids (\( R^3 = \) OH) are activated with carbonyldimidazole and subsequently reacted with ammonia or an alkylamine in a solvent such as THF or DCM between –20°C to 40°C (see J. Am. Chem. Soc. (1995), 117, 7379).

For compounds of formula I wherein \( R^3 = \) 2-tetrazolyl the corresponding alcohols (\( R^3 = \) OH) are activated as mesylate, tosylate or triflate by substitution with sodium cyanide in a solvent like DCM, THF or DMF. The resulting nitriles (\( R^3 = \) CN) are reacted with sodium azide in the presence of \( \text{NH}_3\text{Cl} \) as described in J. Med. Chem. (1967), 10, 149-154 to yield compound of formula III with \( R^1 = \) 2-tetrazolyl.

For compounds of formula I wherein \( R^3 = \) 3-methyl-1,2,4-oxadiazol-5-yl the corresponding acids (\( R^3 = \) COOH) are reacted with acetanilide oxime in the presence of 1-hydroxy pyridin-2(1H)-one and dicyclohexylcarbodiimide in THF between 0°C and 20°C followed by thermal cyclisation in a solvent like THF or toluene as described in J. Med. Chem. 2004, 47, 1487-1513.

The esters can be reduced into the corresponding alcohol using a suitable reagent such as diisobutyl aluminium hydride in a solvent like THF or ether between –20°C and 40°C.

The following examples illustrate the preparation of pharmacologically active compounds of the invention but do not at all limit the scope thereof.
EXAMPLES

All temperatures are stated in °C. All analytical and preparative HPLC investigations on non-chiral phases are performed using RP-C18 based columns. Analytical HPLC investigations are performed on two different instruments with cycle-times of ~2.5 min and ~3.5 min respectively.

Example 1: 3-(3R,4S)-4-{2-(3-methoxy-quinolin-5-yl)oxy}-ethyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl]-propionic acid:

1.i. 3,5-dibromoquinoline:

To concentrated sulfuric acid (130 ml) was added dropwise at 0°C, over 80 min, 3-bromoquinoline (50 g) at a rate allowing the internal temperature to be maintained between 0° and 10°C. After the addition was complete, NBS (48 g) was added portionwise and the reaction mixture was stirred at rt overnight. The reaction mixture was poured onto ice (2 l) and the formed solid was dissolved in DCM (600 ml). The aq. layer was further extracted once with DCM (600 ml) and the combined extracts were washed with 1 M aq. NaOH (300 ml) and concentrated in vacuo. The residue was dispersed in silica gel and the resulting dispersal was loaded on the top of a column and eluted with DCM-Hex (1:1, 3 l) then DCM (3 l) and finally DCM-ether (1:1, 2 l). The title compound was recovered from the last fraction after evaporation to yield 40 g of a white solid.

$^1$H NMR (CDCl₃) δ: 8.94 (d, J = 2.2 Hz, 1H); 8.73 (d, J = 2.2 Hz, 1H); 8.08 (d, J = 8.5 Hz, 1H); 7.88 (d, J = 7.5 Hz, 1H); 7.62 (dd, J = 7.5, 8.5 Hz, 1H).

1.ii. 5-bromo-3-methoxyquinoline:

To a mixture of sodium methoxide (14.5 g) in DMPU (350 ml) heated at 125°C, was added in one portion 3,5-dibromoquinoline (34.5 g). The reaction was then heated at the same temperature for 1 h. The reaction mixture was then cooled to rt and poured onto ice (300 g). After the ice melt, the solid was filtered off and dried under vacuum. The filtrate was extracted with ether (4 x 150 ml). The combined extracts were washed with brine and dried over Na₂SO₄. After filtration, the solvent was evaporated and the residue purified over silica gel (Hex-EA 4-1) to afford a material that was pooled with the solid. The material was
dissolved in DCM and dried over Na₂SO₄. After filtration and evaporation, the solid was further dried under HV to afford the title compound (24.5 g) as a beige solid.

¹H NMR (CDCl₃) δ: 8.68 (d, J = 2.8 Hz, 1H); 8.03 (d, J = 8.3 Hz, 1H); 7.80 (d, J = 7.5 Hz, 1H); 7.72 (d, J = 2.8 Hz, 1H); 7.42 (dd, J = 7.5, 8.3 Hz, 1H); 4.02 (s, 3H).

MS (ESI, m/z): 239.7 [M+H⁺].

1.iii. 3-methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-vl)-quinoline.

To a mixture of bis(pinacolato)diboron (5.38 g), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride DCM complex (1.5 g) and potassium acetate (5.57 g) was added solution of intermediate 1.ii (4.5 g) in DMSO (135 mL). The resulting mixture was stirred at 80°C overnight. After cooling, the reaction mixture was diluted with water (300 mL) and EA (300 mL). The two layers were decanted and the aq. layer was extracted twice with EA (2 x 300 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. The brown residue was chromatographed (EA-Hex 1-4) to afford the title boronate as a white solid (4.81 g).

¹H NMR (CDCl₃) δ: 8.67 (d, J = 2.9 Hz, 1H); 8.49 (d, J = 2.9 Hz, 1H); 8.12 (m, 2H); 7.55 (m, 1H); 3.97 (s, 3H); 1.42 (s, 12H).

MS (ESI, m/z): 285.8 [M+H⁺].

1.iv. 3-methoxy-quinolin-5-ol:

To an ice-chilled solution of intermediate 1.iii (4.81 g), in THF (125 mL) were added 3M aq. NaOH (15.2 mL) and then 30% aq. hydrogen peroxide (7.2 mL). The reaction mixture was stirred at the same temperature for 1 h. Water (50 mL) and 3N aq. HCl was added until the bright yellow color vanished to leave a colourless reaction mixture (pH 6). The reaction mixture was then diluted with EA (300 mL). The two layers were separated and the aq. layer was extracted twice more (2 x 300 mL). The combined org. layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. The residue was triturated with ether and the solid filtered to afford after drying the title compound (2.61 g).

¹H NMR (d6-DMSO) δ: 10.34 (s, 1H); 8.60 (d, J = 3.0 Hz, 1H); 7.76 (d, J = 3.0 Hz, 1H); 7.39 (m, 2H); 6.92 (dd, J = 1.4, 7.2 Hz, 1H); 3.92 (s, 3H).

MS (ESI, m/z): 175.8 [M+H⁺].
1.v. \( (3R, 4S)-4-\{2-\text{tert-butyldimethylsilyloxy}-\text{ethyl}\}-3\text{-vinylpiperidine-1-carboxylic acid tert-buty1 ester} \):

To a solution of \((3R, 4S)-4-\{(2\text{-hydroxy-ethyl}\}-3\text{-vinylpiperidine-1-carboxylic acid tert-buty1 ester}\) (8.68 g, prepared as described in *Tetrahedron Letters* (2001), 42, 3235-3238) in DCM (100 ml) were added successively TEA (9.5 ml), DMAP (4.15 g) and TBDMS-Cl (5.12 g). The reaction mixture was stirred at rt for 3 h, and was concentrated to dryness. The residue was purified by chromatography (EA-Hex 4:1) to afford the title compound (12.1 g) as a colourless oil.

\(^1\)H NMR (CDCl\(_3\)) \( \delta \): 5.79 (m, 1H); 5.11 (m, 1H); 5.06 (m, 1H); 4.07 (br s, 1H); 3.93 (m, 1H); 3.62 (t, \( J = 6.3 \) Hz, 2H); 2.98 (dd, \( J = 3, 12.9 \) Hz, 1H); 2.81 (br s, 1H); 2.25 (br s, 1H); 1.69 (m, 1H); 1.42 (s, 9H); 1.41 (overlapped m, 4H); 0.89 (s, 9H); 0.03 (s, 6H).

MS (ESI, m/z): 370.5 [M+H\(^+\)].

1.vi. \( (3R, 4S)-4-\{2-\text{tert-butyldimethylsilyloxy}-\text{ethyl}\}-3\text{-\{1,2-dihydroxy-ethyl\}-piperidine-1-carboxylic acid tert-buty1 ester} \):

To a solution of intermediate 1.v (11.4 g) in 2-methyl-2-propanol (150 ml) and water (150 ml) was added AD-mix β (43 g). The reaction mixture was then stirred at rt for 3 days. Sodium bisulfite (45 g) was added portion wise and the resulting mixture was stirred for one hour. The two layers were separated and the aq. layer was extracted three times with EA (3 x 200 ml). The combined extracts were washed with brine and dried over Na\(_2\)SO\(_4\). After concentration to dryness, the residue was quickly filtered through a pad of silica gel (EA) to afford the title compound (12.4 g) as a yellowish oil.

MS (ESI, m/z): 404.5 [M+H\(^+\)].

1.vii. \( (3R, 4S)-4-\{2-\text{tert-butyldimethylsilyloxy}-\text{ethyl}\}-3\text{-formylpiperidine-1-carboxylic acid tert-buty1 ester} \):

To a solution of intermediate 1.vi (12.4 g) in acetone (100 ml) was added at rt a solution of sodium periodate (13.5 g) in water (45 ml). The reaction was stirred 1 h and the solids were filtered off. The filtrate was evaporated in vacuo. The residue was extracted with EA (3 x 150 ml). The combined extracts were washed with brine, dried over Na\(_2\)SO\(_4\), filtered and concentrated to dryness to yield the title aldehyde as a colourless oil (11.4 g).

MS (ESI, m/z): 372.2 [M+H\(^+\)].
1.viii. (3R, 4S)-4-[2-(tert-butyl-dimethyl-silyloxy)-ethyl]-3-(2-ethoxycarbonyl-vinyl)-piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 1.vii (11.4 g) in toluene (200 ml) was added (carbethoxymethylene)triphenylphosphorane (12.9 g). The mixture was refluxed for 1 h. After cooling, silica gel (30 g) was added and the solvent was removed under reduced pressure. The residue was purified by chromatography (EA-Hex 1:1) to afford the title unsaturated ester (13.4 g) as a colourless oil.

$^1$H NMR (CDCl$_3$) $\delta$: 6.94 (dd, $J = 8.7$, 15.9 Hz, 1H); 5.92 (dd, $J = 1.2$, 15.9 Hz, 1H); 4.19 (q, $J = 7.2$ Hz, 2H); 4.19 (overlapped m, 1H); 4.02 (br d, $J = 7.9$ Hz, 1H); 3.64 (t, $J = 6.4$ Hz, 2H); 2.98 (dd, $J = 3$, 12.9 Hz, 1H); 2.81 (br s, 1H); 2.45 (br s, 1H); 1.89 (m, 1H); 1.46 (s, 9H), 1.44 (overlapped m, 4H); 1.28 (t, $J = 7.2$ Hz, 3H); 0.89 (s, 9H); 0.03 (s, 6H).

MS (ESI, m/z): 442.5 [M+H$^+$].

1.ix. (3R,4S)-4-[2-(tert-butyl-dimethyl-silyloxy)-ethyl]-3-(2-ethoxycarbonyl-ethyl)-piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 1.viii (13.4 g) in EA (300 ml) was added 10% palladium on charcoal (4.3 g). The reaction was stirred for 2 h under 1 atm of hydrogen. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to afford the title ester (10.9 g) as a colourless oil.

MS (ESI, m/z): 444.6 [M+H$^+$].

1.x. (3R,4S)-3-(2-ethoxycarbonyl-ethyl)-4-(2-hydroxy-ethyl)-piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 1.ix (10.9 g) in THF (100 ml) was added TBAF (1M in THF, 33 ml). The reaction was stirred at rt for 1h and the solvent was removed under reduced pressure. The residue was chromatographed (EA-Hex 1:1 then 2:1) to afford the title alcohol (6.5 g) as a colourless oil.

$^1$H NMR (CDCl$_3$) $\delta$: 4.13 (q, $J = 7.2$ Hz, 2H); 4.07 (br s, 1H); 3.94 (d, $J = 13.5$ Hz, 1H); 3.71 (td, $J = 2.9$, 6.5 Hz, 2H); 2.86 (dd, $J = 2.2$, 13.7 Hz, 1H); 2.81 (br s, 1H); 2.51 (m, 1H); 2.33 (m, 1H); 1.83 (m, 1H); 1.65-1.41 (m, 8H); 1.47 (s, 9H); 1.27 (t, $J = 7.2$ Hz, 3H).

MS (ESI, m/z): 330.4 [M+H$^+$].
1.\text{\textit{x}}. (3R,4S)-3-\{2-ethoxycarbonyl-ethyl\}-4-\{2-(3-methoxy-quinolin-5-yloxy)-ethyl\}-piperidin-1-carboxylic acid tert-buty1 ester:

To a solution of intermediate 1.x (1.65 g) in THF (25 ml) were added, at rt, 3-methoxy-quinolin-5-ol (0.875 g), PPh$_3$ (2.62 g) and DIAD (2 ml). The reaction was stirred overnight at rt. The reaction mixture was then concentrated to dryness and the residue chromatographed over silica gel (EA-Hex 1-2 then 1-1) to afford the title compound (1.4 g) as an oil.

MS (ESI, m/z) : 487.7 [M+H$^+$].

1.\text{\textit{x}}.ii. 5-\{3R,4S\}-4-\{2-(3-methoxy-quinolin-5-yloxy)-ethyl\}-piperidin-3-yl\}-propionic acid ethyl ester:

A solution of intermediate 1.xi (1.4 g) in TFA (3 mL) was stirred at rt for 20 min. The volatiles were removed under reduced pressure and the residue was partitioned between saturated NaHCO$_3$ (40 ml) and a DCM-MeOH mixture (9-1, 100 ml). The aq. layer was extracted three more times with the same mixture and the combined org. layers were washed with brine and dried over Na$_2$SO$_4$. After concentration to dryness, the residue was chromatographed (DCM-MeOH 9-1 containing 1% concentrated NH$_4$OH) to afford the title compound as a colourless oil (1.18 g).

MS (ESI, m/z) : 387.4 [M+H$^+$].

1.xiii. 3-\{3R,4S\}-4-\{2-(3-methoxy-quinolin-5-yloxy)-ethyl\}-1-\{2-(thiophen-2-ylsulfinyl)-ethyl\}-piperidin-3-yl\}-propionic acid ethyl ester:

To a solution of intermediate 1.xii (1.16 g) in DMF (10 ml) were added 2-(2-bromo-ethyl)sulfinyl)thiophene (0.8 g) and DIPEA (1 ml). The reaction mixture was stirred at 80°C for 90 min. The solvent was removed under HV and the residue was chromatographed (DCM-MeOH 19-1 containing 1% aq. concentrated NH$_4$OH) to afford the title compound (0.58 g) as a colourless oil.

$^1$H NMR (CDCl$_3$) δ: 8.68 (d, J = 2.9 Hz, 1H); 7.78 (d, J = 2.9 Hz, 1H); 7.65 (d, J = 8.5 Hz, 1H); 7.45 (dd, J = 7.3, 8.5 Hz, 1H); 7.35 (dd, J = 1.2, 5.3 Hz, 1H); 7.14 (dd, J = 1.2, 3.5 Hz, 1H); 6.98 (dd, J = 3.5, 5.3 Hz, 1H); 6.88 (d, J = 7.3 Hz, 1H); 4.19 (overlapped m, 2H); 4.13 (q, J = 7.1 Hz, 3H); 3.98 (s, 3H); 2.97 (m, 2H); 2.69-2.57 (m, 4H); 2.47 (m, 1H); 2.36-2.17 (m, 3H); 1.95 (m, 4H); 1.71 (m, 4H); 1.25 (t, J = 7.1 Hz, 3H).

MS (ESI, m/z) : 529.1 [M+H$^+$].
1.xiv. 3-[(3'R,4'S)-4-{2-(3-methoxy-quinolin-5-yl)oxy}-ethyl]-1-{2-(thiophen-2-ylsulfanyl)-ethyl}-piperidin-3-yl}-proptic acid:

To a solution of intermediate 1.xiii (0.4 g) in dioxane (5 ml) was added 5N aq. NaOH (3 ml). The reaction was heated at 98°C overnight. After cooling, 3N aq. HCl (5 ml) was added and the mixture was evaporated to dryness. The residue was then directly purified by chromatography (DCM-MeOH 9:1) to afford the title compound (0.23 g) as a grey solid.

1H NMR (δ6-DMSO) δ: 12.08 (br s, 1H); 8.64 (d, J = 2.9 Hz, 1H); 7.72 (d, J = 2.9 Hz, 1H); 7.62 (m, 1H); 7.50 (m, 2H); 7.20 (m, 1H); 7.05 (m, 2H); 4.21 (m, 2H); 3.92 (s, 3H); 2.96 (m, 2H); 2.78-2.45 (m, 4H); 2.43-2.21 (m, 4H); 1.97-1.55 (m, 8H).

MS (ESI, m/z): 501.5 [M+H+].

Example 2: 3-[(3'R,4'S)-4-{2-(3-methoxy-quinolin-5-yl)oxy}-ethyl]-1-{2-(thiophen-2-ylsulfanyl)-ethyl}-piperidin-3-yl}-propan-1-ol:

To an ice-chilled solution of the compound of Example 1 (0.18 g) in THF (5 ml) was added DIBAH (1M in toluene, 1 ml). After 30 min, water (0.1 ml) was added. The mixture was stirred 40 min at rt. After dilution with ether (40 ml), the solids were filtered off and the filtrate was concentrated to dryness. The residue was chromatographed (DCM-MeOH 19:1) to afford the title compound as a colourless oil (0.098 g).

1H NMR (δ6-DMSO) δ: 8.68 (d, J = 2.9 Hz, 1H); 7.78 (d, J = 2.9 Hz, 1H); 7.65 (d, J = 8.5 Hz, 1H); 7.45 (dd, J = 7.3, 8.5 Hz, 1H); 7.35 (dd, J = 1.2, 5.3 Hz, 1H); 7.14 (dd, J = 1.2, 3.5 Hz, 1H); 6.98 (dd, J = 3.5, 5.3 Hz, 1H); 6.86 (d, J = 7.3 Hz, 1H); 4.19 (m, 2H); 3.98 (s, 3H); 3.69 (t, J = 6 Hz, 2H); 2.97 (t, J = 7.4 Hz, 2H); 2.71-2.55 (m, 4H); 2.23 (m, 2H); 1.96-1.55 (m, 10H); 1.43 (m, 1H).

MS (ESI, m/z): 487.4 [M+H+].

Example 3: (3'R,4'R)-4-[3-(3-methoxy-quinolin-5-yl)propyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-carboxylic acid:

Note: two synthetic approaches, i.e. Approach A and Approach B described hereafter, have been used for preparing the compound of Example 3.
**APPROACH A:**

3.A.i. 3-methoxyquinoline-5-carbaldehyde:

To a solution of 5-bromo-3-methoxyquinoline (10 g) in THF (250 ml) cooled to 
-78°C, was added n-BuLi (22 ml). After 15 min, a solution of DMF (10 ml) in ether (20 ml) was quickly added. The solution was stirred 15 min and ethanol (5 ml), followed with 1M NaHSO₄ (40 ml) were added. After warming to rt, the org. layer was diluted with EA (100 ml). The two layers were separated and the aq. layer was extracted once with EA (100 ml). The combined org. layers were washed with brine and concentrated to dryness. The residue was chromatographed (EA-Hex 1:2 then 1:1) to afford the title compound (4.75 g) as a yellowish solid.

1H NMR (CDCl₃) 8: 10.32 (s, 1H); 9.02 (d, J = 2.9 Hz, 1H); 8.75 (d, J = 2.9 Hz, 1H); 8.31 (d, J = 8.3 Hz, 1H); 8.02 (d, J = 7.1 Hz, 1H); 7.72 (dd, J = 7.1, 3.3 Hz, 1H); 4.02 (s, 3H).

MS (ESI, m/z): 187.9 [M+H⁺].

3.A.ii. (3R,4S)-4’-(1-phenyl-1H-tetrazol-5-ylsulfanyl)-ethyl]-3-vinyl-piperidine-1-carboxylic acid tert-butyl ester:

To an ice-chilled solution of (3R,4S)-4-(2-hydroxy-ethyl)-3-vinyl-piperidine-1-carboxylic acid tert-butyl ester (5.66 g, prepared as described in Tetrahedron Letters (2001), 42, 3235-3238) in THF (200 ml) were added successively PPh₃ (11.7 g), 1-phenyl-1H-tetrazole-5-thiol (5.9 g) and dropwise DIAD (10 ml). The reaction mixture was stirred overnight at rt. The solvent was removed under reduced pressure and the residue chromatographed (Hex-EA 4:1) to afford the title compound (12.9 g) as a white solid. The material was contaminated with a side reaction product.

MS (ESI, m/z): 416.4 [M+H⁺].

3.A.iii. (3R,4S)-4’-2’-(1-phenyl-1H-tetrazol-5-sulfonyl)-ethyl]-3-vinyl-piperidine-1-carboxylic acid tert-butyl ester:

To a stirred solution of intermediate 3.A.ii (11.9 g, contaminated), in EtOH (230 ml) was added at rt, a solution of ammonium heptamolybdiate tetrahydrate (3.5 g) in 30% aq. hydrogen peroxide (30 ml). The reaction mixture was stirred for 3 h, and a saturated sodium thiosulfate solution (160 ml) was added. The solvent was removed under reduced pressure and the residue was extracted with EA (3 x 200 ml). The combined org. extracts were washed with
water, dried over Na₂SO₄, filtered and concentrated to dryness. The residue was chromatographed (EA-Hex 1:3 then 1:2) to afford the title sulfone along with some contaminants. The material was dissolved in EA and Hex was added until a white solid formed. The solid was removed by filtration and the filtrate was concentrated in vacuo to afford 3 g of the sulfone.

MS (ESI, m/z): 448.5 [M+H⁺].

3.A.iii. (3R,4S)-3-(2,2-dihydroxy-ethyl)-4-[2-(1-phenyl-1H-tetrazole-5-y)sulfanyl]-ethylpiperidine-1-carboxylic acid tert-butyl ester:

To a stirred solution of intermediate 3.A.iii (6.3 g) in 2-methyl-2-propanol (70 mL) and water (70 mL) was added at rt AD-mix α (30 g). The reaction mixture was stirred overnight and sodium bisulfite (34 g) was added portion wise. The two layers were separated and the aq. layer was extracted with EA (3 x 150 mL). The combined org. extracts were washed with brine and dried over Na₂SO₄. After filtration and evaporation to dryness, the residue was chromatographed (EA-Hex 4:1) to afford the title diol (3.35 g) as a white solid.

MS (ESI, m/z): 482.4 [M+H⁺].

3.A.v. 3-(2,2-dimethyl-[1.3]dioxolan-4-yi)-4-[2-(1-phenyl-1H-tetrazole-5-y)sulfanyl]-ethylpiperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 3 iv (3.35 g) in DCM (50 mL) was added, at rt, PTSA (0.07 g) and 2,2-dimethoxypropane (1.71 mL). The reaction was stirred at rt for 40 min and 1M aq. NaHCO₃ (10 mL) was added. The two layers were separated and the aq. layer was extracted once with DCM (100 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and filtered. After concentration to dryness, the residue was chromatographed (EA-Hex 1:2) to yield the title acetamide (3.42 g) as a colourless oil.

³¹H NMR (CDCl₃) δ: 7.74-7.60 (m, 5H); 4.20 (m, 1H); 4.02 (m, 2H); 3.93-3.61 (m, 4H);

3.23 (br s, 1H); 2.96 (br d, J = 12.1 Hz, 1H); 2.29 (m, 1H); 2.16-1.91 (m, 2H); 1.84 (m, 1H);

1.68 (m, 2H); 1.47 (s, 9H); 1.69 (s, 3H); 1.34 (s, 3H).

MS (ESI, m/z): 522.5 [M+H⁺].

3.A.vi. (3R,4R)-3-(2,2-dimethyl-[1.3]dioxolan-4-yi)-4-[3-(methoxy-quinolin-5-yi)-allyl]-piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 3.A.v (3.42 g) in 1,2-dimethoxyethane (24 mL) was added 3-methoxyquinoline-5-carbaldehyde (1.1 g). The mixture was cooled to -60°C and a solution
of potassium bis(trimethylsilylamide) (0.5M in toluene, 20 ml) was added dropwise over 20 min. After the addition was complete, the reaction was stirred 10 min at the same temperature and water (20 ml) was added. The mixture was warmed to rt, and was extracted with EA (3 x 150 ml). The combined extracts were washed with brine, dried over Na2SO4, filtered and concentrated to dryness. The residue was chromatographed (EA-Hex 1:2) to afford the title compound (2.52 g) as a white foam. The compound was recovered as a 2:1 mixture of epimers.

1H NMR (CDCl3) δ: 8.70 (d, J = 2.8 Hz, 1H); 7.97 (app d, J = 8.2 Hz, 1H); 7.65-7.50 (m, 3H); 7.02 (d, J = 15.2 Hz, 1H); 6.31 (ddd, J = 6.0, 8.4, 15.2 Hz, 0.66H); 6.17 (td, J = 7.2, 15.2 Hz, 0.33H); 4.16 (m, 2H); 3.72 (m, 1H); 3.69-3.22 (m, 4H); 2.69 (m, 2x0.33H); 2.44 (m, 2x0.66H); 2.19-2.05 (m, 0.66H); 2.03-1.83 (m, 1.33H); 1.69 (m, 2H); 1.49 (s, 9x0.66H); 1.48 (s, 9x0.33H); 1.43 (s, 3x0.66H); 1.42 (s, 3x0.33H); 1.39 (s, 3x0.66H); 1.38 (s, 3x0.33H).

MS (ESI, m/z): 483.3 [M+H+].

3-A.vii. (3R,4R)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-[3-(3-methoxy-quinolin-5-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 3.A.vi (2.52 g) in EA (40 ml) was added 10% palladium on charcoal (2 g). The reaction mixture was stirred under one hydrogen atm for 90 min. The catalyst was removed by filtration and the filtrate concentrated to dryness. The residue was chromatographed (EA-Hex 1:1) to afford the title compound (2.25 g) as a colourless foam.

1H NMR (CDCl3) δ: 8.70 (d, J = 2.8 Hz, 1H); 7.97 (app d, J = 8.2 Hz, 1H); 7.41-7.34 (m, 2H); 7.14 (m, 1H); 3.88-3.75 (m, 2H); 3.76 (s, 3H); 3.38 (m, 1H); 3.26-2.84 (br m, 4H); 2.80 (m, 2H); 1.60-1.24 (m, 8H); 1.23 (s, 9H); 1.16 (s, 3x0.33H); 1.11 (3x0.66H); 1.09 (3x0.33H); 1.07 (3x0.66H).

MS (ESI, m/z): 485.4 [M+H+].

3-A.viii. (3R,4R)-3-(1,2-dihydroxy-ethyl)-4-[3-(3-methoxy-quinolin-5-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 3-A.vii (2.25 g) in MeOH (50 ml) was added PTSA (1 g). After stirring for 20 min at rt, the reaction was heated at 60°C for 90 min. The reaction mixture was cooled to rt, and saturated NaHCO3 (30 ml) was added. The volatiles were removed under reduced pressure and the residue was extracted with EA (3 x 150 ml). The combined extracts were washed with brine, dried over Na2SO4, filtered and concentrated to dryness. The residue
was chromatographed (EA-Hex 4-1 then EA-MeOH 19-1) to afford the title alcohol (0.72 g) as a white foam.

MS (ESI, m/z): 445.6 [M+H⁺].

3. A. ix. (3R, 4R)-3-formyl-4-(3-(3-methoxy-quinolin-5-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 3.A.viii (0.72 g) in acetone (15 ml) was added a solution of sodium periodate (1 g) in water (5 ml). The mixture was stirred at rt for 20 min. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated to dryness. The residue was chromatographed (EA-Hex 1:2) to afford the title aldehyde (0.66 g) as a colourless foam.

MS (ESI, m/z): 413.0 [M+H⁺].

3. A. x. (3R, 4R)-4-[3-(3-methoxy-quinolin-5-yl)-propyl]-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester:

To a solution of intermediate 3.A.ix (0.2 g) in acetone (3.5 ml) and water (1.5 ml) was added potassium permanganate (0.766 g). The reaction was stirred at rt for 30 min and the reaction mixture was concentrated to dryness. The residue was chromatographed (EA then EA containing 1% AcOH) to afford the title acid (0.088 g) as a colourless oil.

MS (ESI, m/z): 429.2 [M+H⁺].

A solution of this acid (0.2 g) in benzene (1.8 ml) and MeOH (0.2 ml) was treated dropwise with trimethylsilyl diazomethane (0.2 ml, 2M in hexanes). After stirring for 30 min, AcOH (3 drops) was added and the volatiles were removed under reduced pressure. The residue was chromatographed (EA-Hex 1:1) to afford the title ester (0.065 g) as a colourless oil.

¹H NMR (CDCl₃) δ: 8.70 (br s, 1H); 7.93 (br d, J = 8.4 Hz, 1H); 7.52-7.45 (m, 2H); 7.34 (d, J = 6.3 Hz, 1H); 4.00 (s, 3H); 3.67 (br s, 2H); 3.60 (s, 3H); 3.24 (dd, J = 3.3, 13.5 Hz, 1H); 3.05 (overlapped m, 1H); 3.00 (t, J = 7.5 Hz, 2H); 2.62 (br s, 1H); 1.88-1.73 (m, 5H); 1.54 m (m, 2H); 1.43 (s, 9H).

MS (ESI, m/z): 429.2 [M+H⁺].

3. A. xi. (3R, 4S)-4-[3-(3-methoxy-quinolin-5-yl)-propyl]-l-2-(thiophen-2-ylsulfanyl)-ethyl]-piperidine-3-carboxylic acid methyl ester:

A solution of intermediate 3.A.x (0.061 g) in TFA (2 ml) was stirred at rt for 20 min. The solvent was evaporated and the residue was co-evaporated twice with toluene. The residue
was dissolved in DMF (1 ml). 2-(2-bromo-ethyl)sulfanyl)-thiophene (0.034 g) and DIPEA (0.048 ml) were added. The residue was heated at 80°C for 1 h and the volatiles were removed under reduced pressure. The residue was purified by preparative TLC (DCM-MeOH 49:1) to afford the title compound (0.021 g) as a colourless oil.

MS (ESI, m/z): 485.4 [M+H⁺].

3. A.xii. (3R,4R)-4-[[3-(methoxy-quinolin-5-yl)-propyl]-1-[[2-(thiophen-2-yl)sulfanyl]-ethyl]-piperidine-3-carboxylic acid:

A solution of intermediate 3. A.xi (0.02 g) in dioxane (0.5 ml) and 3N NaOH (0.1 ml) was heated in a screw-capped vial overnight. 3N HCl (0.1 ml) was added and the residue was directly purified by preparative TLC (DCM-MeOH 9:1) to afford the title compound (0.004 g) as an oil.

MS (ESI, m/z): 471.4 [M+H⁺].

APPROACH B:

3. B.i. 3-methoxyquinoline-5-carboxaldehyde:

To a solution of 5-bromo-3-methoxyquinoline (10 g, 42 mmol) in THF (250 ml) cooled to -78°C, was added n-BuLi (2.35N in Hex, 22 ml, 51.7 mmol). After 15 min, a solution of DMF (10 ml) in ether (20 ml) was quickly added. The solution was stirred 15 min and EtOH (5 ml), followed with 1M NaHSO₄ (40 ml) were added. After warming to rt, the org. layer was diluted with EA (100 ml). The two layers were separated and the eq. layer was extracted once with EA (100 ml). The combined org. layers were washed with brine and concentrated to dryness. The residue was chromatographed over SiO₂ (EA-Hex 1:2 then 1:1) to afford the title compound (4.75 g, 25.3 mmol) as a yellowish solid.

¹H NMR (CDCl₃) δ: 10.32 (s, 1H); 9.02 (d, J = 2.9 Hz, 1H); 8.75 (d, J = 2.9 Hz, 1H); 8.31 (d, J = 8.3 Hz, 1H); 8.02 (d, J = 7.1 Hz, 1H); 7.72 (dd, J = 7.1, 8.3 Hz, 1H); 4.02 (s, 3H).

MS (ESI, m/z): 187.9 [M+H⁺].

3. B.ii. (3R,4S)-4-[[2-(1-phenyl-1H-tetrazol-5-yl)sulfanyl]-ethyl]-3-vinyl-piperidine-1-carboxylic acid tert-butyl ester:

To an ice-chilled solution of (3R,4S)-4-(2-hydroxy-ethyl)-3-vinyl-piperidine-1-carboxylic acid tert-butyl ester (prepared as described in Tetrahedron Letters (2001), 42, 3235-3238; 5.66 g; 22.1 mmol) in THF (200 ml) were added successively PPh₃ (11.7 g, 2 eq.), 1-phenyl-
1H-tetrazole-5-thiol (5.9 g, 33.1 mmol) and dropwise DIAD (10 ml, 50.4 mmol). The reaction mixture was stirred overnight at rt. The solvent was removed under reduced pressure and the residue was chromatographed over SiO₂ (Hex-EA 4:1) to afford the title compound (12.9 g) as a white solid. The material was contaminated with a side product reaction.

MS (ESI, m/z): 416.4 [M+H⁺].

3.B.iii. (3R,4S)-4,2-(1-phenyl-1H-tetrazole-5-sulfonyl)-ethyl]-3-vinyl-piperidine-1-carboxylic acid tert-butyl ester:

To a stirred solution of intermediate 3.B.ii (11.9 g, contaminated) in EtOH (250 ml) was added, at rt, a solution of ammonium heptamolybdate tetrahydrate (3.5 g, 2.8 mmol) in 30% aq. H₂O₂ (30 ml). The reaction mixture was stirred for 3 h, and a saturated sodium thiosulfate solution (100 ml) was added. The solvent was removed under reduced pressure and the residue was extracted with EA (3 x 200 ml). The combined org. extracts were washed with water, dried over Na₂SO₄, filtered and concentrated to dryness. The residue was chromatographed over SiO₂ (EA-Hex 1:3 then 1:2) to afford the title sulphone along with some contaminants. The material was dissolved in EA and Hex was added until a white solid formed. The solid was removed by filtration and the filtrate was concentrated in vacuo to afford the sulphone (3 g, 6.7 mmol) as a colourless oil.

MS (ESI, m/z): 448.5 [M+H⁺].

3.B.iv. (3R,4S)-3-(1,2-dihydroxy-ethyl)-4,2-(1-phenyl-1H-tetrazole-5-sulfonyl)-ethyl]-piperidine-1-carboxylic acid tert-butyl ester:

To a stirred solution of intermediate 3.B.iii (6.3 g, 14.0 mmol) in 2-methyl-2-propanol (70 ml) and water (70 ml) was added, at rt, AD-mix α (30 g). The reaction mixture was stirred overnight and NaHSO₃ (34 g) was added portionwise. The two layers were separated and the aq. layer was extracted with EA (3 x 150 ml). The combined org. extracts were washed with brine and dried over Na₂SO₄. After filtration and evaporation to dryness, the residue was chromatographed over SiO₂ (EA-Hex 4:1) to afford the title diol (3.35 g, 6.95 mmol) as a white solid.

MS (ESI, m/z): 482.4 [M+H⁺].
3.B.v. (3R, 4S)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-[(2-(1-phenyl-1H-tetrazole-5-yl)sulfanyl)ethyl]-piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 3.B.iv (3.35 g, 6.95 mmol) in DCM (50 ml) was added, at rt, PTSA (0.07 g, 0.36 mmol) and 2,2-dimethoxypropane (1.71 ml, 13.9 mmol). The reaction was stirred at rt for 40 min and 1M aq. NaHCO₃ (10 ml) was added. The two layers were separated and the aq. layer was extracted once with DCM (100 ml). The combined org. layers were washed with brine, dried over Na₂SO₄ and filtered. After concentration to dryness, the residue was chromatographed over SiO₂ (EA-Hex 1:2) to yield the title acetonide (3.42 g, 6.55 mmol) as a colourless oil.

1H NMR (CDCl₃) δ: 7.74-7.60 (m, 5H); 4.20 (m, 1H); 4.02 (m, 2H); 3.93-3.61 (m, 4H); 3.23 (br s, 1H); 2.96 (br d, J = 12.1 Hz, 1H); 2.29 (m, 1H); 2.16-1.91 (m, 2H); 1.84 (m, 1H); 1.68 (m, 2H); 1.47 (s, 9H); 1.69 (s, 3H); 1.34 (s, 1H).

MS (ESI, m/z): 522.5 [M+H⁺].

3.B.vi. (3R,4R)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-[(3-methoxy-quinoline-5-yl)allyl]-piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 3.B.v (3.42 g, 6.55 mmol) in DME (24 ml) was added 3-methoxyquinoline-5-carbaldehyde (1.1 g, 5.9 mmol). The mixture was cooled to -60ºC and a solution of potassium bis(trimethylsilylamide) (0.5M in toluene, 20 ml, 10 mmol) was added dropwise over 20 min. After the addition was complete, the reaction was stirred 10 min at the same temperature and water (20 ml) was added. The mixture was warmed to rt, and was extracted with EA (3 x 150 ml). The combined extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. The residue was chromatographed over SiO₂ (EA-Hex 1:2) to afford the title compound (2.52 g, 5.22 mmol) as a colourless foam. The compound was recovered as a 2:1 mixture of epimers.

1H NMR (CDCl₃) δ: 8.70 (d, J = 2.8 Hz, 1H); 7.97 (app d, J = 8.2 Hz, 1H); 7.65-7.50 (m, 3H); 7.02 (d, J = 15.2 Hz, 1H); 6.31 (dd, J = 6.0, 8.4, 15.2 Hz, 0.66H); 6.17 (dd, J = 7.2, 15.2 Hz, 0.33H); 4.16 (m, 2H); 3.72 (m, 1H); 3.69-3.22 (m, 4H); 2.69 (m, 2x0.33H); 2.44 (m, 2x0.66H); 2.19-2.05 (m, 0.66H); 2.03-1.83 (m, 1.33H); 1.69 (m, 2H); 1.49 (s, 9x0.66H); 1.48 (s, 9x0.33H); 1.43 (s, 3x0.66H); 1.42 (s, 3x0.33H); 1.39 (s, 3x0.66H); 1.38 (s, 3x0.33H).

MS (ESI, m/z): 483.3 [M+H⁺].
3.B.vii. (3R,4R)-3-(2,2-dimethyl-1H-dioxolan-4-yl)-4-[3-(3-methoxyquinolin-5-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 3.B.vi (2.32 g, 5.22 mmol) in EA (40 ml) was added 10% palladium on charcoal (2 g). The reaction mixture was stirred under hydrogen (1 atm) for 90 min. The catalyst was removed by filtration and the filtrate concentrated to dryness. The residue was chromatographed over SiO₂ (EA-Hex 1:1) to afford the title compound (2.25 g, 4.64 mmol) as a colourless foam.

^1H NMR (CDCl₃) δ: 8.70 (d, J = 2.8 Hz, 1H); 7.97 (app d, J = 8.2 Hz, 1H); 7.41-7.34 (m, 2H); 7.14 (m, 1H); 3.88-3.75 (m, 2H); 3.76 (s, 3H); 3.38 (m, 1H); 3.26-2.84 (br m, 4H); 2.80 (m, 2H); 1.60-1.24 (m, 8H); 1.23 (s, 9H); 1.16 (s, 3x0.33H); 1.11 (3x0.66H); 1.09 (3x0.33H); 1.07 (3x0.66H).

MS (ESI, m/z): 485.4 [M+H⁺].

3.B.viii. (3R,4R)-3-(1,2-dihydroxy-ethyl)-4-[3-(3-methoxyquinolin-5-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester:

A solution of intermediate 3.B.vii (2.7 g, 5.57 mmol) in TFA (10 ml) was stirred 5 min at rt. Water (20 ml) was added and the mixture was further stirred 10 min. The volatiles were removed under reduced pressure and the residue was diluted in 1N aq. NaOH (20 ml) and THF (20 ml). Solid NaOH (0.5 g) and di-tert-butyl dicarbonate (1.8 g, 8.24 mmol) were added. The mixture was stirred 30 min at rt. The volatiles were removed under reduced pressure and the residue was extracted with EA (2 x 150 ml). The combined org. layers were washed with brine and concentrated to dryness. The residue was chromatographed over SiO₂ (Hex-EA 1:1 then EA then EA-MeOH 9:1) to afford the title diol (2.1 g, 4.72 mmol) as a colourless foam.

MS (ESI, m/z): 445.6 [M+H⁺].

3.B.ix. (3R,4R)-3-formyl-4-[3-(3-methoxyquinolin-5-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 3.B.viii (2.1 g, 4.72 mmol) in acetonitrile (15 ml) was added a solution of NaI (3 g, 14 mmol) in water (10 ml). The mixture was stirred at rt for 20 min. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated to dryness. The residue was chromatographed over SiO₂ (EA-Hex 1:2) to afford the title aldehyde (1.45 g, 3.51 mmol) as a colourless foam.
MS (ESI, m/z): 413.0 [M+H⁺].

3.B.x. (3R,4R)-4-[(3-methoxy-quinolin-5-yl)-propyl]-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester:

To a solution of intermediate 3.B.ix (1.45 g, 3.51 mmol) in acetone (35 ml) and water (5 ml) was added KMnO₄ (1.67 g, 10.5 mmol). The reaction mixture was stirred at rt for 30 min. Na₂S₂O₃ (1.5 g) and saturated sodium thiosulfate (10 ml) were added. After stirring 15 min, the reaction mixture was filtered through a pad of celite (eluent: EA containing 1% acetic acid). The filtrate was concentrated *in vacuo* and partitioned between water (30 ml) and EA (100 ml). The aq. layer was extracted twice more (2 x 100 ml) with EA. The combined extracts were washed with brine and dried over Na₂SO₄. After filtration and concentration to dryness, the residue was filtered quickly through a plug of SiO₂ (EA) to afford the title acid (1.5 g, 3.5 mmol) as an oil.

MS (ESI, m/z): 429.4 [M+H⁺].

To a solution this acid (1.5 g) in benzene (25 ml) and MeOH (5 ml) was added dropwise trimethylsilyldiazomethane (4 ml, 2M in Hex). The reaction proceeded for 30 min and AcOH (3 ml) was added. After stirring 10 min, the reaction mixture was diluted with EA (100 ml) and 1M aq. NaOH (20 ml) was added. The two layers were separated and the aq. layer was extracted once with EA (100 ml). The combined org. extracts were washed with brine and concentrated to dryness. The residue was chromatographed over SiO₂ (EA-Hex 1:1) to afford the title ester (1.16 g, 2.62 mmol) as a colourless oil.

¹H NMR (CDCl₃) δ: 8.70 (d, J = 2.85 Hz, 1H); 7.93 (br d, J = 8.4 Hz, 1H); 7.52-7.45 (m, 2H); 7.34 (d, J = 6.3 Hz, 1H); 4.00 (s, 3H); 3.99 (overlapped m, 1H); 3.75 (m, 1H); 3.60 (s, 3H); 3.24 (dd, J = 3.3, 13.5 Hz, 1H); 3.05 (overlapped m, 1H); 3.00 (t, J = 7.5 Hz, 2H); 2.62 (br s, 1H); 1.83-1.73 (m, 5H); 1.54 (m, 2H); 1.43 (s, 9H).

MS (ESI, m/z): 443.5 [M+H⁺].

3.B.xi. (3R,4R)-4-[(3-methoxy-quinolin-5-yl)-propyl]-piperidine-3-carboxylic acid methyl ester:

A solution of intermediate 3.B.x (1.16 g, 2.62 mmol) in TFA (6 ml) was stirred at rt for 20 min. The solvent was evaporated and the residue was partitioned between water (20 ml) and a DCM-MeOH mixture (9:1, 50 ml). The pH was adjusted to 10 adding 1M aq. NaOH. The aq layer was extracted three times with the same mixture. The combined extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. The residue was
chromatographed over SiO₂ (DCM-MeOH 19:1 containing 1% aq. concentrated NH₄OH) to afford the title compound (0.85 g, 2.47 mmol) as a colourless oil.

¹H NMR (CDCl₃) δ: 2.70 (d, J = 2.8 Hz, 1H); 7.92 (br d, J = 8.3 Hz, 1H); 7.54-7.45 (m, 2H); 7.34 (d, J = 7.1 Hz, 1H); 4.00 (s, 3H); 3.5% (s, 3H); 3.24 (dd, J = 3.3, 13.4 Hz, 1H); 3.11 (td, J = 3.8, 13.4 Hz, 1H); 3.02 (t, J = 7.4 Hz, 2H); 2.85 (dd, J = 3.7, 13.5 Hz, 1H); 2.69 (overlapped dd, J = 3.8, 10.2 Hz, 1H); 2.65 (m, 1H); 2.26 (br s, 1H); 1.82 (m, 3H); 1.69-1.51 (m, 2H); 1.42 (m, 2H).

MS (ESI, m/z): 343.6 [M+H⁺].

3.B.xii. (3R,4R)-4-[(3-methoxy-quinolin-5-yl) propyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidine-3-carboxylic acid methyl ester:

To a solution of intermediate 3.B.xi (0.35 g, 1 mmol) in DMF (4 ml) were added 2-(2-bromo-ethylsulfanyl)-thiophene (0.23 g, 1.25 mmol) and DIPEA (0.35 ml, 2mmol). The reaction was heated at 80°C for 1 h. The volatiles were removed under HV and the residue was chromatographed over SiO₂ (DCM-MeOH 19:1) to afford the title compound (0.24 g, 15 0.5 mmol) as a colourless oil.

¹H NMR (CDCl₃) δ: 8.69 (d, J = 2.8 Hz, 1H); 7.91 (br d, J = 8.3 Hz, 1H); 7.48 (m, 2H); 7.34 (m, 2H); 7.12 (dd, J = 1.2, 3.5 Hz, 1H); 6.97 (dd, J = 3.5, 5.3 Hz, 1H); 3.99 (s, 3H); 3.63 (s, 3H); 2.99 (m, 2H); 2.90 (t, J = 7.5 Hz, 2H); 2.67 (m, 2H); 2.62 (m, 2H); 2.48 (m, 2H); 2.33 (m, 1H); 1.85-1.62 (m, 6H); 1.48 (m, 1H).

MS (ESI, m/z): 485.4 [M+H⁺].

3.B.xiii. (3R,4R)-4-[(3-methoxy-quinolin-5-yl) propyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidine-3-carboxylic acid:

To a solution of intermediate 3.B.xii (0.24 g, 0.5 mmol) in dioxane (5 ml) was added 3M aq. NaOH (1.5 ml). The reaction mixture was heated at 100°C for 4 h. After cooling, 3M aq. HCl (1.5 ml) was added. The volatiles were removed under reduced pressure and the residue was chromatographed over SiO₂ (DCM-MeOH 9:1 containing 1% aq. concentrated NH₄OH) to afford the title acid (0.124 g, 0.26 mmol) as a colourless foam.

¹H NMR (CDCl₃) δ: 8.68 (d, J = 2.1 Hz, 1H); 7.92 (d, J = 8.3 Hz, 1H); 7.64 (d, J = 2.1 Hz, 1H); 7.47 (t, J = 7.0 Hz, 1H); 7.37 (m, 2H); 7.19 (dd, J = 1.2, 3.5 Hz, 1H); 7.0 (dd, J = 3.5, 5.3 Hz, 1H); 4.03 (s, 3H); 3.08 (m, 3H); 2.83 (m, 3H); 2.73 (m, 3H); 2.34 (br d, J = 11.2 Hz, 1H); 2.21 (m, 1H); 2.05 (m, 1H); 1.85-1.45 (m, 7H).
MS (ESI, m/z): 471.4 [M+H⁺].

Example 4: (3R,4S)-1-benzofuran-2-ylmethyl-4-{3-(3-methoxy-quinolin-5-yl)-propyl}-piperidine-3-carboxylic acid.

4.i (3R,4S)-1-benzofuran-2-ylmethyl-4-{3-(3-methoxy-quinolin-5-yl)-propyl}-piperidine-3-carboxylic acid methyl ester.

To a solution of intermediate 3.B.xi (0.25 g, 0.73 mmol) in 1,2-DCE (6 ml) were added benzofuran-2-carbaldehyde (0.118 g, 1.1 eq) and sodium triacetoxymethyldride (0.232 g, 1.5 eq). The reaction was stirred 2 h at rt, and was subsequently filtered through Hydromatrix® (pretreated with water). The filtrate was concentrated to dryness and the residue was purified over SiO₂ (DCM-MeOH 19:1) to afford the title ester (0.32 g, 0.67 mmol) as a colourless oil.

MS (ESI, m/z): 473.2 [M+H⁺].

4.ii. (3R,4S)-1-benzofuran-2-ylmethyl-4-{3-(3-methoxy-quinolin-5-yl)-propyl}-piperidine-3-carboxylic acid.

Starting from intermediate 4.i (0.32 g, 0.67 mmol), the title compound (0.14 g, 0.3 mmol) was obtained as a colourless foam using the protocol of Example 3, step 3.A.xii. The compound was purified by chromatography over SiO₂ using a DCM-MeOH 9:1 mixture containing 1% eq. NH₄OH as an eluent.

MS (ESI, m/z): 459.1 [M+H⁺].

Example 5: (3R,4R)-4-{3-(3-methoxy-quinolin-5-yl)-propyl}-1-{2-(thiophen-2-ylsulfanyl)-ethyl}-piperidin-3-yl]-acetic acid.

5.i. (3R,4S)-4-(tert-butyl-dimethyl-stannyloxymethyl)-3-vinyl-piperidine-1-carboxylic acid tert-butyl ester.

To a solution of (3R,4S)-tert-butyl 4-(2-hydroxyethyl)-3-vinylpiperidine-1-carboxylate (11.8 g, 3.99 mmol) in DCM (250 ml), was added under nitrogen TEA (12.88 ml, 2 eq.), DMAP (0.6 g, 1.9 mmol), and TBDMS-Cl (6.97 g, 1 eq.). The reaction mixture was stirred at rt for 4 h. The reaction mixture was washed with saturated NaHCO₃ (150 ml), saturated copper sulfate (2 x 150 ml) and water (150 ml). After drying over Na₂SO₄ and filtration, the
solvent was evaporated to dryness. The residue (16.8 g, 98% yield) was carried on without further purification.

$^1$H NMR (CDCl$_3$) δ: 5.78 (1H, m); 5.13 (m, 1H); 5.08 (m, 1H); 4.03 (br s, 1H); 3.94 (m, 1H); 3.64 (t, 2H, J = 6.6 Hz); 2.95 (dd, 1H, J = 3.3, 13.2 Hz); 2.80 (br s, 1H); 2.25 (m, 1H); 1.77 (m, 1H); 1.46-1.32 (overlapped m, 4H); 1.44 (s, 9H); 0.89 (s, 9H); 0.05 (s, 6H).

MS (ESI, m/z): [M+H$^+$] 370.5.

5.ii. (3R,4S)-4-(tert-butyl-dimethyl-silanylloxymethyl)-3-(2-hydroxy-ethyl)-piperidine-1-carboxylic acid tert-butyl ester:

To an ice-chilled solution of intermediate 5.i (12 g, 32.4 mmol) in THF (150 ml) was added borane-dimethylsulfide complex (3.6 ml, 35.7 mmol). The reaction was then let under stirring overnight with warming. After cooling to 0°C, 3M aq. NaOH (60 ml) and 30% aq. H$_2$O$_2$ (18.5 ml) were added. The reaction mixture was stirred 1 h. The reaction mixture was diluted with DCM (200 ml). Saturated aq. NaHSO$_3$ was added until the oxidizing agent was completely destroyed. The two layers were separated and the aq. layer was extracted twice with DCM (2 x 200 ml). The combined org. layers were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated to dryness. The residue was purified by chromatography over SiO$_2$ (EA-Hex 4-1) to afford the title alcohol (11.34 g, 29.3 mmol) as a colourless oil.

$^1$H NMR (CDCl$_3$) δ: 4.17 (m, 2H); 3.75 (td, J = 1.8, 6 Hz, 2H); 3.68 (td, J = 1.8, 6 Hz, 2H); 2.92-2.51 (m, 2H); 1.77-1.25 (m, 9H); 1.46 (s, 9H); 0.90 (s, 9H); 0.11 (s, 6H).

MS (ESI, m/z): [M+H$^+$] 383.4.

5.iii. (3R,4S)-4-(tert-butyl-dimethyl-silanylloxymethyl)-3-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 5.ii (11.34 g, 29.2 mmol) in DCM (230 ml) was added PTSA (0.222 g, 1.1 mmol). The reaction mixture was stirred for 15 min and 3,4-dihydro-2H-pyran (5.3 ml, 58.5 mmol) was added dropwise. The reaction mixture was stirred at rt for 90 min. 1M aq. NaHCO$_3$ (50 ml) was added and the two layers were separated. The org. layer was washed with brine (50 ml), dried over Na$_2$SO$_4$ and filtered. The solvent was evaporated and the residue was chromatographed over SiO$_2$ (EA-Hex 1-4) to afford the title derivative (12 g, 25.4 mmol) as a colourless oil.
$^1$H NMR (CDCl$_3$) δ: 4.59 (m, 1H); 4.02 (br s, 1H); 3.90-3.78 (m, 3H); 3.65 (m, 2H); 3.54-3.43 (m, 2H); 2.90-2.85 (m, 2H); 1.83-1.22 (m, 14H); 1.45 (s, 9H); 0.89 (s, 9H); 0.06 (s, 6H).
MS (ESI, m/z): [M+H$^+$] 472.7.

5. iv. (3R,4S)-tert-butyl-4-(2-hydroxyethyl)-3-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)piperidine-1-carboxylate:

To a solution of intermediate 5.iii (11.99 g, 25.4 mmol) in THF (100 ml) was added TBAF (1M in THF, 35.7 ml). The reaction mixture was stirred for 1 h. The volatiles were removed under vacuum and the residue was chromatographed over SiO$_2$ (EA-Hex 2:1) to afford the title alcohol (9.2 g, 25.7 mmol) as a thick oil.

$^1$H NMR (CDCl$_3$) δ: 4.57 (m, 1H); 4.02 (br s, 1H); 3.91-3.79 (m, 3H); 3.70 (m, 2H); 3.54-3.48 (m, 2H); 2.90-2.80 (m, 2H); 1.83-1.38 (m, 15H); 1.45 (s, 9H).
MS (ESI, m/z): [M+H$^+$] 358.5.

5. v. (3R,4S)-4-(1-phenyl-1H-tetrazol-5-ylmethyl)sulfanylmethyl)-3-(2-(tetrahydro-pyran-2-yloxy)-ethyl)piperidine-1-carboxylic acid tert-butyl ester:

To an iced chilled solution of intermediate 5.iv (9.2 g, 25.7 mmol) in THF (10 ml), were added successively PPh$_3$ (10.12 g, 38.6 mmol), phenyltetrazole diol (5.5 g, 30.9 mmol) and dropwise DIAD (7.6 ml, 38.6 mmol). The reaction mixture was stirred overnight at rt. The volatiles were removed under reduced pressure and the residue was chromatographed over SiO$_2$ (Hex-EA 4:1). The relevant fraction were pooled, concentrated to dryness. Hex (100 ml) was added in order to crystallize the hydrazine side product. The mixture was filtered and solvent was evaporated in vacuum to afford the title compound as a colourless oil (29.1 g) still contaminated with the hydrazine side product.
MS (ESI, m/z): [M+H$^+$] 518.5.

5. vi. (3R,4S)-3-[2-(tert-butyldimethylsilyl)oxy-ethyl]-4-[2-(1-phenyl-1H-tetrazole-5-sulfonyl)-ethyl]-piperidine-1-carboxylic acid tert-butyl ester:

To a stirred solution of intermediate 5.v (20.2 g, 39.02 mmol) in EtOH (400 ml) at rt, was added dropwise ammonium molybdate (6.06 g, 4.904 mmol) in 30% aq. H$_2$O$_2$ (51.4 ml). The mixture reaction was stirred vigorously for 4 h. Water (200 ml) was added and the volatiles were evaporated. The aq. layer was extracted twice with EA (2 x 150 ml), and the combined org. phases were washed with water (250 ml), dried over Na$_2$SO$_4$, filtered and evaporated to
dryness. The residue (9.23 g, 19.93 mmol) was taken up in DCM (100 ml) and TEA (5.5 ml, 39.8 mmol), DMAP (0.3 g, 2 mmol) and TBDMS-Cl (3.5 g, 19.9 mmol) were added. The reaction mixture was stirred at rt for 3 h. The solvent was removed under reduced pressure and the residue was chromatographed over SiO₂ (Hex-EA 2:1) to afford the title compound as a colourless oil (10.33 g, 17.8 mmol).

MS (ESI, m/z): [M+H⁺] 550.5.

5.vii. (3R,4R)-3- [[2-(tert-butyldimethylsilyloxy)ethyl]-4-trans-[3-(3-methoxyquinolin-5-yl)-allyl]-piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 5.vi (10.33 g, 17.8 mmol) in 1,2-DME (80 ml) was added 3-methoxy-quinoline-5-carbaldehyde (3 g, 16 mmol). After cooling to −60°C, a solution of potassium bis(trimethylsilyl)amide (0.5 M in toluene, 60 ml, 30 mmol) was added over 20 min. The reaction proceeded for 30 min., and 10% aq. NaN₃O₃ (200 ml) was added. After warming to rt, the two layers were separated. The aq. layer was extracted twice with EA (2 × 200 ml). The combined org. layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. The residue was chromatographed over SiO₂ (Hex-EA 3:1) to afford the title alkene (7.85 g, 14.5 mmol) as a viscous oil.

MS (ESI, m/z): [M+H⁺] 541.3.

5.viii. (3R,4R)-3-[[2-hydroxy-ethyl]-4-trans-[3-(3-methoxy-quinolin-5-yl)-allyl]-piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 5.vii (7.85 g, 14.5 mmol) in THF (100 ml) was added at rt TBAF (1 M in THF, 20 ml, 20 mmol). The reaction mixture was let under stirring for 3 h. After concentration to dryness, the residue was chromatographed over SiO₂ (DCM-MeOH 19:1) to afford the title alcohol (6.22 g, 14.6 mmol) as a colourless oil.

MS (ESI, m/z): [M+H⁺] 427.0.

5.ix. (3R,4R)-3-[[2-hydroxy-ethyl]-4-[3-(3-methoxy-quinolin-5-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester:

To a stirred solution of intermediate 5.viii (6.22 g, 14.5 mmol) in EA (100 ml) was added palladium on activated charcoal (3.5 g). The reaction mixture was vigorously stirred for 1 h under hydrogen (1 atm). The residue was diluted with EA, the catalyst was removed by filtration and the solvent was evaporated under HV to yield the title alcohol (5.75 g, 13.4 mmol). It was carried on in the next reaction without further purification.
MS (ESI, m/z): [M+H+] 429.2.

5.x. (3R,4R)-4-[(3-methoxy-quinolin-5-yl)-propyl]-3-(2-oxo-ethyl)-piperidine-1-carboxylic acid tert-butyl ester:

To a solution of oxalyl chloride (3.5 ml, 38.9 mmol) in DCM (25 ml) cooled to -78°C, was added a solution of DMSO (3.5 ml, 46.9 mmol) in DCM (25 ml) over 10 min. After stirring further 15 min, a solution of intermediate 5.ix (5.75 g) in DCM (25 ml) was added and the resulting mixture was stirred 1 h at the same temperature. TEA (15 ml, 134.1 mmol) in DCM (15 ml) was added dropwise and the reaction mixture was stirred at -78°C for 30 min before a slow warming. The reaction mixture was quenched with saturated aq. NaHCO₃ (50 ml). The two layers were separated and the org. layer was concentrated to dryness. The residue was quickly filtered through SiO₂ (Hex:EA 1:4) to afford the title aldehyde (5.08 g, 11.92 mmol) as a colourless oil.

MS (ESI, m/z): [M+H+] 427.1.

5.xi. (3R,4R)-3-carboxymethyl-4-[(3-methoxy-quinolin-5-yl)-propyl]-piperidine

1-carboxylic acid tert-butyl ester:

To a solution of intermediate 5.x (5.08 g, 11.9 mmol) in acetone (120 ml) and water (18 ml) was added KMnO₄ (5.65 g, 35.7 mmol). The reaction mixture was stirred at rt for 30 min. NaHSO₃ (5.3 g) and saturated aq. sodium thiosulfate (35 ml) were added. After stirring 15 min, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo and diluted with EA (300 ml) and water (100 ml). The phases were separated and the aq. layer was extracted twice more with EA (2 x 250 ml). The combined org. layers were washed with brine, filtered and dried over Na₂SO₄. After filtration, the residue was concentrated to dryness and the residue was filtered quickly over SiO₂ (EA) to afford the title acid (3.1 g, 11.5 mmol).

MS (ESI, m/z): [M+H+] 443.1.

5.xii. (3R,4R)-3-methoxycarbonylmethyl-4-[(3-methoxy-quinolin-5-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 5.xi (5.1 g, 11.17 mmol) in benzene (75 ml) and MeOH (15 ml) was added dropwise trimethylsilyl diazomethane (2M in ether, 8 ml, 16 mmol). The reaction mixture was stirred for 1 h. AcOH (3 ml) was added and the mixture was concentrated to dryness. The residue was partitioned between EA (200 ml) and 0.5N aq. NaOH (100 ml). The
org. layer was washed once more with 0.5N NaOH (100 ml), water (100 ml), and brine (100 ml). After drying over Na₂SO₄, filtration and concentration to dryness, the residue was dried under HV to afford the title ester (4 g, 8.76 mmol) as a viscous oil.

MS (ESI, m/z): [M+H⁺] 457.5.

5.xiii. (3R,4R)-4-{3-(methoxy-quinolin-5-yl)-propyl}-piperidin-3-yl)-acetic acid methyl ester:

A solution of intermediate 5.xii (4 g, 8.761 mmol) in TFA (20 ml) was let under stirring at rt for 20 min. After the volatiles were removed under reduced pressure, the residue was partitioned between DCM-MeOH (9:1, 200 ml) and 0.5N NaOH (100 ml). The aq. layer was extracted three more times (3 x 100 ml) and the combined org. extracts were washed with brine (100 ml), dried over Na₂SO₄, filtered and concentrated to dryness. The residue was chromatographed over SiO₂ (DCM-MeOH 9:1 1% NH₄OH) to afford the title amine (2.3 g, 6.45 mmol) as a colourless oil.

1H NMR (CDCl₃): 8.68 (d, J = 2.7 Hz, 1H); 7.92 (d, J = 8.1 Hz, 1H); 7.53-7.45 (m, 2H); 7.34 (dd: J = 0.9, 7.2 Hz, 1H); 3.98 (s, 3H); 3.67 (s, 3H); 2.99 (m, 3H); 2.91 (dd, J = 3, 12.6 Hz, 1H); 2.70-2.51 (m, 3H); 2.26-2.14 (m, 2H); 1.82 (br s, 1H); 1.81-1.63 (m, 3H); 1.50-1.26 (m, 4H).

MS (ESI, m/z): [M+H⁺] 357.3.

5.xiv. (3R,4R)-4-[(3-(methoxy-quinolin-5-yl)-propyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl]-acetic acid methyl ester:

To a solution of intermediate 5.xiii (1 g, 2.8 mmol) in DMF (11.4 ml) were added 2-(2-bromo-ethyl)sulfanyl)-2,5-dihydro-thiophene (1.194 g, 5.35 mmol) and DIPA (1.241 ml, 7.51 mmol). The reaction mixture was heated at 80°C for 1 h. The volatiles were removed under HV and the residue was chromatographed over SiO₂ (DCM-MeOH 19:1) to afford the title compound (0.836 g, 1.67 mmol) as a colourless oil.

1H NMR (CDCl₃): 8.69 (d, J = 3 Hz, 1H); 7.92 (d, J = 8.4 Hz, 1H); 7.52-7.45 (m, 2H); 7.35-7.32 (m, 2 H), 7.12 (d, J = 2.7 Hz, 1H), 6.96 (dd, J = 3.6, 5.4 Hz, 1H); 3.98 (s, 3H); 3.64 (s, 3H); 2.98 (m, 2H); 2.88 (m, 2H); 2.71-2.43 (m, 4H); 2.22 (m, 2H); 2.03 (m, 2H); 1.74 (m, 2H); 1.62-1.32 (m, 6H).

MS (ESI, m/z): [M+H⁺] 499.4.
5.xv. (3R,4R)-4-[3-(3-methoxy-quinolin-5-yl)-propyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-2-yl]-acetic acid:

To a solution of intermediate 5.xiv (0.836 g, 1.67 mmol) in dioxane (10 ml) was added 3M NaOH (8.1 ml, 24.3 mmol). The reaction mixture was heated at 100°C overnight. After cooling, 3M HCl (8.1 ml) was added. The volatiles were removed under reduced pressure and the residue was chromatographed over SiO₂ (DCM-MeOH 9:1 to 6:1 1% NH₄OH) to afford the title compound (0.634 g, 1.30 mmol) as a colourless foam.

¹H NMR (CDCl₃): 8.69 (d, J = 3.3 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.58-7.45 (m, 2H); 7.38-7.33 (m, 2H); 7.17 (d, J = 2.8 Hz, 1H), 6.98 (m, 1H), 4.8 (br s, 1H), 3.98 (s, 3H); 3.10-2.92 (m, 5H); 2.88-2.71 (m, 3H); 2.51-2.42 (m, 2H); 2.18 (m, 1H); 2.08 (m, 1H); 1.72-1.32 (m, 8H).

MS (ESI, m/z): [M+H⁺] 485.6.

Example 6: 2-{(3R,4S)-4-[3-(3-methoxy-quinolin-5-yl)-propyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl}-ethanol:

To an ice-cooled solution of intermediate 5.xiv (0.35 g, 0.75 mmol) in THF (10 ml) was added DIBAH (1.5M in toluene, 2 ml). The reaction was stirred 30 min at this temperature and water (0.2 ml) was added. The reaction mixture was diluted with ether (20 ml) and was filtered through a pad of celite. The filtrate was concentrated to dryness and the residue was chromatographed over SiO₂ (DCM-MeOH 9:1) to afford the title alcohol (0.200 g, 0.42 mmol) as a colourless oil.

MS (ESI, m/z): [M+H⁺] 471.4.

Example 7: carbamic acid 2-{(3R,4S)-4-[3-(3-methoxy-quinolin-5-yl)-propyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl}-ethyl ester:

To an ice-chilled solution of the compound of Example 6 (0.1 g) in DCM (1.5 ml) was added trichloroacetyl isocyanate (0.03 ml). After stirring at rt for 1 h, the reaction mixture was concentrated to dryness. The residue was taken up in 2-methyl-2-propanol (1 ml) and MeOH (0.5 ml). A saturated K₂CO₃ solution (0.5 ml) was added and the mixture was heated at 70°C for 2 h. After concentration in vacuo, the residue was directly subjected to chromatography over SiO₂ (DCM-MeOH 19:1 containing 1% aq. NH₄OH) to afford the title compound as a colourless foam.
MS (ESI, m/z): [M+H⁺] 514.5.

Example 8: 4-[3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-1-{2-(thiophen-2-yl sulfonyl)-ethyl}piperidine-3-carboxylic acid;

8.i. (3R,4S)-4-[2-(tert-butyldimethyl-silanyloxy)-ethyl]-3-(1,2-dihydroxy-ethyl)piperidine-1-carboxylic acid tert-butyl ester:

To a mixture of intermediate 5.i (16.8 g, 45.4 mmol) in DCM (220 ml) and water (20 ml) were added NMO (16 g, 136 mmol) and potassium osmate dihydrate (0.33 g, 0.9 mmol). The mixture was vigorously stirred at rt overnight. The reaction mixture was diluted with water (100 ml). The two layers were decanted and the org. layer was dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was chromatographed over SiO₂ (Hex-EA 1:1 then 1:3) to afford the title alcohol (16 g, 87% yield) as a brown oil.
MS (ESI, m/z): [M+H⁺] 404.1.

8.ii. (3R,4S)-4-[2-(tert-butyldimethyl-silanyloxy)-ethyl]-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 8.i (17.14 g, 42.4 mmol) in DCM (200 ml) was added dropwise at rt PTSA (0.4 g) and 2,2 dimethoxypropane (10.4 ml, 2 eq.). The reaction mixture was stirred at rt for 1 h. 1 M aq. NaHCO₃ (100 ml) was added and the two phases were separated. The aq. layer was extracted with DCM (200 ml). The combined org. layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. The acetonide was engaged in the next step without purification.
MS (ESI, m/z): [M+H⁺] 444.2.

8.iii. (3S,4R)-8-(2,2-dimethyl-[1,3]dioxolan-4-yl)-4-(2-hydroxy-ethyl)piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 8.ii (42.4 mmol theoretically) in THF (200 ml) was added TBAF (1 M in THF, 55 ml). The reaction was stirred at rt overnight. The reaction was concentrated in vacuo and chromatographed over SiO₂ (EA-Hex 3:1) to afford the title alcohol (13.04 g, 39.6 mmol) as a colourless oil.
MS (ESI, m/z): [M+H⁺] 330.2.
8. iv. (3R,4S)-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-4-(2-oxo-ethyl)piperidine-1-carboxylic acid tert-butyl ester:

To a mixture of oxalyl chloride (10 ml, 114.8 mmol) in DCM (95 ml) cooled to -78°C was added dropwise a solution of DMSO (10 ml, 139 mmol) in DCM (95 ml). The reaction mixture was stirred at this temperature 15 min. Then, a solution of intermediate 8.iii (13.04 g, 39.6 mmol) in DCM (95 ml) was added dropwise at -78°C and the reaction mixture was stirred at this temperature for 1 h. A solution of TEA (33 ml, 237 mmol) was added dropwise at -78°C and the reaction mixture was stirred for 1 h at this temperature and allowed to warm slowly to rt over 1 h. The reaction mixture was quenched with 10% aq. NaHSO₄ (100 ml).

The two phases were separated and the org. layer was washed with water (100 ml) and brine (100 ml). The org. layer was dried over Na₂SO₄, filtered and concentrated to dryness. The residue was chromatographed over SiO₂ (EA: Hex 2:1) to afford the title aldehyde (12.16 g, 93% yield) as slightly coloured oil which was directly used in the next step.

8.v. (3R,4R)-4-allyl-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)piperidine-1-carboxylic acid tert-butyl ester:

To a suspension of methyltriphenylphosphonium bromide (21.3 g, 59.5 mmol) in THF (200 ml) cooled to -78°C, was added n-BuLi (2.35N in hexanes, 23 ml). The reaction mixture was stirred at this temperature for 15 min. and at 0°C for 45 min. Then, the reaction mixture was cooled to -78°C and a solution of intermediate 8.iv (12.16 g, 37 mmol) in THF (50 ml) was quickly added. The reaction mixture was stirred overnight at rt. The reaction was quenched with EtOH (50 ml) and concentrated to dryness. The residue was dispersed on SiO₂, loaded on the top of a column and purified by chromatography (Hex-EA 9:1) to afford the title alkene (10.74 g, 85% yield) as clear oil. The compound was obtained as a mixture of diastereomers.

25 MS (ESI, m/z): [M+H⁺] 326.3.

8.vi. (3R,4R)-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-4-(3-hydroxy-propyl)piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 8.v (5.64 g, 17.3 mmol) in THF (60 ml) was added 9-BBN (6.35 g, dimer, 26 mmol). The reaction mixture was stirred at rt under nitrogen for 16 h. The reaction mixture was cooled to 0°C and EtOH (50 ml), 3M aq. NaOH (100 ml) and 50% aq. H₂O₂ (78 ml) were added carefully. The reaction mixture was stirred vigorously at rt for 1 h.
The reaction mixture was cooled to 0°C and saturated sodium thiosulfate (100 ml) was added carefully. The reaction mixture was stirred at rt 20 min and diluted with EA (200 ml). The two phases were separated and the aq. layer was extracted twice with EA (2 x 200 ml). The combined org. layers were washed with brine, dried over Na2SO4, filtered and concentrated under reduced pressure. The residue was chromatographed over SiO2 (EA-Hex 2-1 to 3-1) to afford the first diastereoisomer (Rf = 0.42 in EA-Hex 2-1 [TLC over SiO2]), then the second one (Rf = 0.27 in EA-Hex 2-1 [TLC over SiO2]). The diastereomers were combined to give a clear oil (5.54 g, 92% yield).

First eluting isomer:

1H NMR (CDCl3): 4.15-4.94 (m, 2H); 3.72-3.63 (m, 3H); 3.45-3.05 (br m, 4H); 1.92-1.82 (m, 2H); 1.70-1.45 (m, 7H); 1.47 (s, 9H); 1.41 (s, 3H); 1.36 (s, 3H).

MS (ESI, m/z): [M+H+] 344.3.

Second eluting isomer:

1H NMR (CDCl3): 4.07-3.99 (m, 2H); 3.69 (br s, 1H); 3.67-3.60 (m, 3H); 3.54 (m, 2H); 3.35 (m, 2H); 1.74-1.40 (m, 8H); 1.47 (s, 9H); 1.40 (s, 3H); 1.35 (s, 3H).

MS (ESI, m/z): [M+H+] 344.4.

8.vi. (3R,4R)-3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-4-(3-oxo-propyl)-piperidine-1-carboxylic acid tert-butyl ester:

To a mixture of oxalyl chloride (8.5 ml, 97.1 mmol) in DCM (80 ml) cooled to -78°C was added dropwise a solution of DMSO (8.3 ml, 117.2 mmol) in DCM (80 ml). The reaction mixture was stirred at this temperature 15 min. A solution of intermediate 8.vi (11.5 g, 33.5 mmol) in DCM (80 ml) was added dropwise at -78°C and the reaction mixture was stirred at this temperature for 1 h. A solution of TEA (28 ml, 200 mmol) was added dropwise at -78°C and the reaction mixture was stirred for 1 h at this temperature before allowing the reaction mixture to reach rt over 30 min. The reaction mixture was quenched adding 10% aq. NaHSO4 (100 ml). The two phases were separated and the org. layer was washed with water (100 ml) and brine (100 ml). The combined org. layer was dried over Na2SO4, filtered and concentrated to dryness. The residue was chromatographed over SiO2 (EA-Hex 2-1) to afford first isomer of the title aldehyde (7.3 g, 21.4 mmol) and its epimer (3.05 g, 8.79 mmol). Both compounds were obtained as clear oil.
First eluting isomer:
\(^1H\) NMR (CDCl\(_3\)): 9.80 (t, J = 1.7 Hz, 1H); 4.15 (m, 1H); 4.11 (br s, 1H); 3.78 (br s, 1H); 3.63 (t, J = 8.0 Hz, 1H); 3.57 (br s, 1H); 3.08-3.01 (br m, 2H); 2.56-2.50 (m, 2H); 1.93 (m, 1H); 1.82 (m, 2H); 1.73 (m, 1H); 1.59 (m, 2H); 1.46 (s, 9H); 1.38 (s, 3H); 1.34 (s, 3H).

Second eluting isomer:
\(^1H\) NMR (CDCl\(_3\)): 9.80 (t, J = 1.4 Hz, 1H); 4.11-4.02 (m, 2H); 3.60-3.15 (br m, 3H); 3.23 (br s, 2H); 2.56-2.50 (m, 2H); 1.74-1.54 (m, 6H); 1.46 (s, 9H); 1.40 (s, 3H); 1.35 (s, 3H).

8.vii. (3R,4R)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester:

To a solution of 5-bromo-3-methoxy-quinoline (11.8 g, 50 mmol) in THF (200 ml) was added at -78°C, \(\nu\)-BuLi (2.35N in Hex, 22 ml). The mixture was stirred 15 min at this temperature and a solution of intermediate 8.vii (second eluting isomer, 7.3 g, 21.4 mmol) in ether (25 ml) was added. The mixture was stirred 15 min at this temperature and EtOH (5 ml) was added. 10% aq. NaHSO\(_4\) (50 ml) was added. The two layers were decanted and the aq. layer was extracted once with EA (100 ml). The combined org. extracts were washed with brine, dried over Na\(_2\)SO\(_4\), filtered and concentrated to dryness. The residue was chromatographed over SiO\(_2\) (Hex:EA 1:1 then 1:3) to afford the title alcohol (3.28 g, 6.47 mmol) as a 1:1 mixture of epimers.

MS (ESI, m/z): [M+H\(^+\)] 501.2.

The same experiment was performed with intermediate 8.vii (first eluting isomer, 3.05 g, 8.79 mmol) to afford the diastereomeric derivative (1.6 g, 3.16 mmol) as a 1:1 mixture of epimers.

MS (ESI, m/z): [M+H\(^+\)] 501.2.

8.ix. (3R,4R)-3-formyl-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-piperidine-1-carboxylic acid tert-butyl ester:

A solution of intermediate 8.viii (3.28 g, 6.47 mmol) was treated with AcOH (45 ml), water (15 ml) and THF (15 ml) at 65°C overnight. The solvent was removed in vacuo. The residue was taken up in EA (200 ml) and saturated NaHCO\(_3\) (150 ml). 1M NaOH was added until pH 10 was reached. The two layers were decanted. The aq. layer was washed with brine, dried over Na\(_2\)SO\(_4\), filtered and concentrated to dryness. The residue was chromatographed over SiO\(_2\) (DCM-MeOH 19:1) to afford the expected intermediate triol (2.67 g) as a foam. To a solution of the latter (2.67 g, 5.8 mmol) in acetonitrile (100 ml) was added a solution of NaO\(_4\)
(3.02 g, 14.1 mmol) in water (30 ml). The mixture was stirred at rt for 30 min. The solvent was evaporated and the residue was partitioned between water (200 ml) and EA (300 ml). The org. layer was washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated to dryness to afford the title aldehyde (2.41 g).

5. MS (ESI, m/z): [M+H$^+$] 428.8.

8.x. (3R,4R)-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester:

To a solution of intermediate 8.x (2.41 g, crude) in acetone (70 ml) and water (10 ml) was added KMnO$_4$ (3.5 g). The mixture was stirred at rt for 90 min. NaHSO$_3$ (5 g) was added. The reaction mixture was diluted with acetone (100 ml) and water (50 ml). After stirring 15 min, the solids were filtered off. The pH of the filtrate was adjusted to 5-6 with 1N HCl, whereupon a solid formed. The solid was filtered off, washed with water and dried in vacuo to afford the title acid (2.16 g, 4.36 mmol) as a colourless solid.

MS (ESI, m/z): [M-H$^-$$^1$] 443.0.

8.xi. (3R,4R)-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester:

To a solution of intermediate 8.x (2.13 g, 4.8 mmol) in benzene (40 ml) and MeOH (8 ml) was added trimethylsilyl diazomethane (4 ml). The mixture was stirred at rt for 30 min. AcOH (1.5 ml) was added and stirring was maintained for 10 min. The reaction mixture was partitioned between saturated NaHCO$_3$ (50 ml) and EA (100 ml). The org. layer was washed with saturated NaHCO$_3$ (50 ml) and brine. After drying over Na$_2$SO$_4$, filtration and evaporation to dryness, the residue was chromatographed over SiO$_2$ (EA-Hex 2:1) to afford the title alcohol (1.6 g, 3.49 mmol) as a colourless foam. The compound was obtained as a 1:1 mixture of epimers.

25. $^1$H NMR (CDCl$_3$) mixture of epimers: 8.67 (d, J = 2.8 Hz, 1H); 7.98 (d, J = 8.0 Hz, 1H); 7.77 (m, 1H); 7.61-7.50 (m, 2H); 5.26 (br t, J = 6.4 Hz, 1H); 3.98 (br s, 1H); 3.96 (s, 1.5H); 3.97 (s, 1.5H); 3.85 (br s, 1H); 3.60 (s, 1.5H); 3.58 (s, 1.5H); 3.21 (m, 1H); 3.01 (m, 1H); 2.61 (m, 1H); 2.20 (m, 1H); 2.90-1.93 (m, 2H); 1.85-1.78 (m, 2H); 1.75-1.43 (m, 3H); 1.43 (s, 9H).

30. MS (ESI, m/z): [M+H$^+$] 459.2.
8.xii. \((3R,4R)-4-f(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl\)-piperidine-3-carboxylic acid methyl ester:

A solution of intermediate 8.xi (1.6 g, 3.49 mmol) in TFA (6 ml) was stirred at rt for 20 min. The volatiles were removed in vacuo and the residue was partitioned between saturated NaHCO₃ (100 ml) and DCM-MeOH (9:1, 100 ml). The pH was adjusted to 9 adding 1M NaOH. The aq. layer was further extracted three times. The combined org. layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. The residue was chromatographed (DCM-MeOH 9:1 1% concentrated NH₄OH) to afford the title piperidine (1.16 g, 94% yield) as a colourless foam. The compound was obtained as a 1:1 mixture of epimers.

\(^1\)H NMR (CDCl₃) mixture of epimers: 8.67 (d, J = 2.8 Hz, 1H); 7.98 (d, J = 7.8 Hz, 1H); 7.82 (d, J = 2.8 Hz, 0.5H); 7.78 (d, J = 2.8 Hz, 0.5H); 7.61-7.50 (m, 2H); 5.29 (overlapped t, J = 5.9 Hz, 0.5H); 5.24 (overlapped t, J = 6.1 Hz, 0.5H); 3.98 (s, 1.5H); 3.97 (s, 1.5H); 3.56 (s, 1.5H); 3.52 (s, 1.5); 3.16 (m, 1H); 3.04 (m, 1H); 2.76 (d, J = 3.5 Hz, 0.5H); 2.71 (d, J = 3.7 Hz, 0.5H); 2.60-2.54 (m, 2H); 2.06-1.74 (m, 6H); 1.59-1.26 (m, 3H).

MS (ESI, m/z): 359.2 [M+H⁺].

8.xiii. \((3R,4R)-4-f(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl\)-1-[2-\((\text{thiophen}-2-\text{ylsulfanyl})-\text{ethyl}\)]-piperidine-3-carboxylic acid methyl ester:

To a solution of intermediate 8.xii (0.2 g, 0.55 mmol) in DMF (3 ml) were added DIPEA (0.184 ml) and 2-(2-bromo-ethyl)sulfanyl)-thiophene (0.186 g, 1.5 eq.). The reaction mixture was heated at 70°C for 3 h. After cooling the solvent was removed in vacuo and the residue was purified by chromatography over SiO₂ (DCM-MeOH 9:1) to afford the title compound (0.24 g, 85% yield) as a colourless oil.

MS (ESI, m/z): 501.4 [M+H⁺].

8.xiv. \((3R,4R)-4-f(3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl\)-1-[2-\((\text{thiophen}-2-\text{ylsulfanyl})-\text{ethyl}\)]-piperidine-3-carboxylic acid:

To a solution of intermediate 8.xiii (0.24 g, 0.48 mmol) in dioxane (5 ml) was added 3M aq. NaOH (1.5 ml). The mixture was heated at 70°C overnight. The reaction mixture was cooled to rt. The solvent was removed in vacuo and the pH of the aq. layer was adjusted to 4 adding 3M aq. HCl. The aq. layer was extracted twice with DCM-MeOH mixture (9:1, 2 x 100 ml). The combined extracts were dried over Na₂SO₄, filtered and concentrated to dryness. The
residue was chromatographed over SiO₂ (DCM-MeOH 6:1 1% concentrated NH₄OH) to afford the title acid (0.18 g, 77% yield) as a colourless foam. The compound was obtained as a 1:1 mixture of isomers.

¹H NMR (CDCl₃) mixture of epimers: 8.66 (d, J = 2.6 Hz, 1H); 7.96 (d, J = 8.6 Hz, 1H); 7.82 (d, J = 2.6 Hz, 0.5H); 7.68 (m, 1H); 7.60-7.48 (m, 1.5H); 7.38 (dd, J = 1.1, 5.4 Hz, 1H); 7.18 (dd, J = 1.1, 3.5 Hz, 1H); 6.98 (dd, J = 3.5, 5.4 Hz, 1H); 5.36 (dd, J = 3.2, 8.5 Hz, 0.5H); 5.25 (dd, J = 4.4, 8.5 Hz, 1H); 4.03 (s, 1.5H); 3.98 (s, 1.5H); 3.17-3.02 (m, 2H); 2.93 (br t, J = 6.8 Hz, 2H); 2.30-2.69 (m, 3H); 2.36-2.17 (m, 4H); 1.90-1.25 (m, 7H).

MS (ESI, m/z): 487.3 [M+H⁺].

Example 9: 1-benzofuran-2-ylmethy-(3R,4R)-4-[3RS]-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl-piperidine-3-carboxylic acid:

9.i. 1-benzofuran-2-ylmethyl-(3R,4R)-4-[3RS]-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl-piperidine-3-carboxylic acid methyl ester:

To a solution of intermediate 8.xii (0.15 g, 0.42 mmol) in 1,2-DCE (3 ml) were added benzofuran-2-carboxaldehyde (0.057 ml, 1.1 eq.) and sodium triacetoxyborohydride (0.115 g, 1.3 eq). The reaction proceeded overnight. The reaction mixture was filtered through a pad of Hydromatrix® (pretreated with saturated NaHCO₃). The filtrate was concentrated to dryness and the residue was chromatographed over SiO₂ (DCM-MeOH 19:1 1% concentrated NH₄OH) to afford the title ester (0.167 g, 0.34 mmol) as a colourless oil.

MS (ESI, m/z): 499.3 [M+H⁺].

9.ii. 1-benzofuran-2-ylmethy-(3R,4R)-4-[3RS]-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl-piperidine-3-carboxylic acid:

The title compound (0.13 g, 79% yield; 1:1 mixture of epimers) was obtained as a beige solid from intermediate 9.i (0.167 g, 0.34 mmol), using the protocol of Example 1, step 1.xiv.

MS (ESI, m/z): 475.3 [M+H⁺].
Example 10: (3R,4R)-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolina-5-yl)-propyl]-1-trans-(3-phenyl-allyl)-piperidine-3-carboxylic acid:

10.i. (3R,4R)-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolina-5-yl)-propyl]-1-trans-(3-phenyl-allyl)-piperidine-3-carboxylic acid methyl ester:

The title ester (0.163 g, 82% yield; 1:1 mixture of epimers) was obtained as a colourless oil, starting from intermediate 8.xii (0.15 g, 0.42 mmol) and trans-cinnamaldehyde (0.058 ml, 1.1 eq) and using the protocol of Example 4, step 4.i.
MS (ESI, m/z): 475.2 [M+H⁺].

10.ii. (3R,4R)-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolina-5-yl)-propyl]-1-trans-(3-phenyl-allyl)-piperidine-3-carboxylic acid:

The title compound (0.12 g, 75% yield) was obtained as a beige solid starting from intermediate 10.i (0.167 g, 0.34 mmol) and using the protocol of Example 1, step 1.xiv.
MS (ESI, m/z): 461.1[M+H⁺].

Example 11: (3R,4R)-1-[3-(2,5-difluoro-phenyl)-allyl]-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolina-5-yl)-propyl]-piperidine-3-carboxylic acid:

11.i. tran3-(2,5-difluoro-phenyl)-acrylic acid ethyl ester:

To an iced chilled suspension of sodium hydride (1.13 g, 60% in oil dispersion, 28.2 mmol) in THF (32 ml) was added triethylphosphonoacetate (5.6 ml, 28.2mmol). The reaction mixture was stirred at rt for 20 min. 2,5-difluoro-benzaldehyde (3.34 g, 23.5 mol) was added dropwise. After 30 mm, 10% aq. NaHSO₄ (100 ml) was added and the mixture was diluted with EA (150 ml). The two phases were separated and the aq. layer was extracted twice (2 x 100 ml). The combined org. layers were washed with brine (100 ml), dried over Na₂SO₄, filtered and concentrated to dryness. The residue was chromatographed over SiO₂ (Hex-EA 19-1) to afford the title unsaturated ester (5.0 g, 100%) as a colourless oil.

¹H NMR (CDCl₃): 7.76 (dd, J = 1, 16.1 Hz, 1H); 7.26-7.21 (m, 1H); 7.13-7.03 (m, 2H); 6.52 (d, J = 16.1 Hz, 1H); 4.29 (q, J = 7.1 Hz, 2H); 1.36 (t, J = 7.1 Hz, 3H).
11.ii. trans-3-(2,5-difluoro-phenyl)-prop-2-en-1-ol:

To a solution of intermediate 11.i (5.0 g, 23.5 mmol) in ether (100 ml), cooled to 0°C, was added a DIBALH (1M in Hex, 60 ml, 60 mmol). The mixture was stirred at the same temperature for 40 min. Water (6 ml) was added and the mixture was stirred 30 min. The solid was filtered off and thoroughly washed with ether. The filtrate was concentrated to dryness to afford the title alcohol (4.0 g, 98% yield) as a colourless oil.

$^1$H NMR (CDCl$_3$): 7.15 (dd, $J = 3.1, 5.9, 9.0$ Hz, 1H); 7.00 (td, $J = 4.6, 9.0$ Hz, 1H); 6.95-6.87 (m, 1H); 6.75 (dd, $J = 1.3, 16.1$ Hz, 1H); 6.45 (td, $J = 5.3, 16.1$ Hz, 1H); 4.38 (br d, $J = 5.3$ Hz, 2H); 1.63 (s, 1H).

11.iii. trans-3-(2,5-difluoro-phenyl)-propenal:

To a solution of intermediate 11.ii (1.70 g, 10 mmol) in DCM (20 ml) was added, at rt, a solution of Dess-Martin periodinane (15 wt% in DCM, 20 ml). The mixture was stirred at rt for 3 h. After concentration to dryness, the residue was chromatographed over SiO$_2$ (Hex-EA 9:1) to afford the title aldehyde (1.06 g, 63% yield) as a white solid.

$^1$H NMR (d$_6$-DMSO): 9.74 (d, $J = 7.6$ Hz, 1H); 7.88-7.81 (m, 1H); 7.79 (overlapped dd, $J = 1.4, 16.0$ Hz, 1H); 7.46-7.37 (m, 2H); 6.67 (dd, $J = 7.6, 16.0$ Hz, 1H).

11.iv. (3R,4R)-1-trans-[3-(2,5-difluoro-phenyl)-allyl]-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]piperidine-3-carboxylic acid methyl ester:

The title ester (0.26 g, 91% yield; 1:1 mixture of epimers) was obtained as a colourless oil, starting from intermediate 8.xii (0.2 g, 0.56 mmol) and intermediate 11.iii (0.103 g, 1.1 eq.) and using the protocol of Example 4, step 4.i.

MS (ESI, m/z): 511.1 [M+H$^+$].

11.v. (3R,4R)-1-[3-(2,5-difluoro-phenyl)-allyl]-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]piperidine-3-carboxylic acid:

The title compound (0.17 g, 67% yield; 1:1 mixture of epimers) was obtained as a beige solid from intermediate 11.iv (0.26 g, 0.51 mmol) using the protocol of Example 1, step 1.xiv.

MS (ESI, m/z): 497.2 [M+H$^+$].
Example 12: (3R,4R)-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)propyl]-1-(thiazol-2-yl)carbamoylmethyl]-piperidine-3-carboxylic acid:

12.i. (3R,4R)-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)propyl]-1-(thiazol-2-yl)carbamoylmethyl]-piperidine-3-carboxylic acid methyl ester.

The title ester (0.195 g, 93% yield; 1:1 mixture of epimers) was obtained as a colourless oil, starting from intermediate 8.xii (0.15 g, 0.56mmol) and 2-bromo-N-thiazol-2-yl-acetamide (0.138g, 1.5eq) and using the protocol of Example 8, step 8.xiii.

MS (ESI, m/z): 499.2 [M+H+].

12.ii. (3R,4R)-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)propyl]-1-(thiazol-2-yl)carbamoylmethyl]-piperidine-3-carboxylic acid.

To a solution of intermediate 12.i (0.195 g, 0.39 mmol) in dioxane (5 ml) was added 3M NaOH (0.5 ml). The mixture was stirred at rt for 2 h, then overnight at 60°C. After cooling, water was added and the volatiles were removed in vacuo. The aq. layer was then washed twice with EA and the pH was adjusted to 7 by addition of 1N HCl. The aq. layer was extracted four times with DCM-MeOH 9:1 (4 x 100 ml). The combined extracts were washed with brine (30 ml) and dried over Na2SO4, filtered and concentrated to dryness to leave a semi-solid residue was further triturated in ether to afford the title acid (0.135 g, 71% yield; 1:1 mixture of epimers) as a light beige solid.

MS (ESI, m/z): 485.3 [M+H+].

Example 13: (3R,4S)-4-[(2R,3R)-2,3-dihydroxy-3-(3-methoxy-quinolin-5-yl)propyl]-1-[2-(thiophen-2-ylsulfonyl)-ethyl]-piperidin-3-yl]-acetic acid:

13.i. (3R,4S)-3-[2-(tert-butyl-dimethyl-silyloxy)-ethyl]-4-[(2R,3R)-2,3-dihydroxy-3-(3-methoxy-quinolin-5-yl)propyl]-piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 5.vii (4.1 g, 7.58 mmol) in 2-methyl-2-propanol (40 ml) and water (40 ml) were added successively at rt with AD-mix β (10.6g) and methanesulfonyl azide (0.793 g, 1.1 eq.). The reaction was vigorously stirred for 3 d. NaHSO3 (12 g) was added portion wise. The two layers were decanted. The aq. layer was extracted twice with EA (2 x 150 ml). The combined org. layers were washed with brine, dried over Na2SO4, filtered
and concentrated to dryness. The residue was chromatographed over SiO2 (Hex-EA 1-4) to 
afford the title diol (3.5 g; 80% yield) as colourless foam.

1H NMR (CDCl3): 8.68 (d, J = 2.7 Hz, 1H); 8.02 (d, J = 8.1 Hz, 1H); 7.68-7.66 (m, 2H); 
7.55 (dd, J = 7.5, 8.1 Hz, 1H); 5.12 (d, J = 6.9 Hz, 1H); 4.72 (br s, 1H); 4.11 (m, 1H); 
4.03 (s, 3H); 4.02 (overlapped m, 1H); 3.66-3.50 (m, 2H); 2.83-2.60 (m, 4H); 1.85 (m, 2H); 
1.45-0.95 (m, 6H); 1.41 (s, 9H); 0.83 (s, 9H); 0.01 (s, 3H); -0.01 (s, 3H).

MS (ESI, m/z): 575.3 [M+H+].

13.ii. (3R,4S)-3-(2-hydroxy-ethyl)-4-[(4R,5R)-5-(3-methoxy-quinolin-5-yl)-2,2-dimethyl-
[1,3]dioxolan-4-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester:

To a solution of intermediate 13.i (3.5 g, 6.0 mmol) in THF (30 ml) were added 
2,2-dimethoxypropane (3.74 ml, 5 eq.) and PTSA (1.39 g, 1.2 eq.). The reaction proceeded at 
rt for 4 h and saturated NaHCO3 (50 ml) and EA (100 ml) were added. The two layers were 
decanted and the eq. layer was further extracted with EA (100 ml). The combined org. layers 
were washed with brine, dried over Na2SO4, filtered and concentrated to dryness. The residue 
was chromatographed over SiO2 (EA-Hex 1-1) to afford (3R,4S)-3-[2-(1-methoxy-
1-methyl-ethoxy)-ethyl]-4-[(4R,5R)-5-(3-methoxy-quinolin-5-yl)-2,2-dimethyl-[1,3]dioxolan-
4-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester (0.7 g, 20% yield) as a colourless 
liquid.

1H NMR (CDCl3): 8.71 (d, J = 2.8 Hz, 1H); 8.05 (d, J = 8.3 Hz, 1H); 7.85 (d, J = 2.8 Hz, 1H); 
7.67 (d, J = 7.2 Hz, 1H); 7.54 (dd, J = 7.2, 8.5 Hz, 1H); 5.15 (d, J = 8.4 Hz, 1H); 4.27 (m, 
1H); 4.10 (br s, 1H); 3.97 (s, 3H); 3.93 (m, 3H); 3.37 (m, 1H); 3.27 (m, 1H); 2.97 (s, 3H); 
2.80-2.65 (m, 2H); 1.87-1.78 (m, 2H); 1.67-1.53 (m, 2H); 1.65 (s, 3H); 1.60 (s, 3H); 1.42 (s, 
9H); 1.42-1.22 (m, 4H); 1.11 (s, 3H); 1.08 (s, 3H).

Elution was then performed using EA to afford the title alcohol (2.0 g, 65% yield) as 
colourless foam.

1H NMR (CDCl3): 8.71 (d, J = 2.8 Hz, 1H); 8.06 (d, J = 8.1 Hz, 1H); 7.91 (d, J = 2.8 Hz, 1H); 
7.54-7.64 (m, 2H); 5.13 (d, J = 8.5 Hz, 1H); 4.26 (d, J = 2.5, 8.5 Hz, 1H); 3.85-4.10 (br m, 
2H); 3.98 (s, 3H); 3.52 (br s, 2H); 2.68-2.72 (m, 2H); 1.80-1.59 (m, 5H); 1.63 (br s, 3H); 
1.59 (s, 3H); 1.53-1.40 (m, 2H); 1.42 (s, 9H); 1.29 (m, 2H).

MS (ESI, m/z): 501.5 [M+H+].
13.iii. (3R,4S)-3-methoxycarbonylmethyl-4-[(4R,5R)-5-(3-methoxy-quinolin-5-yl)-2,2-dimethyl-3-[(3,4dioxolan-4-yl)methyl]-piperidine-1-carboxylic acid tert-butyl ester:

Starting from intermediate 13.ii (2.0 g, 4 mmol), the title ester (1.5 g, 71%) was obtained as a colourless foam using a three-step sequence (oxidation to the aldehyde, oxidation to the acid and esterification) according to the protocols reported respectively in steps 5.x, 5.xi and 5.xii of Example 5.

MS (ESI, m/z): 529.0 [M+H⁺].

13.iv. (3R,4S)-4-[(2R,3R)-2,3-dihydroxy-3-(3-methoxy-quinolin-5-yl)propyl]-piperidin-3-yl]-acetic acid methyl ester:

A solution of intermediate 13.iii (1.5 g, 2.83 mmol) in TFA (10 ml) was stirred at rt for 15 min. Water (6 ml) was added and the mixture was further stirred for 2 h. After evaporation to dryness, the residue was partitioned between 2N NaOH (20 ml) and DCM-MeOH (9:1, 100 ml). The aq. layer was extracted four more times with the same mixture. The combined org. layers were dried over Na₂SO₄, filtered and concentrated to dryness. The title diol (0.26 g, 23% yield) was obtained as colourless oil.

MS (ESI, m/z): 389.1 [M+H⁺].

13.v. (3R,4S)-4-[(2R,3R)-2,3-Dihydroxy-3-(3-methoxy-quinolin-5-yl)propyl]-1-[2-(thiophen-2-ylsulfanyl)ethyl]-piperidin-3-yl]-acetic acid methyl ester:

Starting from intermediate 13.iv (0.224 g, 1.5 eq.), the title ester (0.2 g, 56%) was obtained as a colourless foam according to the protocol reported in Example 8, step 8.xiii. The compound was purified by chromatography over SiO₂ (DCM-MeOH 19:1 containing 1% NH₄OH).

¹H NMR (CDCl₃): 8.68 (d, J = 2.7 Hz, 1H); 8.02 (dd, J = 1.8, 7.5 Hz, 1H); 7.80 (d, J = 2.7 Hz, 1H); 7.59-7.51 (m, 2H); 7.30 (dd, J = 1.2, 5.4 Hz, 1H); 7.07 (dd, J = 1.2, 3.6 Hz, 1H); 6.94 (dd, J = 3.6, 5.4 Hz, 1H); 5.05 (d, J = 6.6 Hz, 1H); 4.15 (m, 1H); 3.97 (s, 3H); 3.57 (s, 3H); 2.88 (overlapped m, 1H); 2.83 (t, J = 7.2 Hz, 2H); 2.58-2.73 (m, 3H); 2.36-2.55 (m, 3H); 2.17 (m, 1H); 2.03-1.96 (m, 2H); 1.55 (m, 1H); 1.53 (overlapped dd, J = 2.7, 16.2 Hz, 1H); 1.43-1.20 (m, 3H); 1.17 (m, 1H).

MS (ESI, m/z): 531.2 [M+H⁺].
13.vi. \((3R,4S)-4-\{(3R,3R)-2,3\text{-}dihydroxy\text{-}3\text{-}\{3\text{-}methoxy\text{-}quinolinol\text{-}5\text{-}yl\}\text{-}propyl\}\text{-}1\text{-}\{(2\text{-}thieno\text{-}2\text{-}ylsulfanyl\text{-}ethyl\}\text{-}piperidinol\text{-}3\text{-}yl\}\text{-}acetic acid:

Starting from intermediate 13.v (0.2 g, 0.377 mmol), the title compound (0.106 g, 54% yield) was obtained as a colourless solid using the protocol of Example 1, step 1.xiv. The compound was purified by chromatography over SiO₂ (DCM-MeOH 4:1 containing 1% NH₄OH) and further triturated in ether.

\(^1\)H NMR (d6-DMSO): 8.62 (d, J = 2.6 Hz, 1H); 7.92 (d, J = 2.5 Hz, 1H); 7.85 (d, J = 7.7 Hz, 1H); 7.50-7.60 (m, 3H); 7.13 (dd, J = 1.2, 2.4 Hz, 1H); 7.02 (dd, J = 3.4, 5.2 Hz, 1H); 5.41 (br s, 1H); 5.08 (d, J = 4.3 Hz, 1H); 4.65 (br s, 1H); 3.91 (s, 3H); 3.81 (m, 1H); 2.79 (t, J = 7.2 Hz, 2H); 2.62 (m, 2H); 2.30-2.50 (m, 4H); 2.03 (m, 1H); 1.89-1.93 (m, 2H); 1.73-1.80 (m, 2H); 1.19-1.05 (m, 4H).

MS (ESI, m/z): 517.3 [M+H⁺].

Example 14: \((R,R,R)-\{(3R,4S)-3\text{-}\{3\text{-}\{(2\text{-}hydroxy\text{-}ethyl\}\text{-}ethyl\}\text{-}piperidinol\text{-}4\text{-}yl\}\text{-}1\text{-}\{(3\text{-}methoxy\text{-}quinolinol\text{-}5\text{-}yl\}\text{-}propylenol\text{-}1,2\text{-}diol:

14.i. \((R,R,R)-\{(3R,4S)-3\text{-}\{3\text{-}\{(2\text{-}hydroxy\text{-}ethyl\}\text{-}piperidinol\text{-}4\text{-}yl\}\text{-}1\text{-}\{(3\text{-}methoxy\text{-}quinolinol\text{-}5\text{-}yl\}\text{-}propylenol\text{-}1,2\text{-}diol:

Starting from \((3R,4S)-3\text{-}\{2\text{-}\{(1\text{-}methoxy\text{-}1\text{-}methyl\text{-}ethoxy\}\text{-}ethyl\}\text{-}4\text{-}\{(4R,5R)-5\text{-}\{3\text{-}methoxy\text{-}quinolinol\text{-}5\text{-}yl\}\text{-}2,2\text{-}dimethyl\text{-}1,3\text{-}dioxolanol\text{-}4\text{-}ymenthyl\text{-}piperidinol\text{-}1\text{-}carboxylic acid tert-butyl ester (side product of Example 13, step ii; 0.7 g, 1.22 mmol), the title piperidine (0.24 g, 0.66 mmol) was obtained as a colourless foam using the protocol of Example 13, step 1.xiv.

MS (ESI, m/z): 361.3 [M+H⁺].

14.ii. \((R,R,R)-\{(3R,4S)-3\text{-}\{3\text{-}\{(2\text{-}hydroxy\text{-}ethyl\}\text{-}piperidinol\text{-}4\text{-}yl\}\text{-}1\text{-}\{(3\text{-}methoxy\text{-}quinolinol\text{-}5\text{-}yl\}\text{-}propylenol\text{-}1,2\text{-}diol:

Starting from intermediate 14.i (0.112 g, 1.5 eq.), the title alcohol (0.078 g, 46% yield) was obtained as a beige solid using the protocol of Example 1, step 1.xiii. This compound was purified by chromatography over SiO₂ (DCM-MeOH 8:1 containing 1% NH₄OH).

\(^1\)H NMR (CDCl₃): 8.68 (d, J = 2.8 Hz, 1H); 8.02 (d, J = 7.8 Hz, 1H); 7.75 (d, J = 2.7 Hz, 1H); 7.63-7.52 (m, 2H); 7.33 (dd, J = 1.2, 5.3 Hz, 1H); 7.10 (dd, J = 1.2, 3.5 Hz, 1H); 6.96 (dd, J = 2.5, 5.3 Hz, 1H); 5.09 (d, J = 6.5 Hz, 1H); 4.06 (m, 1H); 3.96 (s, 3H); 3.39 (m, 2H);
3.03 (br s, 1H); 2.90-2.64 (m, 5H); 2.64 (m, 2H); 2.05-1.86 (m, 2H); 1.80-1.61 (m, 4H);
1.48-1.33 (m, 3H); 1.29 (t, 1H); 1.12 (m, 1H).

MS (ESI, m/z): 503.1 [M+H]+.

Example 15: (1R,2R)-{[(3R,4S)-3-[1-[3-trans-(2,5-difluoro-phenyl)-allyl]-3-(2-hydroxy-ethyl)-piperidin-4-yl]}-1-(3-methoxy-quinolin-5-yl)-propane-1,3-diol:

Starting from intermediate 14.i (0.1 g, 0.27 mmol) and intermediate 11.iii (0.051 g, 1.1 eq.),
the title alcohol (0.056 g, 39% yield) was obtained as a beige solid using the protocol of
Example 4, step 4.i. The compound was purified by chromatography over SiO2 (DCM-MeOH
8:1 containing 1% N[LOH]).

MS (ESI, m/z): 513.1 [M+H]+.

Example 16: (3R,4R)-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-
1-(3-phenyl-propyl)-piperidine-3-carboxylic acid:

16.i. (3R,4R)-4-{[(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-1-(3-phenyl-propyl)-
piperidine-3-carboxylic acid methyl ester:

This ester (1:1 mixture of epimers; 0.170 g, 98% yield) was obtained as a colourless oil,
starting from intermediate 8.xii (0.13 g, 0.36 mmol) and 3-phenyl-propionaldehyde (0.053 ml,
1.1 eq.) and using the protocol of Example 9, step 9.i.

MS (ESI, m/z): 477.1 [M+H]+.

16.ii. (3R,4R)-4-{[(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-1 (3-phenyl-propyl)-piperidine-3-carboxylic acid:

This compound (1:1 mixture of epimers; 0.13 g, 78% yield) was obtained as a colourless solid
from intermediate 16.i (0.170 g, 0.357 mmol) using the protocol of Example 8, step 8.xiv.

MS (ESI, m/z): 463.1[M+H]+.
Example 17: (3R,4R)-4-{(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl}-1-(2-phenylsulfanyl-ethyl)-piperidine-3-carboxylic acid: 

17.i. (3R,4R)-4-{(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl}-1-(2-phenylsulfanyl-ethyl)-piperidine-3-carboxylic acid methyl ester: 

The title ester (0.112 g, 62% yield; 1:1 mixture of epimers) was obtained as a colourless oil, starting from intermediate 8.xii (0.13 g, 0.36 mmol) and (2-bromo-ethylsulfanyl)-benzene (0.087 g, 1.1 eq.) and using the protocol of Example 8, step 8.xiii. 

MS (ESI, m/z): 495.1 [M+H⁺] 

17.ii. (3R,4R)-4-{(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl}-1-(2-phenylsulfanyl-ethyl)-piperidine-3-carboxylic acid: 

The title compound (0.06 g, 55% yield; 1:1 mixture of epimers) was obtained as a colourless solid from intermediate 17.i (0.112 g, 0.22 mmol) using the protocol of Example 8, step 8.xiv. 

MS (ESI, m/z): 481.1 [M+H⁺].

Example 18: (1R,2R)-3-{(3R,4S)-3-(2-hydroxy-ethyl)-1-[2-(thiophen-2-yl)sulfanyl]-ethyl}-piperidin-4-yl)-1-(3-methoxy-quinoxalin-5-yl)-propane-1,2-diol: 

18.i. 2-cyano-N-(2-methyl-6-nitro-phenyl)-acetamide: 

To a solution of 2-methyl-6-nitroaniline (25 g, 164.3 mmol) in benzene (200 ml) were added cyanoacetic acid (14.5 g, 170.46 mmol) and PCl₅ (35 g, 168 mmol). The reaction mixture was heated at 60°C for 7 h. After cooling to rt, the reaction mixture was filtered and the solid was washed with benzene and water. The solid was dried under reduced pressure to afford the title acetamide (24 g, 109 mmol) as a yellow solid. 

¹H NMR (d₆-DMSO) δ: 10.2 (s, 1H); 7.78 (d, J = 8.3 Hz, 1H); 7.65 (d, J = 8.3 Hz, 1H); 7.43 (t, J = 8.3 Hz, 1H); 3.95 (s, 2H); 2.30 (s, 3H).

18.ii. 3-hydroxy-5-methyl-1-oxo-quinoxaline-2-carbonitrile: 

To a mixture of intermediate 18.i (24 g, 109.5 mmol) and 1Maq. NaOH (100 ml) was added pyridine (100 ml). The reaction mixture was stirred at rt for 4 h. The pH was adjusted to 6 by addition of 1Maq. HCl. The solid was filtered off and washed with water. The solid was
triturated with EtOH. After drying under HV, the title nitrile (17.7 g, 87.9 mmol) was obtained as a yellow solid.

MS (ESI, m/z): 202.1 [M+H⁺].

18.iii. 8-methyl-quinazalin-2-ol:

To a solution of intermediate 18.ii (17.7 g, 87.9 mmol) in water (300 ml) and EtOH (24 ml) was added sodium dithionite (35.4 g, 203.9 mmol). The reaction mixture was heated at 60°C for 1 h. The reaction mixture was filtered till warm, and the pH of the filtrate adjusted to 2 by adding 1M aq. HCl. The pH of the solution was subsequently made basic by adding solid NaOH (10 g). EA (150 ml) was added. The aq. layer was extracted twice more with EA (2 x 150 ml). The combined org. extracts were dried over Na₂SO₄, filtered and concentrated to dryness. The residue was dried under HV to afford the title intermediate (11.1 g, 69 mmol) as a yellow solid.

¹H NMR (d₆-DMSO) δ: 11.75 (br s, 1H); 8.17 (s, 1H); 7.62 (d, J = 8.4 Hz, 1H); 7.40 (d, J = 8.4 Hz, 1H); 7.21 (t, J = 8.4 Hz, 1H); 2.42 (s, 3H).

MS (ESI, m/z): 161.1 [M+H⁺].

18.iv. 2-chloro-8-methyl-quinazaline:

A solution of intermediate 18.iii (11.1 g, 69.5 mmol) in phosphorus oxychloride (80 ml) was heated at 110°C during 2 h. After cooling to rt, the reaction mixture was poured onto ice (200 g). The aqueous layer was extracted with EA (2 x 200 ml). The combined extracts were washed with brine (100 ml), dried over Na₂SO₄, filtered and concentrated to dryness. The residue was chromatographed over silica gel (Hex-EA 1:1) to afford the title intermediate (12.5 g, 69.5 mmol) as a red solid.

¹H NMR (d₆-DMSO) δ: 8.99 (s, 1H); 7.97 (m, 1H); 7.80 (m, 2H); 2.68 (s, 3H).

MS (ESI, m/z): 179.2 [M+H⁺].

18.v. 2-methoxy-8-methyl-quinazaline:

To a solution of intermediate 18.iv (12.5 g, 69.5 mmol) in DMF (80 ml) was added sodium methoxide (9 g, 166 mmol). The reaction mixture was heated at 45°C for 4 h. After cooling to rt, the reaction mixture was partitioned between water (10 ml) and EA (200 ml). The organic layer was washed once with water (100 ml), dried over Na₂SO₄, filtered and concentrated to dryness. The residue was chromatographed over silica gel (Hex-EA 1:4) to afford the title intermediate (10.2 g, 58.55 mmol) as a yellow solid.
$^1$H NMR (CDCl$_3$) $\delta$: 8.48 (s, 1H); 7.88 (d, $J = 7.9$ Hz, 1H); 7.55 (d, $J = 7.9$ Hz, 1H); 7.47 (t, $J = 7.9$ Hz, 1H); 4.12 (s, 3H); 2.69 (s, 3H).
MS (ESI, m/z): 175.4 [M+H$^+$].

5.8-vi. 8-dibromomethyl-2-methoxy-quinoxaline.

To a solution of intermediate 5.8 (10.2 g) in CCl$_4$ (560 ml) were added AIBN (0.96 g) and NBS (25.9 g, 145.5 mmol). The reaction mixture was heated at 80°C for 3 h. After cooling to rt, the reaction mixture was washed with water (200 ml) and the organic layer was dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The residue was triturated with MeOH to give, after drying under HV, the title dibromide (14.4 g, 43.3 mmol) as a slightly beige solid.

$^1$H NMR (d$_6$-DMSO) $\delta$: 8.69 (s, 1H); 8.25 (dd, $J = 1.3$, 7.5 Hz, 1H); 8.07 (dd, $J = 1.3$, 8.3 Hz, 1H); 8.02 (s, 1H); 7.74 (dd, $J = 7.5$, 8.3 Hz, 1H); 4.14 (s, 3H).
MS (ESI, m/z): 332.8 [M+H$^+$].

5.8-vii. 3-methoxy-quinoxaline-5-carbaldehyde.

To a solution of intermediate 5.8-v (10.7 g, 32.2 mmol) in EtO (330 ml) was added, at rt, a solution of silver nitrate (15 g) in water (70 ml). The reaction was stirred at rt for 1 h. The reaction mixture was diluted with MeCN (200 ml) and the solids were filtered off and the filtrate was concentrated in vacuo. The residue was filtered over a silica gel pad (eluent: EA) to afford the title aldehyde (6.2 g, 32.2 mmol) as a slightly yellow solid.

$^1$H NMR (d$_6$-DMSO) $\delta$: 11.15 (s, 1H); 8.74 (s, 1H); 8.36 (dd, $J = 1.3$, 8.1 Hz, 1H); 8.21 (dd, $J = 1.3$, 7.9 Hz, 1H); 7.80 (dd, $J = 7.9$, 8.1 Hz, 1H); 4.14 (s, 3H).
MS (ESI, m/z): 189.2 [M+H$^+$].

5.8-viii. 8-((3R,4R)-trans-3-[2-(tert-butyldimethylsilyloxy)-ethyl]-1-[2-(thiophen-2-ylsulfanyl)ethyl]-piperidine-4-yl]-propenyl)-2-methoxy-quinoxaline.

This alkene (4.6 g, 74% yield) was obtained as a colourless oil, starting from intermediate 5.vi (6.6 g, 11.38 mmol) and intermediate 5.8-vii (2.35 g, 1.1 eq) and using the protocol of Example 5, step 5.vii.
MS (ESI, m/z): 542.0 [M+H$^+$].
18.ix. \((1R,2R)-3-\{(3R,4S)-3-\{2-(\text{3-ethyl-propyl-}2\text{-methyl-silanyl})\text{-ethyl}\}-1-\{2-(\text{thiophen-}
2\text{-ylsulfanyl})\text{-ethylyl-piperidin-4-yl}\}-1-(3\text{-methoxy-quinoxalin-5-yl})\text{-propane-1,2-diol;}
\]

The title diol (2.5 g, 67% yield) was obtained as a colourless foam, starting from
intermediate 18.viii (3.5 g, 6.46 mmol) and using the protocol of Example 13, step 13.i.

5

MS (ESI, m/z): 576.2 [M+H⁺].

18.x. \((1R,2R)-3-\{(3R,4S)-3-(2\text{-hydroxy-ethyl})\text{-piperidin-4-yl}\}-1-(3\text{-methoxy-quinoxalin-5-yl})
\text{-propane-1,2-diol;}
\]

To a solution of intermediate 18.ix (1.8 g, 3.32 mmol) in dioxane (10 ml) was added 5N HCl
in dioxane (10 ml). After stirring at rt for 1 h, ether (50 ml) was added. The solids were
filtered off, taken up in water, and the resulting solution was concentrated to dryness and the
residue dried to constant weight to yield the title piperidine (1.44 g, 100% yield) as a
dihydrochloride salt.

MS (ESI, m/z): 362.1 [M+H⁺].

18.xi. \((1R,2R)-3-\{(3R,4S)-3-(2\text{-hydroxy-ethyl})\text{-1-\{2-(\text{thiophen-2-ylsulfanyl})\text{-ethyl}\}-piperidin-}
4\text{-yl}\}-1-(3\text{-methoxy-quinoxalin-5-yl})\text{-propane-1,2-diol;}
\]

To a mixture of intermediate 18.x (1.44 g, 3.31 mmol) and 2-(2-bromo-ethyl)sulfanyl-
thiophene (1 g, 1.35 eq.) in DMF (15 ml) was added DIPEA (2.3 ml). The mixture was heated
at 80°C for 4 h. After concentration to dryness, the residue was partitioned between saturated
NaHCO₃ (100 ml) and DCM-MeOH (9:1, 100 ml). The aq. layer was extracted once with the
same mixture. The combined org. layers were washed with brine, dried over Na₂SO₄, filtered
and concentrated to dryness. The residue was purified over silica gel (DCM-MeOH 93:7
containing 1% NH₄OH) to afford the title compound (0.058 g, 3% yield) as a brown foam.

¹H NMR (d6-DMSO) δ: 8.59 (s, 1H); 7.90-7.84 (m, 2H); 7.63 (d, J = 7.7 Hz, 1H); 7.58 (dd,
J = 1.2, 5.3 Hz, 1H); 7.16 (dd, J = 1.3, 3.5 Hz, 1H); 7.03 (dd, J = 3.5, 5.3 Hz, 1H); 5.47 (dd,
J = 4.0, 5.9 Hz, 1H); 5.17 (d, J = 5.9 Hz, 1H); 4.27 (t, J = 3.3 Hz, 1H); 4.23 (d, J = 6.9 Hz,
1H); 4.02 (s, 3H); 3.73 (m, 1H); 3.40-3.30 (m, 2H); 2.89 (m, 2H); 2.63-2.50 (m, 2H);
2.48-2.37 (m, 2H); 1.99-1.87 (m, 2H); 1.65 (m, 2H); 1.46-1.35 (m, 5H); 1.15 (m, 1H).

MS (ESI, m/z): 504.0 [M+H⁺].
BIOLOGICAL ASSAYS

\textit{In vitro} assay

\textbf{Experimental method:}

These assays have been performed following the description given in "Methods for dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, 4th ed.; Approved standard: NCCLS Document M7-A4; National Committee for Clinical Laboratory Standards: Villanova, PA, USA, 1997". Minimal inhibitory concentrations (MICs; mg/l) were determined in cation-adjusted Mueller-Hinton Broth (BBL) by a microdilution method following NCCLS guidelines (National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility). The pH of the test medium was 7.2–7.3. All Examples were tested against several Gram positive and Gram negative bacteria.

\textbf{Results:}

Typical antibacterial spectra are given hereafter (MIC in mg/l).

<table>
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<th>Example No.</th>
<th>\textit{S. aureus} 29213</th>
<th>\textit{S. aureus} A798</th>
<th>\textit{E. faecalis} 29212</th>
<th>\textit{E. faecium} A949</th>
<th>\textit{S. Pneumoniae} 49619</th>
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The compounds predominantly have MIC values of \( \leq 4 \text{ mg/l} \) against \textit{S. aureus} 29213, \textit{S. aureus} A798 and \textit{S. pneumoniae} 49619.
1. A compound selected selected from the group consisting of a compound of the formula I

\[
\begin{align*}
&\text{wherein} \\
&\text{one of } U \text{ and } V \text{ represents } N, \text{ the other represents } N \text{ or } CH; \\
&M \text{ represents } CH_2CH_2, \text{ CH}=CH, \text{ CH(OH)CH( OH), CH(OH)CH}_2, \text{ CH(NH}_2)CH_2, \text{ COCH}_2 \text{ or } OCH_2; \\
&R^1 \text{ represents alkyl, haloalkyl, alkoxy, haloalkoxy, halogen or cyano; } \\
&R^2 \text{ represents hydrogen or halogen; } \\
&R^3 \text{ represents carboxy, carboxamido, alkylaminocarbonyl, hydroxy, aminocarbonyloxy, 2-} \\
&tetrazolyl \text{ or } 3\text{-methyl-1,2,4-oxadiazol-5-yl; } \\
&R^4 \text{ represents alkyl, } (\text{C}_1\text{-C}_6)\text{alkoxy-(C}_1\text{-C}_6)\text{alkyl, haloalkyl, alkenyl, arylalkyl, ary}-
&(\text{S(O)}_m\text{-alkyl, heteroaryalkyl, heteroarylaminocarbonylalkyl, heteroaryls(O)}_m\text{-alkyl, } \text{CH}_2\text{-CH}=CH\text{-} \\
&\text{aryl or cycloalkyl-S(O)}_m\text{-alkyl; } \\
&n \text{ is an integer from } 0 \text{ to } 3; \text{ and } \\
&m \text{ is } 0 \text{ or } 2; \\
\text{and a prodrug, a tautomier, an optically pure enantiomer, a mixtures of enantiomers, a } \\
racemate, \text{ an optically pure diastereoisomer, a mixtures of diastereoisomer, a } \\
diastereoisomeric \text{ racemate, mixtures of diastereoisomeric racemates, a meso-form, a } \\
morphological form, \text{ a salt or a solvent complex of such a compound.}
\end{align*}
\]
2. A compound according to claim 1, wherein U is CII and V is N.

3. A compound according to claim 1, wherein M is CH₂CH₃, CH(OH)CH(OH), CH(OH)CH₂ or OCH₂.

4. A compound according to claim 1, wherein R¹ is (C₁-C₂)alkyl, (C₁-C₂)haloalkyl, (C₁-C₂)alkoxy, (C₁-C₂)haloalkoxy, halogen or cyano.

5. A compound according to claim 1, wherein R² is hydrogen or fluorine.

6. A compound according to claim 1, wherein R³ is carboxy.

7. A compound according to claim 1, wherein R⁴ is arylalkyl, aryl-S(O)₉-alkyl, heteroarylalkyl, heteroarylaminocarbonylalkyl, heteroaryl-S(O)₉-alkyl or CH₂-CH=CH-aryl, in representing each time 0.

8. A compound according to claim 1, which is selected from the group consisting of:
   - 3-[(3R,4S)-4-[2-(3-methoxy-quinolin-5-yloxy)-ethyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl]-propionic acid;
   - 3-[(3R,4S)-4-[2-(3-methoxy-quinolin-5-yloxy)-ethyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl]-propan-1-ol;
   - (3R,4R)-4-[3-(3-methoxy-quinolin-5-yl)-propyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidine-3-carboxylic acid;
   - (3R,4S)-1-benzofuran-2-ylmethyl-4-[3-(3-methoxy-quinolin-5-yl)-propyl]-piperidine-3-carboxylic acid;
   - (3R,4R)-4-[3-(3-methoxy-quinolin-5-yl)-propyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl]-acetic acid;
   - 2-[((3R,4S)-4-[3-(3-methoxy-quinolin-5-yl)-propyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl]-ethanol;
   - carbamic acid 2-((3R,4R)-4-[3-(3-methoxy-quinolin-5-yl)-propyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidin-3-yl)-ethyl ester;
   - 4-[3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-1-[2-(thiophen-2-ylsulfanyl)-ethyl]-piperidine-3-carboxylic acid;
   - 1-benzofuran-2-ylmethyl-(3R,4R)-4-[(3R,5S)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-piperidine-3-carboxylic acid;
• (3R,4R)-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-1-trans-(3-phenylallyl)-piperidine-3-carboxylic acid;

• (3R,4R)-1-[3-(2,5-difluoro-phenyl)-allyl]-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-piperidine-3-carboxylic acid;

• (3R,4R)-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-1-(thiazol-2-yl-carbamoylmethyl)-piperidine-3-carboxylic acid;

• [(3R,4S)-4-[(2R,3R)-2,3-dihydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-1-[2-(thiophen-2-yl-sulfanyl)-ethyl]-piperidin-3-yl]-acetic acid;

• (1R,2R)-[(3R,4S)-3-{3-(2-hydroxy-ethyl)-1-[2-(thiophen-2-yl-sulfanyl)-ethyl]-piperidin-4-yl}]]-1-(3-methoxy-quinolin-5-yl)-propane-1,2-diol;

• (1R,2R)-{(3R,4S)-3-[1-[3-trans-(2,5-difluoro-phenyl)-allyl]-3-(2-hydroxy-ethyl)-piperidin-4-yl]}]-1-(3-methoxy-quinolin-5-yl)-propane-1,2-diol;

• (3R,4R)-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-1-(3-phenyl-propyl)-piperidine-3-carboxylic acid;

• (3R,4R)-4-[(3RS)-3-hydroxy-3-(3-methoxy-quinolin-5-yl)-propyl]-1-(2-phenylsulfanyl-ethyl)-piperidine-3-carboxylic acid;

• (1R,2R)-3-[(3R,4S)-3-{2-hydroxy-ethyl}-1-[2-(thiophen-2-yl-sulfanyl)-ethyl]-piperidin-4-yl]-1-(3-methoxy-quinoxalin-5-yl)-propane-1,2-diol;

and the pharmaceutically acceptable salts of the latter.

9. A compound according to claim 8, which is selected from the group consisting of:

• 3-{(3R,4S)-4-[2-(3-methoxy-quinolin-5-yl-oxo)-ethyl]-1-[2-(thiophen-2-yl-sulfanyl)-ethyl]-piperidin-3-yl]-propionic acid;

• 3-{(3R,4S)-4-[2-(3-methoxy-quinolin-5-yl-oxo)-ethyl]-1-[2-(thiophen-2-yl-sulfanyl)-ethyl]-piperidin-3-yl]-propan-1-ol;

• (3R,4R)-4-[3-(3-methoxy-quinolin-5-yl)-propyl]-1-[2-(thiophen-2-yl-sulfanyl)-ethyl]-piperidine-3-carboxylic acid;

and the pharmaceutically acceptable salts of the latter.

10. As a medicament, a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof.
11. A pharmaceutical composition containing, as active principle, a compound of formula I as defined in claim 1 or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

12. Use of a compound according to claim 1 for the manufacture of a medicament for the prevention or treatment of infection(s).
### INTERNATIONAL SEARCH REPORT

**A CLASSIFICATION OF SUBJECT MATTER**

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<th>International Application No</th>
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According to International Patent Classification (IPC) and to the national classification 1 IPC:

**B. FIELDS SEARCHED**

[Fields searched...]

Documentation searched other than documentation in the international search:

[Documentation searched...]

EPO-Internal, CHEM ABS Data, WPI Data

### DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 00/43383 A (SMITHKLINE BEECHAM P.L.C.; DAVIES, DAVID; THOMAS, HENRY; CAROLINE, JOAN) 27 July 2000 (2000-07-27) examples</td>
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<td>Y</td>
<td>DE 102 47 233 A1 (MORPHOCHEM AG AKTIENGESELLSCHAFT FÜR KOMBINATORISCHE CHEMIE) 17 June 2004 (2004-06-17) examples</td>
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**Further documents are listed in the continuation for C.**

**X**

**X**

[Special categories of documents considered:]

- **X** document only includes the general subject of the invention and is not relevant to the novelty of the invention.
- **Y** earlier documents, but not considered to be of particular relevance.
- **Z** earlier documents, but not considered to be of particular relevance.
- **Q** document relating to the general subject of the invention and is not relevant to the novelty of the invention.
- **R** document which may throw doubts on priority data and is not in conflict with the claims.
- **O** document relating to the general subject of the invention and is not relevant to the novelty of the invention.
- **P** document relating to the general subject of the invention and is not relevant to the novelty of the invention.

**Case of the search completed on 27 December 2005**

**Date of mailing of the international search report:** 13/01/2006

**Authorised officer:** Lauro, P.
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<td>WO 2004/002490 A (GLAXO GROUP LIMITED; AXTEN, JEFFREY; DAINES, ROBERT, A; DAVIE) &amp; January 2004 (2004-01-08) cited in the application examples 3,5</td>
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Title: 6,7-DIHYDROIMIDAZO[2,1-B][1,3]OXAZINE BACTERICIDES

Abstract: The present invention provides a novel 6,7-dihydroimidazo[2,1-B][1,3]oxazine compound that has excellent bactericidal action against tubercle bacillus, multibacil-resistant tubercle bacillus, and atypical acid-fast bacillus. Specifically, the present invention provides a compound represented by Formula (1), or a salt thereof, wherein R1 represents tetrahydrofuran, tetrahydropyranyl, tetrahydropyrimidyl, tetrahydropyridyl, benzoxazolinyl, benzoxazolyl, 4-hydroxyphenyl, 4-hydroxyphenyl, or 4-pyridyl, these groups being optionally substituted, the phenyl, 4-methylphenyl, and pyridyl, and represented by R1 each being substituted directly or via a linker with at least one group selected from the group consisting of tetrahydropyridyl, diacetyl, diacetylsulfonyl, tetrahydrocinnamyl, tetrahydrocinnamyl, benzoyl, benzoyl, benzyl, benzyl, and benzyl, and the like, each of these groups being optionally substituted, and R1 represents hydrogen or a lower alkyl. The present invention further provides a pharmaceutical composition containing the above.
Title of Invention:

6,7-DIHYDROIMIDAZO [2,1-B][1,3]OXAZINE BACTERICIDES

Technical Field

The present invention relates to a 6,7-dihydroimidazole[2,1-b][1,3]oxazine compound.

Background Art

Among acid-fast bacilli, Mycobacterium tuberculosis is widely known, and one-third of the human population are said to be infected therewith. In addition to Mycobacterium tuberculosis, Mycobacterium africanum and Mycobacterium bovis are also known to be grouped in the Mycobacterium tuberculosis complex, and are known as mycobacteria, which are highly pathogenic to humans.

The treatment of these tuberculosis uses three agents, i.e., rifampicin, isoniazid, and ethambutol (or streptomycin), or four agents, i.e., the above three agents and pyrazinamide, which serve as first-line drugs.

However, the treatment of tuberculosis requires a distinctly long-term drug administration, which causes poor compliance, often resulting in treatment failure.

Further, the aforementioned agents have been reported to cause side effects as exemplified below: rifampicin causes hepatopathy, flu syndrome, and drug allergy, and is contraindicated for use in combination with other agents due to P450 related enzyme induction; isoniazid causes peripheral neuropathy and induces serious hepatopathy when used in combination with rifampicin; ethambutol causes failing vision due to optic neuropathy; streptomycin causes hearing deterioration due to eighth cranial nerve neuropathy; and pyrazinamide causes hepatopathy, gout attacks accompanied by an increase in the uric acid level, as well as vomiting, and the like (Non-patent Literature 1 and 2).
As a practical matter, cases have been reported where standard chemotherapy could not be performed due to the aforementioned side effects, which account for 70% of the cases where drug administration was discontinued (approximately 23%, 52 cases) of the total number of cases (228 hospital patients surveyed in all) [Non-patent Literature 3].

In particular, out of the above-mentioned five agents, which are used in combination as first-line drugs, rifampicin, isoniazid, and pyrazinamide commonly cause hepatotoxicity, which is known as the most frequently occurring side effect. Meanwhile, tubercle bacilli that are resistant to antituberculosis agents, tubercle bacilli that are resistant to multiple drugs, etc., have been increasing, making treatment more difficult.

A WHO survey (2008) reported that there are 390,000 to 510,000 patients with multidrug-resistant tuberculosis in the world, which account for 3.6% of the total number of tuberculosis patients, and that 5.4% of multidrug-resistant tuberculosis are equal to extensively drug-resistant tuberculosis [Non-patent Literature 4].

Further, one-third of HIV positive patients are suspected of being co-infected with tuberculosis; the number of such patients is said to be 14 million [Non-patent Literature 5]. It is also reported that co-infection of HIV and tuberculosis poses a 20 to 37 times greater risk of developing tuberculosis than usual [Non-patent Literature 6].

In view of the above-described current status, examples of the profiles of a desired antituberculosis agent include (1) an agent that is also effective against multidrug-resistant tubercle bacilli; (2) an agent that enables short-term chemotherapy; (3) an agent with few side effects; (4) an agent that shows efficacy against latent infection with tubercle bacilli (latent tuberculosis); (5) an agent that can be administered orally; and the like.

Examples of bacteria known to be pathogenic to humans include pathogens of recently increasing MAC infections.
(Mycobacterium avium-intracellularare complex infections), such as Mycobacterium avium and Mycobacterium intracellularare; and other atypical acid-fast bacilli, such as Mycobacterium kansasii, Mycobacterium marinum, Mycobacterium simiae, Mycobacterium scrofulaceum, Mycobacterium szulgai, Mycobacterium xenopi, Mycobacterium malmoense, Mycobacterium haemophilum, Mycobacterium ulcerans, Mycobacterium shimoidei, Mycobacterium fortuitum, Mycobacterium chelonae, Mycobacterium smegmatis, and Mycobacterium aurum.

At present, there are few promising therapeutic agents against atypical mycobacteriosis, and the current status is that an antituberculosis agent, such as rifampicin, isoniazid, ethambutol, streptomycin, and kanamycin, is used in combination with a therapeutic agent against general bacterial infections, such as a new quinolone agent, a macrolide antimicrobial agent, an aminoglycoside antimicrobial agent, and a tetracycline antimicrobial agent.

However, compared with the treatment of infections with common bacteria, the treatment of atypical mycobacteriosis requires long-term drug administration, and in some cases, according to reports, atypical mycobacteriosis become intractable, possibly causing death. In order to overcome the current status, the development of a drug with a higher efficacy is in demand.

For example, Patent Literature 1 discloses that a 6-nitro-1,2,3,4-tetrahydro[2,1-b]imidazopyran compound is useful as an antituberculosis agent, because the compound has bactericidal action in vitro against tubercle bacilli (H37Rv strain) and multidrug-resistant tubercle bacilli, as well as because the compound shows, when orally administered, a therapeutic effect on an animal model infected with tuberculosis.

Patent Literature 2 and 3 disclose that a 2,3-dihydroimidazo[2,1-b]oxazole compound has bactericidal action against tubercle bacilli, multidrug-resistant tubercle bacilli, and atypical acid-fast bacilli.

Patent Literature 4 discloses that nitroimidazooxazine
and nitroimidazooxazole compounds can be used as a drug against Mycobacterium tuberculosis.

However, the compounds disclosed in the above-mentioned literature have a structure different from that of the compounds of the present invention, and thus are dissimilar compounds.

Citation List

Patent Literature

PTL 4: WO 2011/014776

Non Patent Literature

NPL 2: Keckaku, Second edition, Pumiyuki KUER, Takateru IZUMI, Igaku-Shoin, 1992
NPL 3: Keckaku Vol.74: 77-82, 1999
NPL 5: The Internet Journal of Pulmonary Medicine 2006: Volume 10, Number 1

Summary of Invention

Technical Problem

An object of the present invention is to provide a compound having excellent bactericidal action against tubercle bacilli and multidrug-resistant tubercle bacilli. It is a further object of the present invention to provide a compound having excellent bactericidal action against atypical acid-fast bacilli.
Solution to Problem

In order to achieve the aforementioned objects, the present inventors conducted extensive research and, as a result, accomplished the synthesis of a novel 6,7-dihydroimidazo[2,1-b][1,3]oxazine compound that has excellent bactericidal action against tubercle bacilli, multidrug-resistant tubercle bacilli, and atypical acid-fast bacilli. The present invention was completed based on such findings.

The present invention provides a compound represented by Formula (1):

\[
\begin{array}{c}
\text{O}_2\text{N} \\
\text{N} \\
\text{O} \\
\text{O} \\
\text{R}^2 \\
\text{R}^1
\end{array}
\]  

or a salt thereof,

wherein \( R^1 \) represents tetrahydroisoquinolyl, tetrahydroquinolyl, tetrahydrobenzoxazepinyl, benzoxazolyl, benzothiazolyl, indolyl, isoindoliny, naphthyl, quinolyl, phenyl, biphenyl, or pyridyl, these groups being optionally substituted, the phenyl and pyridyl represented by \( R^1 \) each being substituted directly or via a linker with at least one group selected from the group consisting of tetrahydropyridyl, diazepanyl, diazabicycloheptanyl, tetrahydrotriazolopyrazinyl, tetrahydroimidazopyrazinyl, azabicyclooctanyl, oxazolyl, piperazinyl, piperidyl, and thiazolyl, each of these groups being optionally substituted, the biphenyl represented by \( R^1 \) being substituted directly or via a linker with at least one group selected from the group consisting of tetrahydropyridyl, diazepanyl, diazabicycloheptanyl, tetrahydrotriazolopyrazinyl, tetrahydroimidazopyrazinyl, azabicyclooctanyl, oxazolyl, piperazinyl, piperidyl, thiazolyl, and phenyl, each of these groups being optionally substituted; and

\( R^2 \) represents hydrogen or lower alkyl.
The present invention further provides a compound represented by Formula (1) above, or a salt thereof, wherein R¹ is a group represented by Formula (2):

-Å-L1-B-L2-C-D (2)

wherein A represents a divalent group selected from (A1) to (A12):

(A1) tetrahydroisoquinolinediyl,
(A2) tetrahydroquinolinediyl,
(A3) tetrahydrobenzoazepinediyl,
(A4) benzoazolediyl,
(A5) benzothiazolediyl,
(A6) indolediyl,
(A7) isoindolenediyl,
(A8) naphthalenediyl,
(A9) quinolinediyl,
(A10) phenylene,
(A11) biphenyldiyl, and
(A12) pyridinediyl,

these groups (A1) to (A12) being optionally substituted on the ring(s) with at least one group selected from the group consisting of halogen and lower alkyl;

L1 represents a single bond, lower alkylene, -W(lower alkyl)-, -O-, -O-lower alkylene, -O-lower alkylene-O-, lower alkylene-O-, lower alkylene-O-lower alkylene, or lower alkylene;

B represents a divalent group selected from (B1) to (B8):

(B1) tetrahydropyridinediyl,
(B2) diazapinediyl,
(B3) diazabicycloheptanediyl,
(B4) tetrahydrotriazolopyrazinediyl,
(B5) tetrahydroimidazopyrazinediyl,
(B6) azabicyclooctanediyl,
(B7) oxazolinediyl,
(B8) piperazinediyl,
(B9) piperidinediyi, 
(B10) thiazolidinediyi, and 
(B11) phenylene,

these groups (B1) to (B11) being optionally substituted on the ring(s) with at least one group selected from the group consisting of lower alkyl, halo-lower alkyl, alkenyl, lower alkoxy, halo-lower alkoxy, lower alkoxy carbonyl, lower alkenyloxycarbonyl, hydroxy, lower alkylsulfonyl, and halo-lower alkyl sulfonyl;

L2 represents a single bond, -CO-, -COO-, -COO-lower alkenylene, -COO-lower alkylene (this lower alkenylene is optionally substituted with phenyl), -COO-lower alkylene, -N(lower alkyl)-, -N(lower alkyl)-lower alkylene, -NH-, -NH-lower alkylene, -O-, -O-lower alkylene, -S-, lower alkylene (this lower alkylene is optionally substituted with optionally protected hydroxy), lower alkylene (this lower alkylene is optionally substituted with optionally protected hydroxy)-O-, lower alkylene-N-(lower alkyl)-, lower alkylene-N(lower alkyl)-lower alkylene, lower alkylene-O-lower alkylene, lower alkylene-S-, or lower alkynylene (this lower alkynylene is optionally substituted with lower alkyl or phenyl);

C represents a divalent group or a single bond selected from (C1) to (C28):
(C1) tetrahydroquinolinediyi,
(C2) dihydrobenzodioxindiyi,
(C3) dihydrobenzoxazolenediyi,
(C4) dihydrobenzofurandiyi,
(C5) dihydrobenzoxazinediyi,
(C6) adamantanediyi.
(C7) benzothiophanediyi,
(C8) benzodioxolediyi,
(C9) benzimidazolenediyi,
(C10) benzofurandiyi,
(C11) carbazolediyi,
(C12) chromandiyl.
(C13) cyclohexanediyl,
(C14) fluorenediyl,
(C15) furandiy.
(C16) imidazopyridinediyl,
5  (C17) imidazolediyl,
(C18) indolediyl,
(C19) naphthalenediyl.
(C20) piperidinediyl,
(C21) pyrazolediyl,
10  (C22) pyridinediyl.
(C23) pyrrolediyl,
(C24) quinolinediyl,
(C25) thiazolidiyl,
(C26) thiophenediyl,
15  (C27) phenylene, and
(C28) single bond,
these groups (C1) to (C27) being optionally substituted
on the ring(s) with at least one group selected from the group
consisting of alkoxy, halo-lower alkoxy, alkyl, haloalkyl,
20  halogen, hydroxy, lower alkoxy carbonyl, oxo, lower alkanoylamino,
lower alkanoyloxy, nitro, lower alkylthio, halo-lower alkylthio,
cyclo-lower-alkyl, cyclo-lower alkoxy, cyano, lower
alkoxycarbonylamino, nitro, amino, (mono- or di-lower alkyl)amino,
lower alkylsulfonyl, lower alkylsulfonlamino, alkenyloxy, and
25  (mono- or di-lower alkyl)amino lower alkoxy;

D represents a group or an atom selected from (D1) to
(D35):
(D1) oxadiazolyl-lower alkoxy,
(D2) triazolyl,
30  (D3) isoxazolyl-lower alkoxy.
(D4) imidazolyl,
(D5) imidazolyl-lower alkyl,
(D6) thiazolyl-lower alkoxy,
(D7) thieryl.
35  (D8) thieryl-lower alkoxy,
(D9) furyl-lower alkoxy,
(D10) tetrahydropyranyl,
(D11) pyrazinyl-lower alkoxy,
(D12) piperazinylphenyl,

5  (D13) pyrazolyl,
(D14) pyridyl,
(D15) pyridyloxy,
(D16) pyridyl-lower alkoxy,
(D17) pyrrolidinyl,

10  (D18) pyrrolyl,
(D19) phenyl,
(D20) (mono- or di-phenyl)amino,
(D21) phenyl-lower alkyl,
(D22) phenyl-lower alkenyl,

15  (D23) (phenyl-lower alkyl)(lower alkyl)amino,
(D24) (phenyl-lower alkyl)amino,
(D25) phenyl-lower alkylsulfonyl,
(D26) phenyl-lower alkylsulfanyl,
(D27) phenyl-lower alkylthio,

20  (D28) phenyl-lower alkenyloxy,
(D29) phenyl-lower alkoxy,
(D30) phenyl-lower alkoxyphenyl,
(D31) phenoxy,
(D32) phenoxy-lower alkyl,

25  (D33) phenoxyphenyl,
(D34) morpholinyl-lower alkyl, and
(D35) hydrogen,

these groups (D1) to (D34) being optionally substituted
on the ring(s) with at least one group selected from the group

30  consisting of lower alkyl, halo-lower alkyl, lower alkylthio,
    lower alkoxy, halo-lower alkoxy, and halogen,

    with the proviso that when A is group (A10) or (A12),
    and B is group (B11), C is selected from groups (C1) to (C27).

The present invention provides a pharmaceutical

35  composition comprising a compound represented by Formula (1)
(including all subclasses of the compounds of Formula (1) stated in this specification: the same applies hereinafter) or a salt thereof, and a pharmaceutically acceptable carrier.

The present invention provides a prophylactic and/or therapeutic agent for tuberculosis, comprising a compound of Formula (1), or a salt thereof, and a pharmaceutically acceptable carrier.

The present invention provides a compound represented by Formula (1), or a salt thereof, for use in the prevention and/or treatment of tuberculosis.

The present invention provides the use of a compound represented by Formula (1), or a salt thereof, for the production of a pharmaceutical composition.

The present invention provides the use of a compound of Formula (1), or a salt thereof, as a pharmaceutical composition.

The present invention provides a method for preventing and/or treating tuberculosis, comprising administering an effective amount of a compound of Formula (1), or a salt thereof, to a patient.

Advantageous Effects of Invention

The compounds of the present invention have specific efficacy against, in particular, acid-fast bacilli (mycobacterium tuberculosis complex and nontuberculosis mycobacterium complex).

The compounds of the present invention have an excellent effect on multidrug-resistant tubercle bacilli. The compounds of the present invention have an antibacterial action against anaerobic bacteria.

The compounds of the present invention exert the above-described activities not only in vitro but also in oral administration.

The compounds of the present invention do not cause diarrhea, which can be caused by a known antimicrobial agent that has a broad spectrum against general bacteria, such as gram positive and gram negative bacteria. In addition, the compounds
of the present invention have fewer side effects than existing drugs. Therefore, the compounds of the present invention can serve as pharmaceutical preparations that can be administered for a long period of time.

The compounds of the present invention can be satisfactorily distributed throughout the lung tissue, which is a main organ infected with mycobacteriosis. In addition, the compounds of the present invention have properties such as sustained drug efficacy and excellent safety. For this reason, the compounds of the present invention are expected to have high therapeutic effects.

Additionally, compared with existing antituberculosis agents, the compounds of the present invention exhibit stronger bactericidal activity against intracellular parasites, such as parasitic tubercle bacillus in human-derived macrophages. Therefore, the compounds of the present invention enable a reduction in the tuberculosis relapse rate and also enable short-term chemotherapy. Further, the compounds of the present invention are also expected to be used as a principal drug for preventive administration that is performed against a mixed infection with HIV and tuberculosis, which has become a serious problem.

The compounds of the present invention exhibit excellent metabolic stability in plasma, and thus have a feature of providing satisfactorily sustained bactericidal action in vivo.

Description of Embodiments

The groups represented by R¹, R², A, B, C, D, L1, and L2, and the substituents of these groups, as used herein, are described below.

The term "at least one" means usually one to ten, preferably one to six, and more preferably one to three.

Examples of "alkyl" include straight- or branched-chain alkyl groups having 1 to 12 carbon atoms, such as the "lower alkyl" mentioned below, heptyl, octyl, nonyl, decyl, and dodecyl.
Examples of "lower alkyl" include straight- or branched-chain alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, neopentyl, n-hexyl, isohexyl, and 3-methylnpentyl.

Examples of "alkenyl" include straight- or branched-chain alkenyl groups having 2 to 12 carbon atoms, such as the "lower alkenyl" mentioned below, heptynyl, octenyl, nonenyl, decenyl, dodecenyl, and -CH₂CH=C(CH₃)CH₂CH₂CH=C(CH₃)₂.

Examples of "lower alkenyl" include straight- or branched-chain alkenyl groups having 2 to 6 carbon atoms, such as methyl, vinyl, 1-propenyl, allyl, 1-, 2- or 3-butenyl, 1,3-butanediyl, and 1, 2-, 3-, or 4-pentenyl.

Examples of "lower alkylene" include straight- or branched-chain alkylene groups having 1 to 6 carbon atoms, such as methylene, ethylene, trimethylene, 2-methyltrimethylene, 2,2-dimethyltrimethylene, 1-methyltrimethylene, methyldimethylene, ethyldimethylene, dimethyldimethylene, tetramethylene, pentamethylene, and hexamethylene.

Examples of "lower alkenylene" include straight- or branched-chain alkenylene groups having 2 to 6 carbon atoms, such as ethylenylene, propylenylene, butylenylene, pentenylenylene, and hexylenylene.

Examples of "lower alkynylene" include straight- or branched-chain alkynylene groups having 2 to 6 carbon atoms, such as ethynylene, propynylene, butynylene, pentynylene, and hexynylene.

Examples of "cyclo-lower alkyl" include cycloalkyl having 3 to 8, preferably 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropymethyl, and cyclohexymethyl.

Examples of "alkoxy" include straight- or branched-chain alkoxy groups having 1 to 12 carbon atoms, such as the "lower alkoxy" mentioned below, n-heptyloxy, n-octyloxy, n-nonyloxy, n-decyloxy, and n-dodecyloxy.
Examples of "lower alkoxy" include straight- or branched-chain alkoxy groups having 1 to 6 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, sec-butoxy, n-pentyloxy, neopentyloxy, n-hexyloxy, isohexyloxy, and 3-methylpentyloxy.

Examples of "cyclo-lower alkoxy" include cycloalkoxy having 3 to 8, preferably 3 to 7 carbon atoms, such as cyclopropoxy, cyclobutoxy, cyclopentxyloxy, cyclohexyloxy, cyclopropylmethoxy, and cyclohexylmethoxy.

Examples of "lower alkanoyl" include straight- or branched-chain alkanoyl groups having 1 to 6 carbon atoms, such as formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, tert-butylylcarbonyl, and hexanoyl.

Examples of "lower alkoxy carbonyl" include (straight- or branched-chain alkoxy having 1 to 6 carbon atoms) carbonyl, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, and tert-butoxycarbonyl.

Examples of "lower alkenyloxy carbonyl" include (straight- or branched chain alkenyloxy having 2 to 6 carbon atoms) carbonyl, such as vinylloxy carbonyl, allyloxy carbonyl, butenylloxy carbonyl, and isobutenyloxy carbonyl.

"Halogen" represents fluorine, chlorine, bromine, and iodine.

Examples of "haloalkyl" include groups in which at least one hydrogen (for example, 1 to whole, 1 to 10, further 1 to 6, in particular 1 to 3 hydrogen atoms) of the above-mentioned "alkyl" is substituted with halogen(s).

Examples of "halo-lower alkyl" include groups in which at least one hydrogen (for example, 1 to 10, further 1 to 6, in particular 1 to 3 hydrogen atoms) of the above-mentioned "lower alkyl" is substituted with halogen(s), such as tribromomethyl (e.g., -CF₃), trihaloethyl (e.g., CH₃CF₃), pentahaloethyl (e.g., -CF₂CF₃), or nonahalobutyl (e.g., -CF₂CF₂CF₂CF₃).

Examples of "halo-lower alkoxy" include groups in which at least one hydrogen (e.g., 1 to 10, further 1 to 6, in
particular 1 to 3 hydrogen atoms) of the above-mentioned "lower alkoxy" is substituted with halogen(s), such as tribromomethoxy (e.g., -OCF₃), pentahaloethoxy (e.g., -OCF₂CF₃), or nonahalobutoxy (e.g., -OC(CF₃)₂CF₂CF₃).

Examples of protecting groups of "optionally protected hydroxy" include tetrahydropyranyl, acetyl, trialkylsilyl, (e.g., trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl), alkylidiphenylsilyl, (e.g., tert-butyldimethylsilyl), and the like.

The present invention provides a 6,7-dihydroimidazo[2,1-b][1,3]oxazine compound represented by Formula (1):

![Chemical Structure](image)

or a salt thereof.

wherein R¹ represents tetrahydroisoquinolyl, tetrahydroquinolyl, tetrahydrobenzoazepinyl, benzoazolyl, benzothiazolyl, indolyl, isoindoliny1, naphthyl, quinolyl, phenyl, biphenyl, or pyridyl, these groups being optionally substituted,

the phenyl and pyridyl represented by R¹ each being substituted directly or via a linker with at least one group selected from the group consisting of tetrahydropyridyl, diazepanyl, diazabicycloheptanyl, tetrahydrotriazolopyrazinyl, tetrahydroimidazopyrazinyl, azabicyclooctanly, oxazolyl, piperazinyl, piperidyl, and thiazoly1, each of these groups being optionally substituted.

the biphenyl represented by R¹ being substituted directly or via a linker with at least one group selected from the group consisting of tetrahydropyridyl, diazepanyl, diazabicycloheptanyl, tetrahydrotriazolopyrazinyl, tetrahydroimidazopyrazinyl, azabicyclooctanly, oxazolyl,
piperazinyl, piperidyl, thiazolyl, and phenyl, each of these
groups being optionally substituted; and
R² represents hydrogen or lower alkyl.
The pyridyl represented by R¹ is preferably substituted
directly or via a linker with at least one group selected from
the group consisting of piperazinyl and piperidyl, these groups
(piperazinyl and piperidyl) being optionally substituted.

In Formula (1), the carbon atom at position 7 is an
asymmetric carbon, and the compounds represented by Formula (1)
include R⁻, S⁻, and racemic forms based on the asymmetric carbon
atom, and the mixtures thereof.

In Formula (1), R¹ is preferably a group represented by
Formula (2):
-A-L₁-B₁₂-C-D (2)

In this formula, A represents a divalent group selected
from (A₁) to (A₁₂):
(A₁) tetrahydroisoquinolinediyl,
(A₂) tetrahydroquinolinediyl,
(A₃) tetrahydrobenzoazapinediyl,
(A₄) benzoxazolediyl,
(A₅) benzothiazolediyl,
(A₆) indolediyl,
(A₇) isooindolinediyl,
(A₈) naphthalenediyl.
(A₉) quinolinediyl,
(A₁₀) phenylene,
(A₁₁) biphenyldiyl, and
(A₁₂) pyridinediyl.

These groups (A₁) to (A₁₂) are optionally substituted
on the ring(s) with at least one group (further 1 to 3, in
particular 1 or 2 groups) selected from the group consisting of
halogen and lower alkyl.

The "(A₁) tetrahydroisoquinolinediyl" represented by A
is a divalent group obtained by removing two hydrogen atoms from
tetrahydroisoquinoline. Examples of tetrahydroisoquinoline
include 1,2,3,4-tetrahydroisoquinoline. Specific examples of
tetrahydroisoquinolinediyi include a group represented by:

Preferable examples thereof include 1,2,3,4-
tetrahydroisoquinoline-2,6-diyi and 1,2,3,4-
tetrahydroisoquinoline-2,7-diyi.

The "(A2) tetrahydroquinolinediyi" represented by A is a
divalent group obtained by removing two hydrogen atoms from
tetrahydroquinoline. Examples of tetrahydroquinoline include
1,2,3,4-tetrahydroquinoline. Specific examples of
tetrahydroquinolinediyi include a group represented by:

Preferable examples thereof include 1,2,3,4-tetrahydroquinoline-
1,6-diyi.

The "(A3) tetrahydrobenzoazepinediyi" represented by A is a
divalent group obtained by removing two hydrogen atoms from
tetrahydrobenzoazepine. Examples of tetrahydrobenzoazepine
include 2,3,4,5-tetrahydro-1H-benzo[b]azepine and 2,3,4,5-
tetrahydro-1H-benzo[c]azepine. Specific examples of
tetrahydrobenzoazepinediyi include a group represented by:

Preferable examples thereof include 2,3,4,5-tetrahydro-1H-
benzo[b]azepine-1,7-diyi and 2,3,4,5-tetrahydro-1H-
benzo[c]azepine-2,7-diyi.

The "(A4) benzoazolediyi" represented by A is a
divalent group obtained by removing two hydrogen atoms from benzoxazole. Examples of benzoxazole include benzo[d]oxazole. Specific examples of benzoxazolediyl include a group represented by:

\[ \text{2-methylbenzo[d]thiazole} \]

Preferable examples thereof include 2,5-benzo[d]oxazolediyl and 2,6-benzo[d]oxazolediyl.

The "(A5) benzothiazolediyl" represented by \( \text{A} \) is a divalent group obtained by removing two hydrogen atoms from benzothiazole. Examples of benzothiazole include benzo[d]thiazol. Specific examples of benzothiazolediyl include a group represented by:

\[ \text{Preferable examples thereof include 2,6-benzo[d]thiazolediyl.} \]

The "(A6) indolediyl" represented by \( \text{A} \) is a divalent group obtained by removing two hydrogen atoms from indole. Specific examples of indolediyl include a group represented by:

\[ \text{Preferable examples thereof include 1,5-indolodiyl.} \]

The "(A7) isoindolenediyil" represented by \( \text{A} \) is a divalent group obtained by removing two hydrogen atoms from isoindoline. Specific examples of isoindolenediyil include a group represented by:
Preferable examples thereof include 2,5-isoindolinediyl.

The "(A8) naphthalenediyl" represented by A is a divalent group obtained by removing two hydrogen atoms from naphthalene. Specific examples of naphthalenediyl include a group represented by:

Preferable examples thereof include 2,6-naphthalenediyl.

The "(A9) quinolinadiyl" represented by A is a divalent group obtained by removing two hydrogen atoms from quinoline.

Specific examples of quinolinadiyl include a group represented by:

Preferable examples thereof include 2,6-quinolinadiyl.

The "(A10) phenylene" represented by A is a divalent group obtained by removing two hydrogen atoms from benzene. Specific examples of phenylene include 1,2-phenylene, 1,3-phenylene, and 1,4-phenylene, with 1,4-phenylene being preferable.

The "(A11) biphenyldiyl" represented by A is a divalent group obtained by removing two hydrogen atoms from biphenyl.

Specific examples of biphenyldiyl include a group represented by:

Preferable examples thereof include 4,4'-biphenyldiyl.

The "(A12) pyridinediyl" represented by A is a divalent group obtained by removing two hydrogen atoms from pyridine.

Specific examples of pyridinediyl include 2,3-pyridinediyl, 2,4-pyridinediyl, 2,5-pyridinediyl, 2,6-pyridinediyl, 3,4-pyridinediyl, and 3,5-pyridinediyl, with 2,5-pyridinediyl being
preferable.

L represents a single bond or a linker. Specifically, L represents a single bond, lower alkylene, -N(lower alkyl)-, -O-, -O-lower alkylene, -O-lower alkylene-O-, lower alkylene-O-, lower alkylene-O-lower alkylene, or lower alkenylene.

B represents a divalent group selected from (B1) to (B11):

(B1) tetrahydropyridinediyl,  
(B2) diazopinediyl,  
(B3) diazabicycloheptanediyl,  
(B4) tetrahydrotriazolopyrazinediyl,  
(B5) tetrahydroimidazopyrazinediyl,  
(B6) azabicyclooctanediyl,  
(B7) oxazolinediyl,  
(B8) piperazinediyl,  
(B9) piperidinediyl,  
(B10) thiazolinediyl, and  
(B11) phenylene.

These groups (B1) to (B11) are optionally substituted on the ring(s) with at least one group (further 1 to 3, in particular 1 or 2 groups) selected from the group consisting of lower alkyl, halo-lower alkyl, alkenyl, lower alkoxy, halo-lower alkoxy, lower alkoxyalkyl, lower alkoxyalkyl, lower alkoxyalkyl, hydroxy, lower alkylsulfonyl, and halo-lower alkylsulfonyl.

The "(B1) tetrahydropyridinediyl" represented by B is a divalent group obtained by removing two hydrogen atoms from tetrahydropyridine. Examples of tetrahydropyridine include 1,2,3,4-tetrahydropyridine and 1,2,3,6-tetrahydropyridine. Specific examples of tetrahydropyridinediyl include a group represented by:

\[ \begin{align*}  
\text{or} \quad &  
\end{align*} \]

Preferable examples thereof include 1,2,3,6-tetrahydropyridine-
1,4-diyl.

The "(B2) diazepinediyl" represented by B is a divalent group obtained by removing two hydrogen atoms from diazepine. Specific examples of diazepinediyl include a group represented by:

\[
\begin{align*}
\text{or } & \quad \begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\end{array} \\
\text{N} \\
\text{N} \\
\text{N} \\
\end{align*}
\]

Preferable examples thereof include 1,4-diazepinediyl.

The "(B3) diazabicycloheptanediyl" represented by B is a divalent group obtained by removing hydrogen atoms from diazabicycloheptane. Examples of diazabicycloheptane include 2,5-diazabicyclo[2,2,1]heptane. Specific examples of diazabicycloheptanediyl include a group represented by:

\[
\begin{align*}
\text{or } & \quad \begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\end{array} \\
\text{N} \\
\text{N} \\
\text{N} \\
\end{align*}
\]

The "(B4) tetrahydrotriazolopyrazinediyl" represented by B is a divalent group obtained by removing two hydrogen atoms from tetrahydrotriazolopyrazine. Examples of tetrahydrotriazolopyrazine include 5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazine. Specific examples of tetrahydrotriazolopyrazinediyl include a group represented by:

\[
\begin{align*}
\text{or } & \quad \begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\end{array} \\
\text{N} \\
\text{N} \\
\text{N} \\
\end{align*}
\]

Preferable examples thereof include 5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazine-3,7-diyl.

The "(B5) tetrahydroimidazopyrazinediyl" represented by B is a divalent group obtained by removing two hydrogen atoms from tetrahydroimidazopyrazine. Examples of tetrahydroimidazopyrazine include 5,6,7,8-tetrahydroimidazo[1,2-
a) pyrazine. Specific examples of tetrahydroimidazopyrazinediyl include a group represented by:

Preferable examples thereof include 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3,7-diyl.

The "(B6) azabicyclooctanediyl" represented by B is a divalent group obtained by removing two hydrogen atoms from azabicyclooctane. Examples of azabicyclooctane include 8-azabicyclo[3,2,1]octane. Specific examples of azabicyclooctanediyl include a group represented by:

The "(B7) oxazolinediyl" represented by B is a divalent group obtained by removing two hydrogen atoms from oxazoline. Specific examples of oxazolinediyl include a group represented by:

Preferable examples thereof include 2,4-oxazolinediyl.

The "(B8) piperazinediyl" represented by B is a divalent group obtained by removing two hydrogen atoms from piperazine. Specific examples of piperazinediyl include a group represented by:

Preferable examples thereof include 1,4-piperazinediyl.

The "(B9) piperidinediyl" represented by B is a
divalent group obtained by removing two hydrogen atoms from piperidine. Specific examples of piperidine diyl include a group represented by:

5 Preferable examples thereof include 1,4-piperidine diyl.

The "(B10) thiazoline diyl" represented by B is a divalent group obtained by removing two hydrogen atoms from thiazoline. Specific examples of thiazoline diyl include a group represented by:

Preferable examples thereof include 2,4-thiazoline diyl.

The "(B11) phenylene" represented by B is a divalent group obtained by removing two hydrogen atoms from benzene. Examples of phenylene include 1,2-phenylene, 1,3-phenylene, and 1,4-phenylene, with 1,4-phenylene being preferable.

L2 represents a single bond or a linker. Specifically, L2 represents a single bond, -CO-, -COO-, -COO-lower alkylene, -COO-lower alkylene (this lower alkylene is optionally substituted with phnyl), -COO-lower alkylene, -N(lower alkyl)-, -N(lower alkyl)-lower alkylene, -NH-, -NH-lower alkylene, -O-, -O-lower alkylene, -S-, lower alkylene (this lower alkylene is optionally substituted with optionally protected hydroxy), lower alkylene (this lower alkylene is optionally substituted with optionally protected hydroxy)-O-, lower alkylene-N-(lower alkyl)-, lower alkylene-N(lower alkyl)-lower alkylene, lower alkylene-O-lower alkylene, lower alkylene-O-lower alkylene, lower alkylene-S-, or lower alkylene (this lower alkylene is optionally substituted with lower alkyl or phenyl).

C represents a divalent group or a single bond selected from (C1) to (C28):
(C1) tetrahydroquinolinediyl,
(C2) dihydrobenzodoxindiylyl,
(C3) dihydrobenzoazolediyl,
(C4) dihydrobenzofuranediyl,
(C5) dihydrobenzoxazinediyl,
(C6) adamantaneadiyl,
(C7) benzothiophenediyl,
(C8) benzodioxolediyl,
(C9) benzimidazolediyl.
(C10) benzofurandiyl,
(C11) carbazolediyl,
(C12) chromandiyl,
(C13) cyclohexamediyl,
(C14) fluorenediyl,
(C15) furandiyl,
(C16) imidazopyridinediyl,
(C17) imidazoleadiyl,
(C18) indoleadiyl,
(C19) naphthalenediyl,
(C20) piperidinediyl,
(C21) pyrazolediyl,
(C22) pyridinediyl,
(C23) pyrrolediyl,
(C24) quinolinediyl,
(C25) thiazolediyl,
(C26) thiophenediyl,
(C27) phenylene, and
(C28) single bond.

These groups (C1) to (C27) are optionally substituted
on the ring(s) with at least one group (further 1 to 3, in
particular 1 or 2 groups) selected from the group consisting of
alkoxy, halo-lower alkoxy, alkyl, haloalkyl, halogen, hydroxy,
lower alkoxy carbonyl, oxo, lower alkanoylamino, lower alkanoyloxy,
nitro, lower alkylthio, halo-lower alkylthio, cyclo-lower alkyl,
cyclo-lower alkoxy, cyano, lower alkoxy carbonylamino, nitro,
-24-

amino, (mono- or di-lower alkyl)amino, lower alkylsulfonyl, lower alkylsulfonylamino, alkenyloxy, and (mono- or di-lower alkyl)amino-lower alkoxy.

D represents a group or an atom selected from (D1) to

5  {D35}:
(D1) oxadiazolyl-lower alkoxy,
(D2) triazolyl,
(D3) isoxazolyl-lower alkoxy,
(D4) imidazolyl,
10 (D5) imidazolyl-lower alkyl.
(D6) thiazolyl-lower alkoxy,
(D7) thiethyl,
(D8) thienyl-lower alkoxy,
(D9) furyl-lower alkoxy,
15 (D10) tetrahydropyranyl,
(D11) pyrazinyl-lower alkoxy,
(D12) piperazinylphenyl,
(D13) pyrazolyl,
(D14) pyridyl,
20 (D15) pyridyloxy,
(D16) pyridyl-lower alkoxy,
(D17) pyrrolidinyl,
(D18) pyrrolyl,
(D19) phenyl,
25 (D20) {mono- or di-phenyl}amino,
(D21) phenyl-lower alkyl,
(D22) phenyl-lower alkenyl,
(D23) (phenyl-lower alkyl){lower alkyl}amino,
(D24) (phenyl-lower alkyl)amino,
30 (D25) phenyl-lower alkylsulfonyl,
(D26) phenyl-lower alkylsulfinyl,
(D27) phenyl-lower alkylthio,
(D28) phenyl-lower alkenyloxy,
(D29) phenyl-lower alkoxy,
35 (D30) phenyl-lower alkoxyphenyl,
(D31) phenoxy,
(D32) phenoxy-lower alkyl,
(D33) phenoxy-piperidyl,
(D34) morpholine-lower alkyl, and
(D35) hydrogen.

These groups (D1) to (D34) are optionally substituted on the ring(s) with at least one group (further 1 to 3, in particular 1 or 2 groups) selected from the group consisting of lower alkyl, halo-lower alkyl, lower alkylthio, lower alkoxy, halo-lower alkoxy, and halogen.

In Formula (2), when A is group (A10) or (A12), and B is group (B11), C is preferably selected from groups (C1) to (C27).

In Formula (2), A is preferably
(A1) tetrahydroisoquinolinediyl,
(A2) tetrahydroquinolinediyl,
(A9) quinolinediyl,
(A10) phenylene,
(A11) biphenyldiyl, or
(A12) pyridinediyl,
these groups (A1), (A2), and (A9) to (A12) being optionally substituted on the ring(s) with at least one group (preferably 1, 2, or 3 groups) selected from the group consisting of halogen and lower alkyl.

Among the compounds represented by Formula (1), preferable compounds are those in which R¹ is a group represented by Formula (2), wherein A is
(A1) tetrahydroisoquinolinediyl (preferably 1,2,3,4-tetrahydroisoquinoline-2,6-diyl),
(A2) tetrahydroquinolinediyl (preferably 1,2,3,4-tetrahydroquinoline-1,6-diyl),
(A9) quinolinediyl (preferably 2,6-quinolinediyl),
(A10) phenylene (preferably 1,4-phenylene),
(A11) biphenyldiyl (preferably 4,4'-biphenyldiyl), or
(A12) pyridinediyl (preferably 2,5-pyridinediyl), these groups (A1), (A2), (A9) to (A12) being optionally substituted on the ring(s) with one or two halogen atoms (preferably fluorine);

L1 is a single bond, lower alkylene, -O-, -O-lower alkylene, or lower alkylene-O-;

B is

(B7) oxazolinediyl (preferably 2,4-oxazolinediyl),

(B8) piperazinediyl (preferably 1,4-piperazinediyl),

(B9) piperidinediyl (preferably 1,4-piperidinediyl),

(B10) thiazolinediyl (preferably 2,4-thiazolinediyl),
or

(B11) phenylene (preferably 1,4-phenylene),

these groups (B7) to (B11) being optionally substituted on the ring with at least one or two groups selected from the group consisting of lower alkyl, lower alkoxy, halo-lower alkyl, halo-lower alkoxy, hydroxy, and halo-lower alkylsulfonyl;

L2 is a single bond, -N(lower alkyl)-, -O-, -O-lower alkylene, lower alkylene, lower alkylene-O-, or lower alkenylene;

C is

(C13) cyclohexanediyl,

(C20) piperidinediyl,

(C27) phenylene, or

(C28) single bond,

(with the proviso that when A is (A10) or (A12), and B is (B11), C is (C13), (C20), or (C27)),

these groups (C13), (C20), and (C27) being optionally substituted on the ring with one or two groups selected from the group consisting of halo-lower alkoxy, halo-lower alkyl, hydroxy, and halo-lower alkylthio;

D is

(D21) phenyl-lower alkyl,

(D24) (phenyl-lower alkyl)amino,

(D29) phenyl-lower alkoxy,

(D31) phenoxy, or
(D35) hydrogen,
these groups (D21), (D24), (D29), and (D31) being optionally substituted on the ring with one or two groups selected from the group consisting of halo-lower alkyl and halo-lower alkoxy.
Among the compounds represented by Formula (1), preferable compounds are those represented by Formula (1-1):

\[
\text{O}_2\text{N} \xrightarrow{\text{R}^2} \text{O} \xrightarrow{\text{C}} \text{N} \xrightarrow{\text{L}1} \text{B} \xrightarrow{\text{L}2} \text{C} \xrightarrow{\text{D}}
\]

wherein \( R^A \) is halogen or lower alkyl; \( m \) is 0, 1, or 2, wherein when \( m \) is 2, each \( R^A \) may be the same or different; and \( R^2 \), \( L1 \), \( B \), \( L2 \), \( C \), and \( D \) are the same as defined above.
Among these, \( R^A \) is preferably F.
\( m \) is preferably zero.
\( L1 \) is preferably lower alkylene (in particular \(-\text{CH}_2\)-).
\( B \) is preferably 1,4-phenylene.
\( L2 \) is preferably -O-lower alkylene (in particular \(-\text{O-CH}_2\)-).
\( C \) is preferably phenylene optionally substituted on the ring with one halo-lower alkyl (in particular trifluoromethyl).
\( D \) is preferably hydrogen.
Among the compounds represented by Formula (1), preferable compounds are those represented by Formula (1-2):

\[
\text{O}_2\text{N} \xrightarrow{\text{R}^2} \text{O} \xrightarrow{\text{C}} \text{N} \xrightarrow{\text{L}1} \text{B} \xrightarrow{\text{L}2} \text{C} \xrightarrow{\text{D}}
\]

wherein \( R^A \), \( m \), \( R^2 \), \( L1 \), \( B \), \( L2 \), \( C \), and \( D \) are the same as defined above.
Among these, \( m \) is preferably zero.
L1 is preferably lower alkylene-O- (in particular trimethylene-O-).

B is preferably phenylene optionally substituted on the ring with one halo-lower alkoxy (in particular trifluoromethoxy).

L2 and C each represent a single bond.

D is preferably hydrogen.

Among the compounds represented by Formula (1), preferable compounds are those represented by Formula (1-3):

![Chemical Structure](image)

wherein $R^A$, m, $R^2$, L1, B, L2, C, and D are the same as defined above.

Among these, m is preferably zero.

L1 is preferably -O-lower alkylene (in particular -O-CH$_2$-).

B is preferably phenylene optionally substituted on the ring with one halo-lower alkoxy (in particular trifluoromethoxy).

L2 and C each represent a single bond.

D is preferably hydrogen.

Among the compounds represented by Formula (1), preferable compounds are those represented by Formula (1-4):

![Chemical Structure](image)

wherein E is N or CH; $C^1$ is a divalent group selected from groups (C1) to (C27) above (the substituents on the ring(s) of these groups are the same as defined above); and $R^A$, m, $R^2$, L1, B, L2, and D are the same as defined above.

Among these, $R^A$ is preferably F.

m is preferably 0 or 1, more preferably 0.

E is preferably CH.
L1 is preferably a single bond.
B is preferably 1,4-piperidinediyl or 1,4-piperazinediyl, each of which is optionally substituted on the ring with one or two substituents selected from the group consisting of lower alkyl (in particular methyl), halo-lower alkylsulfonyl (in particular perfluorobutylsulfonyl), and lower alkoxy (in particular methoxy).

L2 is preferably a single bond, lower alkyne, -O-, lower alkyne-O-, N(lower alkyl)-, or lower alkenylene.

C is preferably phenylene, cyclohexanediyl, or piperidinediyl, each of which is optionally substituted on the ring with one or two groups selected from the group consisting of halo-lower alkoxy (in particular trifluoromethoxy), halo-lower alkyl (in particular trifluoromethyl), and halo-lower alkylthio (in particular trifluoromethylthio).

D is preferably phenyl-lower alkyl (in particular benzyl), (phenyl-lower alkyl)amino (in particular benzylamino), phenyl-lower alkoxy (in particular benzyloxy), phenoxy, or hydrogen, each of which is optionally substituted on the ring with one or two groups selected from the group consisting of halo-lower alkyl (in particular trifluoromethyl) and halo-lower alkoxy (in particular trifluoromethoxy).

Among the compounds represented by Formula (1), preferable compounds are those represented by Formula (1-5):

\[
\text{O}_2\text{N} \begin{array}{c} \text{R}^1 \\ \text{R}^2 \end{array} \begin{array}{c} \text{O} \\ \text{(R}^A)_{m} \end{array} \begin{array}{c} \text{L}^1 \text{--B--} \text{L}^2 \text{--C--D} \end{array}
\]

(1-5)

wherein \( R^A, m, R^1, R^2, L^1, B, L^2, C \), and \( D \) are the same as defined above.

Among these, \( m \) is preferably zero.
L1 is preferably a single bond.

B is preferably piperidinediyl optionally substituted on the ring with one or two groups selected from the group consisting of halo-lower alkyl (in particular trifluoromethyl)
and hydroxy.

L2 is preferably a single bond or -O-.

C is preferably a single bond or phenylene optionally substituted on the ring with one halo-lower alkoxy (in particular trifluoromethoxy).

D is preferably hydrogen or phenoxy optionally substituted on the ring with one halo-lower alkoxy (in particular trifluoromethoxy).

Among the compounds represented by Formula (1), preferable compounds are those represented by Formula (1a) to (1n) shown in Reaction Schemes 1 to 11 below.

Among the compounds represented by Formula (1), those described in Examples 1 to 772, and the salts thereof are furthermore preferable. The compounds described in the Examples 1, 3, 53, 56, 64, 79, 90, 143, 147, 153, 182, 198, 206, 228, 254, 282, 290, 299, 304, 335, 364, 372, 379, 380, 382, 383, 395, 400, 411, 414, 415, 446, 471, and 490, and salts thereof are still furthermore preferable.

In this specification, each of the divalent groups indicated by the letters A, L1, B, L2, and C, or by the structural formulae, in relation to the groups represented by Formula (2) above, can be attached in an arbitrary direction to the two groups on both sides of the divalent group. For example, when L1 is "lower alkylene-O-", its binding mode with groups A and B represents both "A-(lower alkylene-O)-B" and "A-(C-lower alkylene)-B." Of these, a preferable binding mode is such that the divalent group is attached as is as stated on the paper to a group represented by Formula (2)(-A-L1-B-L2-C-D) as stated on the paper. For example, when L1 is "lower alkylene-O-," a binding mode with groups A and B is preferably "A-(lower alkylene-O)-B."

The 6,7-dihydroimidazo[2,1-b][1,3]oxazine compound represented by Formula (1), or a salt thereof, can be produced, for example, in the following manner.

Reaction Scheme 1
wherein $R^1$ and $R^2$ are the same as defined above; $R^3$ represents lower alkylsulfonyl optionally substituted with halogen, or benzenesulfonyl optionally substituted with lower alkyl or nitro; and $X^1$ and $X^2$ are the same or different and each represent halogen.

Examples of the lower alkylsulfonyl optionally substituted with halogen represented by $R^3$ include $C_{1-6}$ alkylsulfonyl optionally substituted with 1 to 3 halogen atoms, such as methanesulfonyl, ethanesulfonyl, and trifluoromethanesulfonyl.

Examples of the benzenesulfonyl optionally substituted with lower alkyl represented by $R^3$ include benzenesulfonyl optionally substituted with 1 to 3 $C_{1-6}$ alkyl groups, such as benzenesulfonyl and p-toluenesulfonyl.

Examples of the benzenesulfonyl optionally substituted with nitro represented by $R^3$ include benzenesulfonyl optionally substituted with 1 to 3 nitro groups, such as o-nitrobenzenesulfonyl and p-nitrobenzenesulfonyl.

The halogen represented by $X^1$ and $X^2$ is fluorine, chlorine, bromine, or iodine, with chlorine and bromine being preferable.
(2) + (3) → (4):

In the reaction of Compound (2) and Compound (3), the reaction conditions of a general sulfonylation reaction of alcohol can be widely applied. For example, Compound (4) can be produced by using Compound (2) and Compound (3) without a solvent or by dissolving them in an appropriate solvent (e.g., methylene chloride, acetonitrile, dimethylformamide (DMF), dimethylsulfoxide (DMSO), or toluene), and allowing a reaction to occur in the presence of a basic compound (e.g., potassium carbonate, potassium hydrogen carbonate, sodium carbonate, sodium hydrogen carbonate, pyridine, triethylamine, diisopropylethylamine, tetramethylethylenediamine (TMEDA), or tetramethylpropylenediamine (TMPDA)).

The basic compound is used in an amount of usually equimolar to excess mole, preferably 1- to 5-fold mol, and more preferably 1- to 2-fold mol, of Compound (2).

Compound (3) is used in an amount of usually equimolar to excess mole, preferably 0.9- to 2-fold mol, and more preferably 0.9- to 1.5-fold mol, of Compound (2).

The reaction temperature is usually -50 to 150°C, preferably -20 to 100°C, and more preferably -10 to 50°C. The reaction time is usually 10 minutes to 24 hours, preferably 10 minutes to 12 hours.

(4) + (5) → (6):

Compound (4) and Compound (5) can be reacted in an appropriate solvent (e.g., methylene chloride, acetonitrile, DMF, or dimethylacetamide (DMAc)) in the presence of a basic compound (e.g., potassium carbonate, potassium hydrogen carbonate, sodium carbonate, sodium hydrogen carbonate, pyridine, triethylamine, diisopropylethylamine, tetramethylethylenediamine (TMEDA), or tetramethylpropylenediamine (TMPDA)). As an activator, an alkali metal iodide, such as sodium iodide or potassium iodide, may also be added to the reaction system, if necessary.

The basic compound is used in an amount of usually equimolar to excess mole, preferably 1- to 5-fold mol, and more
preferably 1- to 2-fold mol. of Compound (5).

When an activator is used, the amount of the activator is usually equimolar to excess mole, preferably 1- to 5-fold mol, and more preferably 1- to 2-fold mol, of Compound (5).

Compound (4) is used in an amount of usually 0.5-fold mol to excess mole, further equimolar to excess mole, preferably 0.9- to 2-fold mol, and more preferably 0.9- to 1.5-fold mol, of Compound (5).

The reaction temperature is usually -50 to 150°C, preferably -30 to 100°C, and more preferably -10 to 100°C. The reaction time is usually 10 minutes to 48 hours, preferably 10 minutes to 24 hours.

(6) → (7):

Compound (7) can be produced by subjecting Compound (6) to a hydrolysis reaction. In the hydrolysis reaction, known reaction conditions generally employed are applicable. For example, the reaction can be performed in an appropriate solvent (e.g., water or a mixed solvent of water with, for example, ethanol or tetrahydrofuran (THF)) in the presence of an acid (e.g., hydrochloric acid or sulfuric acid).

An acid is used in an amount of a catalytic amount to excess mole of Compound (5). The reaction temperature is usually 0 to 50°C. The reaction time is usually 10 minutes to 24 hours.

(7) + (3) → (8):

In the reaction of Compound (7) and Compound (3), the reaction conditions of a general sulfonylation reaction of alcohol can be widely applied. For example, the reaction can be performed under the same reaction conditions for producing Compound (4) from Compound (2) and Compound (3).

(8) + (9) → (10):

Compound (8) and Compound (9) can be reacted in an appropriate solvent in the presence of a basic compound.

Any known solvent can be used as long as it does not hinder the reaction. Examples of such solvents include water, DMF, DMSO, acetonitrile, and like aprotic polar solvents; benzene,
toluene, xylene, tetralin, liquid paraffin, cyclohexane, and like hydrocarbon solvents; ethanol, isopropanol, n-butanol, tert-butanol, and like alcohol solvents; THF, dioxane, dipropyl ether, diethyl ether, diglyme, and like ether solvents; ethyl acetate, and like ester solvents; acetone, methylethylketone, and like ketone solvents; mixtures of such solvents; and the like.

Examples of basic compounds include sodium hydride and like alkali metal hydrides; sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide, and like metal alcoholates; sodium hydroxide, potassium hydroxide, and like alkali metal hydroxides; sodium carbonate, potassium carbonate, cesium carbonate, and like alkali metal carbonates; sodium hydrogen carbonate, potassium hydrogen carbonate, and like alkali metal hydrogen carbonates; tripotassium phosphate and like alkali metal phosphates; sodium amide; sodium acetate, potassium acetate, and like acetates; triethylamine, trimethylamine, diisopropylethylamine, pyridine, dimethylaniline, 1-methylpyrrolidine, N-methylmorpholine, 1.5-diazabicyclo[4.3.0]nonene-5 (DBN), 1.8-diazabicyclo[5.4.0]undecene-7 (DBU), 1.4-diazabicyclo[2.2.2]octane (DABCO), and like nitrogen-containing organic bases. These bases can be used singly, or in a combination of two or more in an appropriate ratio.

As a catalyst (or a reaction promoter), for example, an alkali metal halide, such as cesium fluoride, or an alkali metal iodide, such as sodium iodide or potassium iodide, may be added, if necessary.

The basic compound is used in an amount of usually equimolar to excess mole, preferably 1- to 5-fold mol, and more preferably 1- to 2-fold mol, of Compound (8).

Compound (9) is used in an amount of usually 0.5- to 5-fold mol, preferably 0.8- to 2-fold mol, and more preferably 0.9- to 1.5-fold mol, of Compound (8).

When a catalyst is used, the amount of the catalyst is usually a catalytic amount to excess mole, preferably 0.01- to 5-
fold mole, and more preferably 0.1- to 2-fold mol, of Compound (8).

The reaction temperature is usually -30 to 150°C, preferably -10 to 100°C, and more preferably -10 to 80°C. The reaction time is usually 10 minutes to 24 hours, preferably 10 minutes to 12 hours, and more preferably 20 minutes to 7 hours.

(10) → (1):

Compound (1) can be produced by subjecting Compound (10) to a ring-closure reaction.

The ring-closure reaction can be performed in an appropriate solvent (e.g., N-methylpyrrolidone (NMP), DMF, or DMAc) in the presence of a basic compound (e.g., sodium hydride or sodium tert-butoxide).

The basic compound is used in an amount of usually equimolar to excess mole, preferably 1- to 5-fold mol, and more preferably 1- to 2-fold mol, of Compound (10).

The reaction temperature is usually -50 to 150°C, preferably -20 to 100°C, and more preferably -10 to 50°C. The reaction time is usually 10 minutes to 100 hours, and preferably 10 minutes to 72 hours.

In the present invention, the reaction mixture obtained by the reaction of Compound (8) and Compound (9) can be subjected to the subsequent ring-closure reaction as is, without isolating Compound (10), to produce target Compound (1). Further, when the reaction is performed at usually -10 to 200°C, and preferably 0 to 100°C, using a basic compound in an amount of equimolar to excess mole of Compound (8), Compound (1) can be produced at once without isolation of the intermediate, i.e., Compound (10). Reaction Scheme 2
wherein $R^1$, $R^2$, $R^3$, $X^1$, and $X^2$ are the same as defined above.

(11) $\rightarrow$ (12):

Compound (12) can be produced by subjecting Compound (11) to an oxidation reaction. In the oxidation reaction, known reaction conditions generally employed can be widely applied. For example, the reaction can be carried out by reacting Compound (12) with an oxidizing agent (e.g., m-chloroperbenzoic acid (mCPBA) or hydrogen peroxide) in an appropriate solvent.

(12) $+ (3) \rightarrow (13)$:

In the reaction of Compound (12) and Compound (3), the reaction conditions of a general sulfonylation reaction of alcohol can be widely applied. For example, the reaction can be performed under the same reaction conditions as employed in Reaction Scheme 1 for producing Compound (4) from Compound (2) and Compound (3).

(13) $+ (5) \rightarrow (14)$:

The reaction of Compound (13) and Compound (5) can be performed under the same reaction conditions as employed in Reaction Scheme 1 for producing Compound (5) from Compound (4) and Compound (5).

(14) $+ (9) \rightarrow (10)$:

The reaction of Compound (14) and Compound (9) can be
performed under the same reaction conditions as employed in Reaction Scheme 1 for producing Compound (10) from Compound (8) and Compound (9).

(10) → (1)

The reaction for producing Compound (1) from Compound (10) can be performed under the same reaction conditions as employed in Reaction Scheme 1 for producing Compound (1) from Compound (10).

In the present invention, the reaction mixture obtained by the reaction of Compound (14) and Compound (9) can be subjected to the subsequent ring-closure reaction as is, without isolating Compound (10), to produce target Compound (1). Further, when the reaction is performed at usually -10 to 200°C, and preferably 0 to 100°C, using a basic compound in an amount of equimolar to excess mole of Compound (14), Compound (1) can be produced at once without isolation of the intermediate, i.e., Compound (10).

Reaction Scheme 3

wherein R¹, R², R³, X¹, and X² are the same as defined above, and X¹⁰ represents halogen.
Examples of the halogen represented by $X^3$ include chlorine, bromine, and iodine.

\[ (11) \rightarrow (15): \]

Compound (15) can be produced by reacting Compound (11) with a benzyl halide (e.g., benzyl chloride or benzyl bromide) in an appropriate solvent in the presence of a basic compound (an $O$-benzylation reaction). In the $O$-benzylation reaction, known reaction conditions generally employed can be widely applied.

\[ (15) \rightarrow (16): \]

The reaction for producing Compound (16) from Compound (15) can be performed under the same reaction conditions as employed in Reaction Scheme 2 for producing Compound (12) from Compound (11).

\[ (16) + (9) \rightarrow (17): \]

The reaction for producing Compound (17) from Compound (16) and Compound (9) can be performed under the same reaction conditions as employed in Reaction Scheme 2 for producing Compound (10) from Compound (14) and Compound (9).

\[ (17) \rightarrow (18): \]

Compound (17) can be produced by subjecting Compound (18) to debenzylation. In the debenzylation reaction, known reaction conditions generally employed can widely be applied. For example, the reaction can be performed by subjecting Compound (17) to catalytic hydrogenation.

\[ (18) + (3) \rightarrow (19): \]

In the reaction of Compound (18) and Compound (3), the reaction conditions of a general sulfonylation reaction of alcohol can be widely applied. For example, the reaction can be performed under the same reaction conditions as employed in Reaction Scheme 1 for producing Compound (4) from Compound (2) and Compound (3).

\[ (19) + (5) \rightarrow (10): \]

The reaction of Compound (19) and Compound (5) can be performed under the same reaction conditions as employed in Reaction Scheme 1 for producing Compound (6) from Compound (4).
and Compound (5).
(10) - {1}:

The reaction for producing Compound (1) from Compound (10) can be performed under the same reaction conditions as employed in Reaction Scheme 1 for producing Compound (1) from Compound (10).

In the present invention, the reaction mixture obtained by the reaction of Compound (19) and Compound (5) can be subjected to the subsequent ring-closure reaction as is, without isolating Compound (10), to produce target Compound (1). Further, when the reaction is performed at usually -10 to 200°C, and preferably 0 to 100°C, using a basic compound in an amount of equimolar to excess mole of Compound (19), Compound (1) can be produced at once without isolation of the intermediate, i.e., Compound (10)

Reaction Scheme 4
wherein R², R³, and X¹ are the same as defined above; R⁴ represents a group represented by the above-mentioned -C-D; R⁵ represents lower alkyl; R⁶ represents lower alkyl; and X² represents a leaving group.

Examples of the lower alkyl represented by R⁵ include straight- or branched-chain alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, neopentyl, n-hexyl, iso-hexyl, and 3-methylpentyl.

Examples of the lower alkyl represented by R⁶ include straight- or branched-chain alkyl groups having 1 to 5 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, and neopentyl.

Examples of the leaving group represented by X² include halogen (e.g., chlorine, bromine, and iodine), sulfonyloxy (e.g., p-toluenesulfonyloxy, o- or p-nitrobenzenesulfonyloxy, and methanesulfonyloxy), and the like.

(8) + (20) → (21):

The reaction for producing Compound (21) from Compound (8) and Compound (20) can be performed under the same reaction conditions as employed in Reaction Scheme 1 for producing Compound (1) through Compound (10) obtained from Compound (8) and Compound (9).

(21) → (22):

The reaction for producing Compound (22) from Compound (21) can be performed under the same reaction conditions as employed in Reaction Scheme 1 for producing Compound (7) from Compound (6).

(22) + (23) → (1a):

The reaction of Compound (22) and Compound (23) can be performed without a solvent or in an appropriate solvent in the presence of a reducing agent (a reductive amination reaction).

Compound (23) is used in an amount of usually 0.5- to 10-fold mol, preferably 0.6- to 5-fold mol, and more preferably 0.7- to 2-fold mol, of Compound (22).
Examples of solvents include water; methanol, ethanol, isopropanol, butanol, tert-butanol, ethylene glycol, and like lower alcohols; acetonitrile; formic acid, acetic acid, trifluoroacetic acid, and like fatty acids; diethyl ether, THF, dioxane, monoglyme, diglyme, and like ethers; benzene, toluene, xylene, and like aromatic hydrocarbons; dichloromethane, dichloroethane, chloroform, carbon tetrachloride, and like halogenated hydrocarbons; mixtures of such solvents; and the like.

Examples of reducing agents include formic acid, sodium formate, and like alkali metal formates; sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, lithium aluminium hydride, and like hydride reducing agents or mixtures of these hydride reducing agents; palladium black, palladium carbon, platinum oxide, platinum black, Raney nickel, and like catalytic hydrogenation reducing agents.

When formic acid and/or an alkali metal formate is used as a reducing agent, a suitable reaction temperature is usually from about room temperature to 200°C, and preferably about 50 to 150°C. The reaction completes in about 10 minutes to 10 hours. The formic acid and/or alkali metal formate is preferably used in a large excess relative to Compound (22).

When a hydride reducing agent is used, a suitable reaction temperature is usually about -80 to 100°C, and preferably about -80 to 70°C, and the reaction completes in about 30 minutes to 100 hours. A hydride reducing agent may be used in an amount of usually about equimolar to 20-fold mol, and preferably about equimolar to 6-fold mol, of Compound (22). To the reaction system of the reaction may be added an acid, such as acetic acid, formic acid, or tetraisopropoxy titanium; an amine, such as trimethylamine, triethylamine, and N-ethyl-diisopropylamine; molecular sieves, such as molecular sieves 3A (MS-3A) and molecular sieves 4A (MS-4A), and the like.

When a catalytic hydrogenation reducing agent is used, the reaction is performed at a temperature of usually about -30 to 100°C, and preferably about 0 to 60°C, in a hydrogen
atmosphere at a pressure of usually about atmospheric pressure to 20 atm, and preferably about atmospheric pressure to 10 atm, or in the presence of a hydrogen donor, such as formic acid, ammonium formate, cyclohexene, or hydrazine hydrate. The reaction usually completes in about 1 to 12 hours. The catalytic hydrogenation reducing agent is usually used in an amount of about 0.1 to 40 wt%, and preferably about 1 to 20 wt%, of compound (22).

(22) + (24) → (1b):

The reaction of Compound (22) and Compound (24) can be performed under the same reaction conditions as employed in the reaction for producing Compound (1a) from Compound (22) and Compound (23).

(1b) + (25) → (1a):

In the reaction of Compound (1b) and Compound (25), the reaction conditions employed in a general N-alkylation reaction can be widely applied. For example, the reaction can be carried out by reacting Compound (1b) with Compound (25) in an appropriate solvent in the presence of a basic compound.

(1b) + (26) → (1c):

The reaction of Compound (1b) and Compound (26) can be performed under the same reaction conditions as employed in the reaction for producing Compound (1a) from Compound (22) and Compound (23).

Reaction Scheme 5

wherein R², R³, and X¹ are the same as defined above; A¹ is
tetrahydroisoquinolinediyl, tetrahydroquinolinediyl,
tetrahydrobenzoazepinediyl, or isoindolinediyl (these groups are
optionally substituted on the ring(s) with at least one group
selected from the group consisting of halogen and lower alkyl)
and represents a group in which the atom attached to P1 is
nitrogen; R7 is a group represented by the above-mentioned -C-D;
and P1 represents a protecting group of nitrogen.

The protecting group of nitrogen represented by P1 is
not particularly limited as long as it does not have an adverse
effect on the reaction. Examples thereof include formyl, lower
alkyl carbonyl (e.g., acetyl and ethylcarbonyl), phenylcarbonyl,
lower alkoxy carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, and
tert-butoxycarbonyl (Boc)), benzyl oxycarbonyl (Cbz),
allyloxycarbonyl (Alloc), and the like. These protecting groups
are further optionally substituted with 1 to 5, (e.g., 1 to 3)
substituents, such as halogen (fluorine, chlorine, bromine, or
iodine) or nitro. Boc is a preferable protecting group of
nitrogen.

(8) + (27) → (28):

The reaction for producing Compound (28) from Compound
(8) and Compound (27) can be performed under the same reaction
conditions as employed in Reaction Scheme 1 for producing
Compound (1) through Compound (10) obtained from Compound (8) and
Compound (9).

(28) → (29):

Compound (29) can be obtained by performing
deprotection of P1 from Compound (28). A deprotection reaction
may be performed in accordance with a general method for
deprotection of a nitrogen protecting group, for example, a
method disclosed in Green's Protective Groups in Organic
Synthesis, -4th ed. John Wiley & Sons, Inc. For example, when P1
is Boc, Compound (28) can be subjected to a deprotection reaction
without a solvent or in an appropriate solvent in the presence of
an acid (e.g., hydrochloric acid or trifluoroacetic acid). When
P1 is Cbz, the reaction can be performed without a solvent or in
an appropriate solvent in the presence of a reducing agent (e.g., an alkali metal formate, a hydride reducing agent, or a catalytic hydrogenation reducing agent). When $P^1$ is Alloc, the deprotection reaction can be performed in the presence of a palladium catalyst.

(29) + (30) → (1a):

The reaction of Compound (29) and Compound (30) can be performed under the same reaction conditions as employed in Reaction Scheme 4 for producing Compound (1a) from Compound (22) and Compound (23).

Reaction Scheme 6

wherein $A$, $L_1$, $R^2$, $R^3$, $R^7$, $X^1$, and $P^1$ are the same as defined above; $R^{61}$ represents lower alkyl, halo-lower alkyl, or alkenyl; and $m_1$ represents 0, 1, or 2.

Examples of the lower alkyl represented by $R^{61}$ include straight- or branched-chain alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, neopentyl, n-hexyl, isohexyl, and 3-methylpentyl.

The halo-lower alkyl represented by $R^{61}$ is a group in which at least one hydrogen atom (e.g., 1 to 10, further 1 to 6,
in particular 1 to 3 hydrogen atoms) of the above-mentioned
"lower alkyl" is substituted with halogen(s). Examples thereof
include trihalomethyl (e.g., -CF₃), trihaloethyl (e.g., -CH₂CF₃),
pentahaloethyl (e.g., -CF₂CF₃), and nonahalobutyl (e.g., -
CF₂CF₃CF₃CF₃).

Examples of the alkenyl represented by R⁴₁ include
straight- or branched-chain alkenyl groups having 2 to 6 carbon
atoms, such as methyl, vinyl, 1-propenyl, allyl, 1-, 2-, or 3-
butenyl, 1,3-butanediyl, 1-, 2-, 3-, or 4-pentenyl, heptenyl,
ocytityl, nonenyl, decenyl, dodecenyl, and -
CH₂CH=C(CH₃)CH₂CH₂CH=C(CH₃)₂.

A is preferably phenylene, and more preferably para-
phenylene.

Li is preferably a single bond.

\[(\text{8}) + (\text{31}) \rightarrow (\text{32})\]:

The reaction for producing Compound (32) from Compound
\{8\} and Compound (31) can be performed under the same reaction
conditions as employed in Reaction Scheme 1 for producing
Compound (1) through Compound (10) obtained from Compound (8) and

\begin{align*}
\text{Compound (32)} & \rightarrow \text{(33)}; \\
\text{Compound (33)} & \text{can be obtained by performing}
\text{deprotection of P¹ from Compound (32). The deprotection}
\text{reaction can be performed under the same reaction conditions}
\text{as employed in Reaction Scheme 5 for producing Compound (29)}
\text{from Compound (28).}
\end{align*}

\[(\text{33}) + (\text{30}) \rightarrow (\text{1e})\]:

The reaction of Compound (33) and Compound (30) can be
performed under the same reaction conditions as employed in

\begin{align*}
\text{Reaction Scheme 4 for producing Compound (1e) from Compound (22)}
\text{and Compound (23).}
\end{align*}
wherein A, L1, R2, R3, R7, X1, and P1 are the same as defined above; R62 represents lower alkyl, halo-lower alkyl, alkenyl, lower alkoxy, halo-lower alkoxy, or hydroxy; m2 represents 0, 1, or 2; and the dashed lines indicate that the bond may be a double bond.

The lower alkyl, halo-lower alkyl, and alkenyl represented by R62 are the same as defined above for R61.

Examples of the lower alkoxy represented by R62 include straight- or branched-chain alkoxy groups having 1 to 6 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, sec-butoxy, n-pentyloxy, neopentyloxy, n-hexyloxy, isohexyloxy, and 3-methylpentylxyloxy.

Examples of the halo-lower alkoxy represented by R62 include a group in which at least one hydrogen atom (e.g., 1 to 10, further 1 to 6, in particular 1 to 3 hydrogen atoms) of the above-mentioned "lower alkoxy" is substituted with halogen(s). Examples thereof include trihalomethoxy (e.g., -OCF3), pentahaloethyl (e.g., -OCF2CF3), and nonahalobutyl (e.g., -CF2CF2CF2CF3).

A is preferably phenylene, and more preferably para-
phenylene.

L1 is preferably a single bond.

(8) + (34) – (35):

The reaction for producing Compound (35) from Compound (8) and Compound (34) can be performed under the same reaction conditions as employed in Reaction Scheme 1 for producing Compound (1) through Compound (10) obtained from Compound (8) and Compound (9).

(35) – (36):

Compound (36) can be obtained by performing deprotection of P² from Compound (35). The deprotection reaction can be performed under the same reaction conditions as employed in Reaction Scheme 5 for producing Compound (29) from Compound (28).

(36) + (30) – (1f):

The reaction of Compound (36) and Compound (30) can be performed under the same reaction conditions as employed in Reaction Scheme 4 for producing Compound (1a) from Compound (22) and Compound (23).

Reaction Scheme 8
wherein \( A, L_1, R^2, R^3, X^1 \), and \( P^1 \) are the same as defined above; \( R^{63} \) and \( R^{64} \) are the same or different and each represent lower alkyl, halo-lower alkyl, alkenyl, lower alkoxy, halo-lower alkoxy, or hydroxy; \( m_3 \) and \( m_4 \) are the same or different and each represent 0, 1, or 2; \( R^{81} \) represents lower alkyl, halo-lower alkyl, lower alkoxy, halo-lower alkoxy, or hydroxy; and \( n_1 \) represents an integer of 1 to 5.

The lower alkyl, halo-lower alkyl, alkenyl, lower alkoxy, halo-lower alkoxy, and hydroxy represented by \( R^{63}, R^{64}, \) or \( R^{81} \) are the same as those defined above for \( R^{62} \).

A is preferably phenylene, and more preferably para-phenylene.

\( L_1 \) is preferably a single bond.

15 \( (8) + (37) \rightarrow (38) \):

The reaction for producing Compound (38) from Compound (8) and Compound (37) can be performed under the same reaction conditions as employed in Reaction Scheme 1 for producing Compound (1) through Compound (10) obtained from Compound (8) and Compound (9).
(38) → (39):

Compound (39) can be obtained by performing deprotection of P¹ from Compound (38). The deprotection reaction can be performed under the same reaction conditions as employed in Reaction Scheme 5 for producing Compound (29) from Compound (28).

(39) + (40) → (1g):

The reaction of Compound (39) and Compound (40) can be performed under the same reaction conditions as employed in Reaction Scheme 4 for producing Compound (1a) from Compound (22) and Compound (23).

Reaction Scheme 9

![Chemical structures](image)

wherein A, L¹, R¹, R³, R⁵, X¹, and P¹ are the same as defined above; R⁶⁵ represents lower alkyl or halo-lower alkyl; and m⁵ represents 0 or 1.

(8) + (41) → (42):

The reaction for producing Compound (42) from Compound (8) and Compound (41) can be performed under the same reaction conditions as employed in Reaction Scheme 1 for producing...

Compound (1) through Compound (10) obtained from Compound (8) and Compound (9).

(42) - (43):

Compound (43) can be produced by performing degprotection of P$_1$ from Compound (42). The deprotection reaction can be performed under the same reaction conditions as employed in Reaction Scheme 5 for producing Compound (29) from Compound (28).

(43) + (30) -> (1b):

The reaction of Compound (43) and Compound (30) can be performed under the same reaction conditions as employed in Reaction Scheme 4 for producing Compound (1a) from Compound (22) and Compound (23).

Reaction Scheme 10
wherein \( A, L^1, R^2, R^{61}, \) and \( m^1 \) are the same as defined above; \( R^{62} \) represents lower alkyl or halo-lower alkyl; \( R^{63} \) represents a group represented by \(-C-D\); \( R^{64} \) represents a group represented by \(-L^2^1-C-D\), wherein \( L^2^1 \) represents lower alkynylene, lower alkylene (this lower alkylene is optionally substituted with phenyl), or lower alkenylene; \( R^{65} \) is a group represented by \(-L^2^2-C-D\), wherein \( L^2^2 \) represents a single bond or lower alkylene-O-; \( R^{66} \) represents a group represented by \(-L^2-C-D\); and \( X^{41}, X^{42}, X^{43}, \) and \( X^{44} \) each
represent a leaving group.

Examples of the leaving group represented by $X^1$ include halogen (e.g., chlorine and bromine) and a group represented by $O-SO_2R^2$.

Examples of the leaving group represented by $X^2$ include halogen (e.g., chlorine and bromine), hydroxy, and the like.

Examples of the leaving group represented by $X^3$ include halogen (e.g., chlorine and bromine).

Examples of the leaving group represented by $X^4$ include halogen (e.g., chlorine and bromine), sulfonyloxy (e.g., p-toluenesulfonyloxy, o- or p-nitrobenzenesulfonyloxy, methanesulfonyloxy, and trifluoromethanesulfonyloxy), and the like.

(33) + (44) → (11):

In the reaction of Compound (33) and Compound (44), the reaction conditions of a general sulfonylation reaction of amine can be widely applied. For example, Compound (11) can be produced by using Compound (33) and Compound (44) without a solvent or by dissolving them in an appropriate solvent (e.g., methylene chloride, acetonitrile, DMF, DMSO, or toluene) and allowing a reaction to occur in the presence of a basic compound (e.g., triethylamine or diisopropylethylamine).

The basic compound is used in an amount of usually equimolar to excess mole, preferably 1- to 5-fold mol, and more preferably 1- to 4-fold mol, of Compound (33).

Compound (44) is used in an amount of usually equimolar to excess mole, preferably 1- to 2-fold mol, and more preferably 1- to 1.5-fold mol, of Compound (33).

The reaction temperature is usually -50 to 150°C, preferably -20 to 100°C, and more preferably -10 to 50°C. The reaction time is usually 10 minutes to 24 hours, and preferably 10 minutes to 12 hours.

(33) + (45) → (1j):

In the reaction of Compound (33) and Compound (45), the reaction conditions of a general acylation reaction of amine can
be widely applied.

For example, when X₁² of Compound (45) is halogen, Compound (1j) can be produced by using Compound (33) and Compound (45) without a solvent or by dissolving them in an appropriate solvent (e.g., methylene chloride, acetonitrile, DMF, DMSO, or toluene) and allowing a reaction to occur in the presence of a basic compound (e.g., potassium carbonate, potassium hydrogen carbonate, sodium carbonate, sodium hydrogen carbonate, pyridine, triethylamine, or diisopropylethylamine).

When X₁² of Compound (45) is hydroxy, Compound (1j) can be produced by using Compound (33) and Compound (45) without a solvent or by dissolving them in an appropriate solvent (e.g., methylene chloride, acetonitrile, DMF, DMSO, or toluene) and allowing a reaction to occur in the presence of a suitable condensing agent (e.g., 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride/1-hydroxybenzotriazole).

{33} + {46} → (1k):

In the reaction of Compound (33) and Compound (46), the reaction conditions of a general urethanation reaction of amine can be widely applied.

For example, Compound (1k) can be produced by using Compound (33) and Compound (46) without a solvent or by dissolving them in an appropriate solvent (e.g., methylene chloride, acetonitrile, DMF, DMSO, or toluene) and allowing a reaction to occur in the presence of a basic compound (e.g., potassium carbonate, potassium hydrogen carbonate, sodium carbonate, sodium hydrogen carbonate, pyridine, triethylamine, or diisopropylethylamine).

{33} + {47} → (1l):

In the reaction of Compound (33) and Compound (47), the reaction conditions of a ring-opening reaction of epoxy with amine can be widely applied.

For example, Compound (1l) can be produced by using Compound (33) and Compound (47) without a solvent or by
dissolving them in an appropriate solvent (e.g., methylene chloride, acetonitrile, DMF, DMSO, NMP, or toluene) and allowing a reaction to occur.

\[
(33) + (48) \rightarrow (1m): \]

In the reaction for producing Compound (1m) from Compound (33) and Compound (48), the reaction conditions of a general alkylation reaction of amine can be widely applied. For example, the reaction can be performed under the same reaction conditions as employed in Reaction Scheme 4 for producing Compound (1e) from Compound (1b) and Compound (25).

Reaction Scheme II

\[
(8) + (49) \rightarrow (50): \]

wherein \( R^2, R^3, R^7, X^1, R^{61}, m1, \) and \( L2 \) are the same as defined above; and \( W \) represents \( N \) or \( CH \).

\[
(8) + (49) \rightarrow (50): \]
The reaction for producing Compound (50) from Compound (8) and Compound (49) can be performed under the same reaction conditions as employed in Reaction Scheme 1 for producing Compound (1) through Compound (10) obtained from Compound (8) and Compound (9).

(50) + (51) -> (1n);

The reaction for producing Compound (1n) from Compound (50) and Compound (51) can be performed under the same reaction conditions as employed in Reaction Scheme 4 for producing Compound (1a) from Compound (22) and Compound (23).

The compounds of Formula (1) according to the present invention, the intermediate compounds thereof, and the starting material compounds thereof can be produced by the above-described synthesis processes. They can also be produced based on the synthesis processes described in the Reference Examples and Examples of this specification in light of a technique that is well known or known at the time of the filing of this application.

Before subjecting the starting material compounds and intermediate compounds shown in each of the schemes above to each reaction, the functional groups thereof can be protected with suitable protecting groups using a well known method, if necessary, and, after completion of the reaction, deprotection of the protecting groups can be carried out by a well known method.

Each of the target compounds obtained in accordance with the above schemes can be isolated and purified. For example, after cooling the reaction mixture, an isolation procedure, such as filtration, concentration, or extraction, is performed to separate a crude reaction product, and thereafter, the crude reaction product is subjected to a general purifying procedure, such as column chromatography or recrystallization, thereby enabling isolation and purification from the reaction mixture.

The starting material compounds and the target compounds shown in each scheme above include those in the form of a solvate with a solvent (e.g., hydrate and ethanol solvate).
The compounds of Formula (1) according to the present invention (the final compound), the intermediate compounds obtained in each scheme above, and the starting material compounds thereof include geometrical isomers, stereoisomers, and optical isomers.

Various isomers can be isolated by well known separation methods. For example, a racemic compound can be led to a stereochemically pure isomer by a general optical resolution method (e.g., optical resolution by crystallization, or direct optical resolution by chromatography). Further, an optically active compound can also be produced by the use of a suitable optically active starting material.

The starting material compounds and the target compounds shown in each of the schemes above can be used in the form of an appropriate salt.

The compounds of the present invention include pharmaceutically acceptable salts. Among the compounds of the present invention, those containing a basic group or basic groups can form salts with general pharmaceutically acceptable acids.

Examples of such acids include hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, and like inorganic acids, and methanesulfonic acid, p-toluenesulfonic acid, acetic acid, citrate, tartaric acid, maleic acid, fumaric acid, malic acid, lactic acid, and like organic acids.

Among the compounds of the present invention, those containing an acidic group or acidic groups can form salts with pharmaceutically acceptable basic compounds. Examples of such basic compounds include sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, and the like.

In the compounds of the present invention, one or more atoms can be substituted with one or more isotope atoms. Examples of isotope atoms include deuterium (²H), tritium (³H), ¹³C, ¹⁴N, ¹⁶O, and the like.
The following describes pharmaceutical preparations (pharmaceutical compositions) comprising a compound of the present invention as an active ingredient.

Such pharmaceutical preparations are obtained by formulating a compound of the present invention into usual pharmaceutical preparations, using a compound of the present invention and a pharmacologically acceptable carrier. Examples of such carriers include usually employed diluents and excipients, such as fillers, extenders, binders, wetting agents, disintegrants, surfactants, and lubricants.

The form of such pharmaceutical preparations can be selected from various forms, depending on the therapeutic purpose. Typical examples thereof include tablets, pills, powders, solutions, suspensions, emulsions, granules, capsules, suppositories, injections (solutions, suspensions, etc.), and the like.

To form tablets, any of various known carriers can be used, including, for example, lactose, sucrose, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, and like excipients; water, ethanol, propanol, simple syrup, glucose solutions, starch solutions, gelatin solutions, carboxymethylcellulose, shellac, methylcellulose, potassium phosphate, polyvinylpyrrolidone, and like binders; dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogen carbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, stearic acid monoglyceride, starch, lactose, and like disintegrants; sucrose, stearin, cacao butter, hydrogenated oils, and like disintegration inhibitors; quaternary ammonium base, sodium lauryl sulfate, and like absorption promoters; glycerin, starch, and other wetting agents; starch, lactose, kaolin, bentonite, colloidal silica, and like absorbents; purified talc, stearates, boric acid powder, polyethylene glycol, and like lubricants; and the like.

Such tablets may be coated with usual coating materials as required, to prepare, for example, sugar-coated tablets.
gelatin-coated tablets, enteric-coated tablets, film-coated tablets, or double- or multi-layered tablets.

To form pills, any of various known carriers can be used, including, for example, glucose, lactose, starch, cacao butter, hydrogenated vegetable oils, kaolin, talc, and other excipients; gum arabic powder, tragacanth powder, gelatin, ethanol, and other binders; laminaran, agar, and other disintegrants; etc.

To form suppositories, any of various known carriers can be used, including, for example, polyethylene glycol, cacao butter, higher alcohols, esters of higher alcohols, gelatin, semi-synthetic glycerides, etc.

To form an injection, a solution, emulsion, or suspension is sterilized and preferably made isotonic with blood. Any of various known widely used diluents can be employed to prepare the solution, emulsion, or suspension. Examples of such diluents include water, ethanol, propylene glycol, ethoxylated isostearil alcohol, polyoxylated isostearil alcohol, fatty acid esters of polyoxyethylene sorbitan, and the like. In this case, the pharmaceutical preparation may contain sodium chloride, glucose, or glycerin in an amount sufficient to prepare an isotonic solution, and may contain usual solubilizers, buffers, analgesic agents, etc., and may further contain, if necessary, coloring agents, preservatives, flavors, sweetening agents, etc., and/or other medicines.

The proportion of the compound of the present invention in the pharmaceutical preparation is not limited and can be suitably selected from a wide range. It is preferable that the pharmaceutical preparation usually contain the compound of the present invention in a proportion of 1 to 70 wt%.

The route of administration of the pharmaceutical preparation according to the present invention is not limited, and the preparation is administered by a route suitable for the form of the preparation, the patient’s age and sex, conditions of the disease, and other conditions. For example, tablets, pills,
solutions, suspensions, emulsions, granules, and capsules are administered orally. Injections are intravenously administered singly or as mixed with usual injection transfusions, such as glucose solutions or amino acid solutions, or singly administered intramuscularly, intracutaneously, subcutaneously or intraperitoneally, as required. Suppositories are administered intrectally.

The dosage of the pharmaceutical preparation is suitably selected according to the method of use, the patient’s age and sex, severity of the disease, and other conditions, and is usually about 0.01 to 100 mg/kg body weight/day, and preferably 0.1 to 50 mg/kg body weight/day, in single or divided doses.

According to variations of various conditions, there may be cases where a dosage smaller than the above range is sufficient or where a dosage larger than the above range is required.

The compounds of the present invention have specific efficacy against tubercle bacilli, such as acid-fast bacilli (the genera of tubercle bacilli and atypical acid-fast bacilli). The compounds of the present invention have an excellent effect on multidrug-resistant tubercle bacilli. The compounds of the present invention have an antibacterial action against anaerobic bacteria. Accordingly, the compounds of the present invention are useful as a prophylactic and/or therapeutic agent for tuberculosis.

The compounds of the present invention do not cause diarrhea, which can be caused by a known antimicrobial agent that has a broad spectrum against general bacteria, such as gram positive and gram negative bacteria. In addition, the compounds of the present invention have fewer side effects than existing drugs. Therefore, the compounds of the present invention can serve as pharmaceutical preparations that can be administered for a long period of time.
The compounds of the present invention can be satisfactorily distributed throughout the lung tissue, which is a main organ infected with mycobacteriosis. In addition, the compounds of the present invention have properties such as sustained drug efficacy and excellent safety. For this reason, the compounds of the present invention are expected to have high therapeutic effects.

Additionally, compared with existing antituberculosis agents, the compounds of the present invention exhibit stronger bactericidal activity against intracellular parasites, such as parasitic tubercle bacillus in human-derived macrophages. Therefore, the compounds of the present invention enable a reduction in the tuberculosis relapse rate and also enable short-term chemotherapy. Further, the compounds of the present invention are also expected to be used as a principal drug for preventive administration that is performed against a mixed infection with HIV and tuberculosis, which has become an acute problem.

The compounds of the present invention exhibit excellent metabolic stability in plasma, and thus have a feature of providing satisfactorily sustained bactericidal action in vivo.

The compounds of the present invention can be used in combination with other therapeutic agents. Examples of drugs that can be used in combination with the compounds of the present invention include first-line antituberculosis drugs, second-line antituberculosis drugs, quinolone antibacterial drugs, macrolide antibacterial drugs, sulfa drugs, anti-HIV drugs, delamanid, PA-824, which is a drug currently being developed, and the like.

Description of Embodiments

The present invention is described in more detail below with reference to Examples. However, the scope of the invention is not limited thereto.

The compounds whose physical property data are not shown
in the Reference Examples were used in the subsequent reaction without further purification.

Reference Example 1

Preparation of 2-chloro-1-[2-(2-methyloxiranyl)ethyl]-4-nitro-1H-imidazol

Potassium carbonate (1.16 g) and cesium fluoride (196 mg) were added to a DMF solution (20 ml) of 2-chloro-4-nitro-1H-imidazole (953 mg) and 4-nitrobenzene sulfonic acid 2-(2-methyloxiranyl) ethyl ester (1.856 g), and the mixture was stirred at 60°C overnight. Thereafter the reaction mixture was cooled to room temperature. Water was added to the reaction solution, and the reaction mixture was then extracted repeatedly with ethyl acetate. The combined organic layer was washed with water and a saturated sodium chloride aqueous solution, and then dried over sodium sulfate. The sodium sulfate was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane:methanol = 20:1) to afford the title compound as a yellow oil (1.1 g).

Reference Example 2

Preparation of 2-chloro-4-nitro-1-(2-oxiranylethyl)-1H-imidazol

The title compound was prepared in the same manner as in Reference Example 1 using suitable starting materials. Yellow oil

Reference Example 3

Preparation of 2-chloro-1-[2-((R)-2,2-dimethyl[1,3]dioxolan-4-yl)ethyl]-4-nitro-1H-imidazol

A solution of (4R)-2'-(2,2-dimethyl[1,3]-dioxolan-4-yl) ethanol (100 g) in acetonitrile (400 ml) at -20°C was treated with N,N,N',N'-tetramethyl-1,3-propanediamine (172 ml). A solution of p-toluenesulfonyl chloride (156.5 g) in acetonitrile
(350 ml) was added dropwise at 0°C or less and then the reaction mixture was stirred at 0 to 10°C for 1 hour. Water was added to the reaction solution, and the reaction mixture was then extracted with ethyl acetate. The organic layer was washed with water and a saturated sodium chloride aqueous solution, and then dried over sodium sulfate. The sodium sulfate was filtered off and the filtrate was concentrated under reduced pressure. Acetonitrile (1,000 ml) was added to the resulting residue. 2-Chloro-4-nitro-1H-imidazole (100.90 g), potassium carbonate (132.35 g) and sodium iodide (122.3 g) were further added, and then the mixture was heated at reflux overnight. Thereafter the reaction mixture was concentrated under reduced pressure, and water was added to the resulting residue, followed by extraction with ethyl acetate. The organic layer was washed with water and a saturated sodium chloride aqueous solution, dried over sodium sulfate, and then subjected to filtration. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:n-hexane = 2:1-1:2) and washed with isopropyl ether to afford the title compound as a pale yellow powder (101.35 g).

1H NMR (CDCl3) δ: 1.35 (3H, s), 1.43 (3H, s), 1.95-2.00 (1H, m), 2.00-2.05 (1H, m), 3.63-3.68 (1H, m), 4.00-4.15 (2H, m), 4.18-4.30 (2H, m), 7.83 (1H, m).

Reference Example 4
Preparation of 2-chloro-1-{2-{(S)-2,2-dimethyl-[1,3]dioxolan-4-yl}ethyl}-4-nitro-1H-imidazole
The title compound was prepared in the same manner as in Reference Example 3 using suitable starting materials.

Reference Example 5
Preparation of 2-chloro-1-{2-(2,2-dimethyl-[1,3]dioxolan-4-yl)ethyl}-4-nitro-1H-imidazole
The title compound was prepared in the same manner as
in Reference Example 3 using suitable starting materials.

Colorless columnar

Reference Example 6

Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-butane-1,2-diol

While stirring a tetrahydrofuran solution (700 ml) of 2-chloro-1-{2-[(R)-2,2-dimethyl-1,3]dioxolan-4-yl}ethyl)-4-nitro-1H-imidazole (196.2 g) at room temperature, 1.0 M hydrochloric acid ethanol solution (1,100 ml) was added thereto and stirred at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure, hexane was added to the residue obtained and concentrated under reduced pressure. Thereafter, ethyl acetate was added thereto and concentrated under reduced pressure. Isopropyl ether was added to the resulting solid and stirred for a while. The precipitated crystal was collected by filtration to afford the title compound as a colorless solid (166.5 g).

1H NMR (DMSO-d6) δ: 1.63-1.74 (1H, m), 1.91-2.01 (1H, m), 3.22-3.28 (1H, m), 3.30-3.36 (1H, m), 3.40-3.49 (1H, m), 4.08-4.23 (2H, m), 4.62 (1H, t, J = 5.6 Hz), 4.81 (1H, d, J = 5.1 Hz), 5.56 (1H, s).

Reference Example 7

Preparation of (S)-4-(2-chloro-4-nitroimidazol-1-yl)butane-1,2-diol

The title compound was prepared in the same manner as in Reference Example 6 using suitable starting materials. Pale yellow solid

Reference Example 8

Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)butane-1,2-diol

The title compound was prepared in the same manner as in Reference Example 6 using suitable starting materials.
White powder

Reference Example 9

Preparation of toluene-4-sulfonic acid (R)-4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutyl ester

2-Chloro-1-[4-((R)-3,2-dihydroxy)butyl]-4-nitro-1H-imidazole (166.5 g) was dissolved in pyridine (333 ml) and cooled to -30°C. p-toluenesulfonyl chloride (148.19 g) was gradually added thereto at -10°C or less, and the mixture was stirred at -10°C for 2 hours. The reaction mixture was added to a mixture of concentrated hydrochloric acid (430 ml) and water (1,500 ml), followed by extraction with ethyl acetate. The organic layer was washed with water and a saturated sodium chloride aqueous solution, dried over sodium sulfate, and subjected to filtration. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylen chloride:ethyl acetate = 96:4-ethyl acetate) and recrystallized from ethyl acetate-isopropyl ether to afford the title compound as a colorless solid (212.12 g).

1H NMR (CDCl3) δ: 1.83-2.00 (2H, m), 2.47 (3H, s), 2.53-2.73 (1H, m), 3.80-3.90 (1H, m), 3.93-3.98 (1H, m), 4.03-4.08 (1H, m), 4.23-4.28 (2H, m), 7.37 (2H, d, J = 8.0 Hz), 7.73-7.80 (3H, m).

Reference Example 10

Preparation of toluene-4-sulfonic acid (S)-4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutyl ester

The title compound was prepared in the same manner as in Reference Example 9 using suitable starting materials.

White powder

Reference Example 11

Preparation of toluene-4-sulfonic acid 4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-butyl ester

The title compound was prepared in the same manner as in Reference Example 9 using suitable starting materials.

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White solid

Reference Example 12
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-{4-{4-(4-trifluoromethoxyphenoxy)piperidin-1-yl}phenoxy}butan-2-ol
Toluene-4-sulfonic acid 4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-butyl ester (0.78 g) was suspended in ethanol (12 ml), an ethanol solution (0.68 ml) of 10% sodium ethoxide was added thereto, followed by stirring at room temperature for 1 hour. 4-{4-{4-Trifluoromethoxyphenoxy)piperidin-1-yl}phenol (0.707 g) and tripotassium phosphate (0.509 g) were added thereto and stirred at 80°C for 2 hours. The mixture was cooled to room temperature and filtered through Celite to remove insoluble matter and, then the residue was washed with ethyl acetate. The filtrate and liquid were combined and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:1-9:1) to afford the title compound as a pale yellow powder (0.314 g).

Reference Example 13
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-{4-{4-(N-(2-chlorophenyl)-N-methylamino)piperidin-1-yl}phenoxy}butan-2-ol
2-Chloro-4-nitro-1-(2-oxiranylethyl)-1H-imidazole (816 mg) was suspended in ethanol (20 ml) and 4-{4-[N-(4-chlorophenyl)-N-methylamino)piperidin-1-yl}phenol (982 mg) and tripotassium phosphate (200 mg) were added thereto, followed by stirring at 70°C overnight. Thereafter the reaction solution was cooled to room temperature, and filtered through Celite to remove insoluble matter and, then the residue was washed with ethyl acetate. The filtrate and liquid were combined and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 10:1) and recrystallized from methylene chloride-ethyl acetate to afford the title compound as a yellow solid (486 mg).
Reference Example 14

Preparation of 4-{4-[4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutoxy]phenyl}piparazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 13 using suitable starting materials. Yellow amorphous

Reference Example 15

Preparation of 4-{2-chloro-4-nitroimidazol-1-yl}-1-{4-[4-(4-trifluoromethylbenzyl)oxy)methyl]piperidin-1-yl}phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 13 using suitable starting materials. Brown oil

Reference Example 16

Preparation of 4-{2-chloro-4-nitroimidazol-1-yl}-1-{4-[4-(4-trifluoromethylphenoxy)methyl]piperidin-1-yl}phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 13 using suitable starting materials. Brown solid

Reference Example 17

Preparation of 4-{2-chloro-4-nitroimidazol-1-yl}-1-{4-[4-(4-trifluoromethoxybenzyl)oxy)piperidin-1-yl}phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. White powder

Reference Example 18

Preparation of 4-{2-chloro-4-nitroimidazol-1-yl}-1-{4-[4-(4-trifluoromethoxybenzyl)piperidin-1-yl]phenoxy)butan-2-ol
The title compound was prepared in the same manner as 
in Reference Example 12 using suitable starting materials.
White powder

5 Reference Example 19

Preparation of 4-{2-chloro-4-nitroimidazol-1-yl}-1-{4-
{4-[N-methyl-N-(4-trifluoromethoxyphenyl)amino]piperidin-1-yl}
phenoxy}butan-2-ol

The title compound was prepared in the same manner as
in Reference Example 12 using suitable starting materials.
White powder

Reference Example 20

Preparation of 4-{2-chloro-4-nitroimidazol-1-yl}-1-{4-
{4-[2-(4-trifluoromethoxyphenyl)ethyl]piperidin-1-yl}
phenoxy}butan-2-ol

The title compound was prepared in the same manner as
in Reference Example 12 using suitable starting materials.
White powder

20 Reference Example 21

Preparation of (S)-4-{2-chloro-4-nitroimidazol-1-yl}-1-
{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxy}butan-2-
ol

The title compound was prepared in the same manner as
in Reference Example 12 using suitable starting materials.
White powder

Reference Example 22

Preparation of 4-{2-chloro-4-nitroimidazol-1-yl}-1-{4-
[4-(4-trifluoromethoxybenzylloxymethyl)piperidin-1-yl]
phenoxy}butan-2-ol

The title compound was prepared in the same manner as
in Reference Example 12 using suitable starting materials.
Pale brown powder
Reference Example 23
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-[(4-trifluoromethoxyphenoxy)methyl]piperidin-1-yl)phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
White powder

Reference Example 24
Preparation of 1-(4-[4-(4-chlorobenzylloxymethyl)piperidin-1-yl]phenoxy)-4-(2-chloro-4-nitroimidazol-1-yl)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
White powder

Reference Example 25
Preparation of 1-(4-[4-(4-chlorobenzyl)oxy]piperidin-1-yl)phenoxy)-4-(2-chloro-4-nitroimidazol-1-yl)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
White powder

Reference Example 26
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale yellow amorphous

Reference Example 27
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-[4-(4-trifluoromethyl)phenoxy)piperidin-1-yl]phenoxy)butan-2-ol
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Reference Example 28
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-
[4-(4-chlorophenoxy)piperidin-1-yl]phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Reference Example 29
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-
[4-(4-trifluoromethoxyphenyl)piperidin-1-yl]phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Reference Example 30
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-
[4-{N-methyl-N-(4-trifluoromethylphenyl)amino}piperidin-1-yl]
phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Reference Example 31
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-
[4-(3-trifluoromethylphenoxy)piperidin-1-yl]phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Reference Example 32
Preparation of 1-[4-[4-(3,5-bis-
-71-

trifluoromethylphenoxy)piperidin-1-yl]phenoxy)-4-{2-chloro-4-
nitroimidazol-1-yl}butan-2-ol

The title compound was prepared in the same manner as
in Reference Example 12 using suitable starting materials.

White powder

Reference Example 33

Preparation of 4-{2-chloro-4-nitroimidazol-1-yl}-1-[4-
[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]phenoxy]butan-2-ol

The title compound was prepared in the same manner as
in Reference Example 12 using suitable starting materials.

Pale yellow powder

Reference Example 34

Preparation of 4-{2-chloro-4-nitroimidazol-1-yl}-1-[4-
[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]phenoxy]butan-2-ol

The title compound was prepared in the same manner as
in Reference Example 12 using suitable starting materials.

White powder

Reference Example 35

Preparation of 4-{4-[4-{2-chloro-4-nitroimidazol-1-yl}]-
2-hydroxybutoxy]phenyl)piperidine-1-carboxylic acid tert-butyl
ester

The title compound was prepared in the same manner as
in Reference Example 12 using suitable starting materials.

White powder

Reference Example 36

Preparation of 4-{2-chloro-4-nitroimidazol-1-yl}-1-[4-
[4-{4-trifluoromethylbenzyl}piperidin-1-yl]phenoxy]butan-2-ol

The title compound was prepared in the same manner as
in Reference Example 12 using suitable starting materials.

White powder
Reference Example 37
Preparation of 1-{4-[4-(4-chlorobenzyl)piperidin-1-yl]phenoxyl}-4-(2-chloro-4-nitroimidazol-1-yl)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Pale yellow powder

Reference Example 38
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-{4-[4-N-(4-chlorophenyl)-N-ethylamino]piperidin-1-yl}phenoxyl)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Brown oil

MS (m/z): 547[M+H]⁺

Reference Example 39
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-{4-[4-ethyl-N-(4-trifluoromethylphenyl)amino]piperidin-2-yl}phenoxyl)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Brown oil

MS (m/z): 582[M+H]⁺

Reference Example 40
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-{4-[4-ethyl-N-(4-trifluoromethoxyphenyl)amino]piperidin-1-yl}phenoxyl)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Brown oil

MS (m/z): 598[M+H]⁺

Reference Example 41
Preparation of 4-\{(4-\{(2-chloro-4-nitroimidazol-1-yl\}-2-hydroxybutoxy)phenyl\}\}-\{(1,4)diazipane-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Brown amorphous

MS (m/z): 510[M+H]^+

Reference Example 42

Preparation of 4-\{(2-chloro-4-nitroimidazol-1-yl\}-1-\{(4-\{(4-trifluoromethoxyphenyl\}-oxazol-2-ylmethyl\}phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Powder

Reference Example 43

Preparation of 4-\{(2-chloro-4-nitroimidazol-1-yl\}-1-\{(4-\{(2-\{(4-trifluoromethoxyphenyl\}-oxazol-4-yl\}phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

White powder

Reference Example 44

Preparation of 4-\{(2-chloro-4-nitroimidazol-1-yl\}-1-\{(4-\{(2-\{(4-trifluoromethoxyphenoxymethyl\}-oxazol-4-yl\}phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Powder

Reference Example 45

Preparation of 4-\{(2-chloro-4-nitroimidazol-1-yl\}-1-\{(4-\{(2-\{(4-trifluoromethoxyphenoxymethyl\}thiazol-4-yl\}phenoxy)butan-2-ol
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

White powder

Reference Example 46
Preparation of 4-\{(2-chloro-4-nitroimidazol-1-yl)-1-\{(4-\{2-(4-trifluoromethoxyphenyl)thiazol-4-yl\}\)phenoxyl\}\}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Yellow powder

Reference Example 47
Preparation of 4-\{(2-chloro-4-nitroimidazol-1-yl)-1-\{(4-\{4-\{2-(4-trifluoromethoxyphenoxyl\}ethyl\}piperidin-1-yl\}\)phenoxyl\}\}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

White powder

Reference Example 48
Preparation of 4-\{(2-chloro-4-nitroimidazol-1-yl)-1-\{(4-\{3-(4-trifluoromethoxyphenoxyl)propyl\}piperidin-1-yl\}\)phenoxyl\}\}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

White powder

Reference Example 49
Preparation of 4-\{(2-chloro-4-nitroimidazol-1-yl)-1-\{(4-\{3-(4-trifluoromethoxyphenoxyl)propyl\}piperidin-1-yl\}\)phenoxyl\}\}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

White powder
Reference Example 50

Preparation of 1-(4-[4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutoxy]phenyl)-4-trifluoromethylpiperidin-4-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

White powder

Reference Example 51

Preparation of 4-(5-[4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutoxy]pyridin-2-yl)piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Pale red powder

MS (m/z): 496[M]+

Reference Example 52

Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-[2-(4-trifluoromethoxybenzyl)thiazol-4-yl]phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Pale yellow powder

Reference Example 53

Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-[4-[4-(2-(5-trifluoromethylpyridin-2-yloxy)ethyl]piperidin-1-yl]phenoxy]butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

White powder

Reference Example 54

Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-[4-[4-(5-trifluoromethylpyridin-2-yloxy)methyl)piperidin-1-yl]phenoxy]butan-2-ol
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The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

White powder

5 Reference Example 55
Preparation of 4-{2-chloro-4-nitroimidazol-1-yl}-1-{4-(4-methoxy-4-trifluoromethylpiperidin-1-yl)phenoxy}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

10 White powder

Reference Example 56
Preparation of 4-{2-chloro-4-nitroimidazol-1-yl}-1-{4-[4-(5-trifluoromethylpyridin-2-yl)oxy]piperidin-1-yl}

15 phenoxy}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Pale yellow powder

20 Reference Example 57
Preparation of 4-{2-chloro-4-nitroimidazol-1-yl}-1-{6-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]pyridin-3-yloxy}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Orange amorphous

Reference Example 58
Preparation of 4-{2-chloro-4-nitroimidazol-1-yl}-1-{6-[4-(4-trifluoromethoxybenzyl)piperidin-1-yl]pyridin-3-yloxy}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Brown amorphous

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Reference Example 59
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-(6-
[4-(4-trifluoromethoxyphenoxy)methyl]piperidin-1-yl)pyridin-3-
yloxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale yellow powder

Reference Example 60
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-(6-
[4-[2-(4-trifluoromethoxyphenoxy)ethyl]piperidin-1-yl)pyridin-3-
yloxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale brown powder

Reference Example 61
Preparation of (S)-4-(2-chloro-4-nitroimidazol-1-yl)-1-
(4-[4-[2-(4-trifluoromethoxyphenyl)ethyl]piperidin-1-yl]
phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale yellow powder

Reference Example 62
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-[4-
(4-propoxy-4-trifluoromethyl)piperidin-1-yl)phenoxy]butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
White powder

Reference Example 63
Preparation of 4-[(S)-4-(2-chloro-4-nitroimidazol-1-
yl)-2-hydroxybutoxy]phenyl)piperazine-1-carboxylic acid tert-
butyl ester
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Brown oil

MS (m/z): 495[M+]²

Reference Example 64

Preparation of \((S)-4-(2\text{-chloro-4-nitroimidazol-1-y1})-1-(4-(4-[N\text{-methyl-N-}[4\text{-trifluoromethoxyphenyl]amino}]piperidin-1-y1)phenoxy)\)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Dark red amorphous

Reference Example 65

Preparation of \((R)-4-(2\text{-chloro-4-nitroimidazol-1-y1})-1-(4-(4\text{-[2-(4\text{-trifluoromethoxyphenyl}ethyl]piperidin-1-y1)phenoxy})\)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Pale yellow powder

Reference Example 66

Preparation of \(4-(2\text{-chloro-4-nitroimidazol-1-y1})-1-(4-(4-[3\text{-chloro-5-trifluoromethylpyridin-2-yl}oxy]piperidin-1-y1)phenoxy)\)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Yellow amorphous

Reference Example 68

Preparation of \((R)-4-(2\text{-chloro-4-nitroimidazol-1-y1})-1-(4-(4-[N\text{-methyl-N-}[4\text{-trifluoromethoxyphenyl]amino}]piperidin-1-y1)phenoxy)\)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Red amorphous

Reference Example 69
Preparation of 4-{(2-chloro-4-nitroimidazol-1-yl)-1-{6-[4-(4-chlorophenoxo)piperidin-1-yl]pyridin-3-yloxy}butan-2-ol}
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Brown amorphous

Reference Example 70
Preparation of 4-{(2-chloro-4-nitroimidazol-1-yl)-1-{6-[4-(4-trifluoromethoxybenzyloloxo)piperidin-1-yl]pyridin-3-yloxy}butan-2-ol}
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale yellow powder

Reference Example 71
Preparation of 4-{(2-chloro-4-nitroimidazol-1-yl)-1-{6-[4-(4-trifluoromethylphenoxo)piperidin-1-yl]pyridin-3-yloxy}butan-2-ol}
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Yellow amorphous

Reference Example 73
Preparation of 4-{(2-chloro-4-nitroimidazol-1-yl)-1-{4-[1-(4-trifluoromethoxyphenyl)piperidin-4-ylmethyl]phenoxo}butan-2-ol}
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale yellow amorphous

Reference Example 74
Preparation of 4-{(2-chloro-4-nitroimidazol-1-yl)-1-{4-
[1-(4-trifluoromethylphenyl)piperidin-4-ylmethyl]phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Yellow amorphous

Reference Example 75
Preparation of 4-(4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutoxy)benzyl)piperidine-1-carboxylic acid tert-buty1 ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale yellow oil

Reference Example 76
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-{6-[4-[3-(4-trifluoromethoxyphenyl)propyl]piperidin-1-yl]pyridin-3-yloxy]butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Yellow oil

Reference Example 77
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-[6-(4-trifluoromethoxybenzyloxy)methyl]pyridin-3-yloxy]butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale yellow solid

Reference Example 78
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-{4-[2-(4-trifluoromethylphenoxy)ethyl]piperidin-1-yl}phenoxy]butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
White powder

Reference Example 79
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-
{4-[2-(4-chlorophenoxy)ethyl]piperidin-1-yl}phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
White powder

Reference Example 80
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-
{4-[2-(4-trifluoromethylphenyl)ethyl]piperidin-1-yl}
phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale yellow powder

Reference Example 81
Preparation of 4-(2-{4-[4-(2-chloro-4-nitroimidazol-1-
yl)-2-hydroxybutoxy]phenyl}-ethyl)piperidine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
White powder

Reference Example 82
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-{2-
chloro-4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-
yl]phenoxy}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale yellow amorphous

Reference Example 83
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-
(4-[2-((4-chlorophenyl)ethyl)piperidin-1-yl]phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale yellow powder

Reference Example 84

Preparation of 4-((2-chloro-4-nitroimidazol-1-yl)-1-(4-
{4-[3-((4-trifluoromethylphenyl)propyl)piperidin-1-
yl]phenoxy}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale yellow powder

Reference Example 85

Preparation of 4-((2-chloro-4-nitroimidazol-1-yl)-1-(4-
{4-[3-((4-trifluoromethylphenoxy)propyl)piperidin-1-yl]
phenoxy}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale yellow powder

Reference Example 86

Preparation of 1-(4-{4-(4-(5-chlorobenzofuran-2-
ylmethyl)piperidin-1-yl]phenoxy)-4-((2-chloro-4-nitroimidazol-1-
yl)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
White powder

Reference Example 87

Preparation of 1-(4-{4-(4-(5-chlorobenzofuran-2-
yl)methoxy)piperidin-1-yl]phenoxy)-4-((2-chloro-4-nitroimidazol-1-
yl)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
White powder

Reference Example 88
Preparation of 4-{4-[4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-methylbutoxy]phenyl}piperazine-1-carboxylic acid tert-butyl ester

4-{4-[2-Hydroxy-2-methyl-4-(toluene-4-sulfonyloxy)butoxy]phenyl}piperazine-1-carboxylic acid tert-butyl ester (4.69 g, 8.77 mmol), 2-chloro-4-nitro-1H-imidazole (1.55 g, 10.52 mmol), sodium hydrogen carbonate (0.88 g) and dimethylformamide (47 mL) were mixed, and the mixture was stirred at 90 to 100°C overnight. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated sodium chloride aqueous solution, and dried over magnesium sulfate. After filtering under reduced pressure, the filtrate was concentrated, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 1:0-3:7) to afford the title compound as a yellow amorphous solid (2.12 g).

MS (m/z): 509[M]⁺

Reference Example 89
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-{4-{4-[3-(4-chlorophenoxy)propyl]piperidin-1-yl}phenoxy}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

White powder

Reference Example 90
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-{4-[4-{5-trifluoromethylbenzofuran-2-ylmethyl]piperidin-1-yl}phenoxy}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

White powder
Reference Example 91
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-[(4-{3-(4-chlorophenyl)propy1}piperidin-1-yl)phenoxy]butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
White powder

Reference Example 92
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-[(4-{5-trifluoromethoxybenzofuran-2-ylmethyl}piperidin-1-yl)phenoxy]butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
White powder

Reference Example 93
Preparation of 1-{[4-[(4-{5-chlorobenzofuran-2-ylmethoxymethyl}piperidin-1-yl)phenoxy]-4-(2-chloro-4-nitroimidazol-1-yl)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Powder

Reference Example 94
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-1-{1-[3-{4-trifluoromethoxyphenoxy}propy1]-1,2,3,4-tetrahydroquinolin-6-yl oxy]butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Orange amorphous

Reference Example 95
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-{1-[3-{4-trifluoromethoxyphenoxy}propy1]-1,2,3,4-tetrahydro-
quinolin-6-yloxy)butan-2-ol.

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Red amorphous.

Reference Example 96
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(1-[3-(4-trifluoromethoxyphenoxo)propyl]-IH-indole-5-yloxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Red amorphous.

Reference Example 97
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(1-[3-(4-trifluoromethoxyphenoxo)propyl]-1,2,3,4-tetrahydroquinolin-5-yloxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Yellow amorphous.

Reference Example 98
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(1-[3-(4-trifluoromethoxyphenoxo)propyl]-2,3,4,5-tetrahydro-1H-benzo(b)azepin-7-yloxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Red amorphous.

Reference Example 99
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(1-[4-(4-trifluoromethoxyphenoxo)benzyl]-1,2,3,4-tetrahydroquinolin-6-yloxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Red amorphous

Reference Example 100
Preparation of \((R)-4-(2\text{-chloro}-4\text{-nitroimidazol-1-yl})-1-\{1-[4-(4\text{-trifluoromethoxyphenoxo})benzy1]-2,3,4,5\text{-tetrahydro-1H-benzo[blazepin-7-yloxy]butan-2-ol}\}

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Yellow amorphous

Reference Example 101
Preparation of \((R)-4-(2\text{-chloro}-4\text{-nitroimidazol-1-yl})-1-\{2-[4-(4\text{-trifluoromethoxyphenoxo})piperidin-1-yl]-quinolin-6-yloxy\}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Brown amorphous

Reference Example 102
Preparation of \(4-\{6-[\{(R)-4-(2\text{-chloro}-4\text{-nitroimidazol-1-yl})-2\text{-hydroxybutoxy}\text{-quinolin-2-yl}\text{piperazine-1-carboxylic acid tert-butyl ester}\}

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Yellow amorphous

Reference Example 103
Preparation of \((R)-4-(2\text{-chloro}-4\text{-nitroimidazol-1-yl})-1-\{2-[4-(4\text{-trifluoromethoxyphenoxo})piperidin-1-yl]benzothiazol-6-yloxy\}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Yellow amorphous

Reference Example 104
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(2-|4-(4-trifluoromethoxybenzyl)piperazin-1-yl|benzothiazol-6-yloxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Yellow amorphous

Reference Example 105

Preparation of 4-|6-(|R)-4-(2-chloro-4-nitroimidazol-1-yl)|2-hydroxybutoxy|benzothiazol-2-yl|piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

White powder

Reference Example 106

Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-|4-(4,4-dimethoxypiperidin-1-yl)phenoxy|butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Orange amorphous

Reference Example 107

Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-|6-(|2-(4-trifluoromethoxyphenyl)ethyl)piperidin-1-yl|naphthalen-2-yloxy|butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Pale yellow solid

Reference Example 108

Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-|4-(4|2-(4-trifluoromethoxyphenoxy)ethyl)piperidin-1-yl|phenoxy|butan-2-ol

The title compound was prepared in the same manner as
in Reference Example 12 using suitable starting materials.
Pale yellow powder

Reference Example 109
Preparation of (R)-4-\((2\text{-chloro-4-nitroimidazol-1-yl})\)-1-(\(4\text{-}[4\text{-}[3\text{-}(4\text{-trifluoromethoxyphenyl)propyl]piperidin-1-yl}\) phenoxy)butan-2-ol
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale yellow powder

Reference Example 110
Preparation of (R)-4-\((2\text{-chloro-4-nitroimidazol-1-yl})\)-1-(\(4\text{-}[2\text{-}[3,4\text{-dichlorophenoxy]}\ethyl]piperidin-1-yl\) phenoxy)butan-2-ol
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Yellow amorphous

Reference Example 111
Preparation of (R)-4-\((2\text{-chloro-4-nitroimidazol-1-yl})\)-1-(\(4\text{-}[2\text{-}[3\text{-chloro-5\text{-trifluoromethylpyridin-2-yloxy}]\ethyl]piperidin-1-yl\)phenoxy)butan-2-ol
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Yellow amorphous

Reference Example 112
Preparation of (R)-4-\((2\text{-chloro-4-nitroimidazol-1-yl})\)-1-(\(4\text{-}[2\text{-}[3,5\text{-dichloropyridin-2-yloxy}]\ethyl]piperidin-1-yl\) phenoxy)butan-2-ol
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Brown amorphous
Reference Example 113

Preparation of (R)-4-{2-chloro-4-nitroimidazol-1-yl}-1-(4-{4-[2-{4-chloro-3-trifluoromethylphenoxy}ethyl]piperidin-1-yl}phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Brown amorphous

Reference Example 114

Preparation of (R)-4-{2-chloro-4-nitroimidazol-1-yl}-1-(4-{4-[2-(tetrahydrofuran-2-yloxy)-2-(4-trifluoromethoxyphenyl)ethyl]piperidin-1-yl}phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Yellow amorphous

Reference Example 115

Preparation of (R)-4-{2-chloro-4-nitroimidazol-1-yl}-1-(4-{4-[2-(2,4-dichlorophenoxy)ethyl]piperidin-1-yl}phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Reference Example 116

Preparation of (R)-4-{2-chloro-4-nitroimidazol-1-yl}-1-(4-{4-[4-(4-trifluoromethoxybenzyl)oxy]phenyl)piperazin-1-yl}phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Yellow solid

Reference Example 117

Preparation of (R)-1-{4-[4-[2-{4-chloro-3-methylphenoxy}ethyl]piperidin-1-yl]phenoxy}-4-{2-chloro-4-nitroimidazol-1-yl}butan-2-ol
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Yellow amorphous

Reference Example 118
Preparation of (R)-4-{2-chloro-4-nitroimidazol-1-yl}-1-(4-{4-[2-(3-trifluoromethylphenoxy)ethyl]piperidin-1-yl}phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Pale yellow powder

Reference Example 119
Preparation of (R)-1-(4-{4-[2-(3-chloro-4-fluorophenoxy)ethyl]piperidin-1-yl}phenoxy)-4-(2-chloro-4-nitroimidazol-1-yl)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Yellow amorphous

Reference Example 120
Preparation of {4-{4-{(R)-4-{2-chloro-4-nitroimidazol-1-yl}-2-hydroxybutoxy}phenyl}piperazin-1-yl}-carbamic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Yellow amorphous

Reference Example 121
Preparation of (R)-4-{2-chloro-4-nitroimidazol-1-yl}-1-(4-{4-{4-(4-trifluoromethoxyphenoxy)phenyl}piperazin-1-yl}phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Pale brown solid
Reference Example 122

Preparation of (R)-4-((2-chloro-4-nitroimidazol-1-yl)-1-((2-[(4-((4-trifluoromethoxyphenoxy)piperidin-1-yl)benzooxazol-5-yloxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Pale yellow powder

Reference Example 123

Preparation of (R)-4-((2-chloro-4-nitroimidazol-1-yl)-1-((4-[(4-((3-((4-trifluoromethoxyphenoxy)propyl)piperidin-1-yl)phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. White powder

Reference Example 124

Preparation of (R)-4-((2-chloro-4-nitroimidazol-1-yl)-1-((4-[(2-((5-trifluoromethylpyridin-2-yloxy)ethyl)piperidin-1-yl)phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Pale yellow powder

Reference Example 125

Preparation of 4-{[(R)-4-((2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutoxy)phenoxy]piperidine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Pale yellow amorphous

Reference Example 126

Preparation of (R)-4-((2-chloro-4-nitroimidazol-1-yl)-1-
(4-{4-[4-(4-trifluoromethoxyphenoxy)butyl]piperidin-1-yl}phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Pale yellow powder

Reference Example 127
Preparation of 4-{4-[(R)-4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutoxy]phenyl)piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 88 using suitable starting materials. Orange amorphous

Reference Example 128
Preparation of (R)-4-{2-chloro-4-nitroimidazol-1-yl)-1-[4-{3-trifluoromethyl-5,6-dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]phenoxy]butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Yellow solid

Reference Example 129
Preparation of (S)-4-{2-chloro-4-nitroimidazol-1-yl)-1-{4-{4-[4-(4-trifluoromethoxybenzyl)oxy]phenoxy)piperidin-1-yl}phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Orange amorphous

Reference Example 130
Preparation of (R)-4-{2-chloro-4-nitroimidazol-1-yl)-1-{4-{4-[4-(4-trifluoromethoxybenzyl)oxy]phenoxy)piperidin-1-yl}phenoxy)butan-2-ol

The title compound was prepared in the same manner as
in Reference Example 12 using suitable starting materials. Brown amorphous

Reference Example 131

Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Pale yellow amorphous

Reference Example 132

Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-{4-[4-(4-trifluoromethoxyphenoxy)methyl]phenyl)piperazin-1-yl)phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Brown amorphous

Reference Example 133

Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-{4-[N-methyl-N-(4-trifluoromethylbenzyl)amino]phenyl)piperazin-1-yl)phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Pale brown solid

Reference Example 134

Preparation of (S)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-{4-(4-trifluoromethylbenzyl)oxy}phenoxy)piperidin-1-yl)phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Yellow powder
Reference Example 135
Preparation of 4-([S]-4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutoxy)phenoxy)piperidine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Yellow solid

Reference Example 136
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-[4-(4-(4-(trifluoromethyl)benzoyloxy)phenoxy)piperidin-1-yl]phenoxy]butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Red powder

Reference Example 137
Preparation of 4-([S]-4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutoxy)benzoxazol-2-yl)piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Pale yellow powder

Reference Example 138
Preparation of 4-([R]-4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutoxy)benzoxazol-2-yl)piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. White powder

Reference Example 139
Preparation of (S)-4-(2-chloro-4-nitroimidazol-1-yl)-1-
[4-(4,4-dimethoxypiperidin-1-yl)phenoxy]butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale yellow powder

Reference Example 140
Preparation of 5-([(S)-4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutoxy]-1,3-dihydroiscindole-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale brown amorphous

Reference Example 141
Preparation of 5-([(R)-4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutoxy]-1,3-dihydroiscindole-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale yellow amorphous

Reference Example 142
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-{4-[4-(4-trifluoromethoxybenzyloxy)phenoxy)methyl]piperidin-1-yl}phenoxy]butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Yellow powder

Reference Example 143
Preparation of (S)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-{4-[4-(4-trifluoromethoxybenzyloxy)phenoxy)methyl]piperidin-1-yl}phenoxy]butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Yellow powder

Reference Example 144
Preparation of (S)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(2-{4-[4-(4-trifluoromethoxybenzyl)oxy]benzyl}piperidin-1-yl)benzothiazol-6-yl)oxy)butan-2-ol
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Yellow amorphous

Reference Example 145
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(4'-diethoxymethylbiphenyl-4-yloxy)butan-2-ol
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Brown oil

Reference Example 146
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(2-{4-[4-(4-trifluoromethoxybenzyl)oxy]benzyl}piperidin-1-yl)benzothiazol-6-yl)oxy)butan-2-ol
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Yellow amorphous

Reference Example 147
Preparation of 7-((S)-4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Reference Example 148
Preparation of 7-((R)-4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic
acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Pale yellow amorphous

Reference Example 149

Preparation of 6-[(S)-4-(2-chloro-4-nitromidazol-1-yl)-2-hydroxybutoxy]-3,4-dihydro-1H- isoquinoline-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Yellow amorphous

Reference Example 150

Preparation of 6-[(R)-4-(2-chloro-4-nitromidazol-1-yl)-2-hydroxybutoxy]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Yellow amorphous

Reference Example 151

Preparation of 7-[(S)-4-(2-chloro-4-nitromidazol-1-yl)-2-hydroxybutoxy]-1,3,4,5-tetrahydrobenzo[c]azepine-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

White amorphous

Reference Example 152

Preparation of 7-[(R)-4-(2-chloro-4-nitromidazol-1-yl)-2-hydroxybutoxy]-1,3,4,5-tetrahydrobenzo[c]azepine-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
White amorphous

Reference Example 153
Preparation of (2R,5S)-4-[(S)-4-{2-chloro-4-nitroimidazo1-1-yl}-2-hydroxybutoxy]phenyl)-2,5-dimethylpiperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Reference Example 154
Preparation of (2R,5S)-4-[(R)-4-{2-chloro-4-nitroimidazo1-1-yl}-2-hydroxybutoxy]phenyl)-2,5-dimethylpiperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Reference Example 155
Preparation of 4-{5-[(R)-4-{2-chloro-4-nitroimidazo1-1-yl}-2-hydroxybutoxy]pyridin-2-yl}piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale brown amorphous

Reference Example 156
Preparation of 4-{5-[(S)-4-{2-chloro-4-nitroimidazo1-1-yl}-2-hydroxybutoxy]pyridin-2-yl}piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale brown amorphous

Reference Example 157
Preparation of 5-{4-[(S)-4-{2-chloro-4-nitroimidazo1-1-yl}-2-hydroxybutoxy]phenyl}-2,5-dimethylpiperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Pale brown amorphous
yl)-2-hydroxybutoxy|phenyl)-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Orange amorphous

Reference Example 158

Preparation of 4-\{(R)-4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutoxy|biphenyl-4-yl\}piperazone-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Pale yellow solid

Reference Example 159

Preparation of 4-\{(S)-4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutoxy|biphenyl-4-yl\}piperazone-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Pale yellow solid

Reference Example 160

Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-[4-\{(N-methyl-N-[4-(4-trifluoromethoxybenzyloxy)phenyl]-amino)-methyl\}piperidin-1-yl]phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Brown amorphous

Reference Example 161

Preparation of (S)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-[4-\{(N-methyl-N-[4-(4-trifluoromethoxybenzyloxy)phenyl]-amino)-methyl\}piperidin-1-yl]phenoxy)butan-2-ol

The title compound was prepared in the same manner as
-100-

in Reference Example 12 using suitable starting materials.
Brown amorphous

Reference Example 162

Preparation of 5-{4-[(R)-4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutoxy]phenyl}-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Brown amorphous

Reference Example 163

Preparation of 4-{4-[(R)-4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutoxy]phenyl}piperidine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Yellow amorphous

Reference Example 164

Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-[4-(4-trifluoromethylphenoxy)methyl]piperidin-1-yl)phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Brown solid

Reference Example 165

Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-[4-(4-trifluoromethoxybenzyl)methyl]piperidin-1-yl)phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Brown oil

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Reference Example 166
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-1-\{(4-\{4-(4-trifluoromethoxyphenyl)ethyl\}piperidin-1-yl\}phenoxy\}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 88 using suitable starting materials.

Brown amorphous

MS (m/z): 596[M]+

Reference Example 167
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-{4-\{4-(4-trifluoromethoxybenzyl)piperidin-1-yl\}phenoxy\}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Reddish brown amorphous

Reference Example 168
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-{4-\{4-(4-trifluoromethylbenzyl)piperidin-1-yl\}phenoxy\}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Yellow-red amorphous

Reference Example 169
Preparation of (R)-1-{4-\{4-(4-chlorobenzyl)piperidin-1-yl\}phenoxy\}-4-(2-chloro-4-nitroimidazol-1-yl)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Yellow-red amorphous

Reference Example 170
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-{4-\{4-(4-trifluoromethoxyphenyl)piperidin-1-yl\}phenoxy\}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Orange amorphous

Reference Example 171
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-
5 (4-{4-(4-trifluoromethylphenyl)piperidin-1-yl}phenoxy)butan-2-ol
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Orange amorphous

Reference Example 172
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-
10 (4-[1-(4-trifluoromethoxyphenyl)piperidin-4-yloxy]phenoxy)butan-
2-ol
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Yellow amorphous

Reference Example 173
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-
20 (4-[1-(4-trifluoromethylphenyl)piperidin-4-yloxy]phenoxy)butan-2-
ol
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.
Yellow-red amorphous

Reference Example 174
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-2-
methyl-1-{4-[4-(4-trifluoromethoxybenzyl)piperidin-1-yl]
phenoxy)butan-2-ol
The title compound was prepared in the same manner as in Reference Example 68 using suitable starting materials.
Yellow oil
MS (m/z): 582(M)'

Reference Example 175
Preparation of 4-(2-chloro-4-nitroimidazol-1-yl)-2-methyl-1-\(\{4-(4-[3-(4-trifluoromethoxyphenyl)propyl]piperidin-1-yl\}phenoxy\}butan-2-ol

The title compound was prepared in the same manner as in Reference Example 88 using suitable starting materials. Yellow oil.

Reference Example 176

Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-[4-[3-(4-trifluoromethylphenyl)propyl]piperidin-1-yl]phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Pale brown oil.

Reference Example 177

Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-[4-[5-trifluoromethylpyridin-2-yloxymethyl]piperidin-1-yl]phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Pale yellow powder.

Reference Example 178

Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-[N-ethyl-N-[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]amino]phenoxy)butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials. Pale yellow powder.

Reference Example 179

Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-(4-[N-methyl-N-[1-(4-trifluoromethoxyphenyl)piperidin-4-yl]amino]phenoxy)butan-2-ol
The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Orange powder

Reference Example 180
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-
[4-{4-(4-trifluoromethylbenzyloxy)methyl]piperidin-1-yl}
phenoxy]butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Red amorphous

Reference Example 181
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-
[4-{4-(2,2,2-trifluoro-ethyl)piperazin-1-yl]phenoxy]butan-2-ol

The title compound was prepared in the same manner as in Reference Example 12 using suitable starting materials.

Brown oil

MS (m/z): 477[M]+

Reference Example 182
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-
[4-{4-(2-[N-methyl-N-(4-trifluoromethoxyphenyl)amino]-
ethyl]piperidin-1-yl]phenoxy]butan-2-ol

Toluene-4-sulfonic acid (R)-4-(2-chloro-4-
nitroimidazol-1-yl)-2-hydroxybutyl ester (988 mg) and 4-{4-(2-[N-
methyl-N-(4-trifluoromethoxyphenyl)amino]ethyl]piperidin-1-
yl]phenol (1.0 g) were suspended in ethanol (30 ml). Tripotassium phosphate (1.05 g) and sodium iodide (418 mg) were added to the suspension, and the mixture was stirred at 80°C under a nitrogen atmosphere for 4.5 hours. After being cooled to room temperature, ethyl acetate (20 ml) was added to the reaction mixture, insoluble matter was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl
acetate=3:l-methylene chloride:methanol = 97:3) to afford the title compound as a reddish brown oil (1.17 g).

Reference Example 183
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-[4-(4-[(N-methyl-N-(4-trifluoromethoxybenzyl)amino)methyl]piperidin-1-yl)phenoxy]butan-2-ol

The title compound was prepared in the same manner as in Reference Example 182 using suitable starting materials.
Orange amorphous

Reference Example 184
Preparation of (R)-4-(2-chloro-4-nitroimidazol-1-yl)-1-[4-{4-(4-trifluoromethylsulfanylbenzyl)piperidin-1-yl}phenoxy]butan-2-ol

Sodium tert-butoxide (0.412 g) was added to an ethanol solution (20 ml) of toluene-4-sulfonic acid (R)-4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutyl ester (1.671 g) under an argon atmosphere in an ice water bath, and the mixture was stirred at room temperature for 30 minutes. Subsequently, 4-{4-(4-trifluoromethylsulfanylbenzyl)piperidin-1-yl}phenol (1.50 g) and tripotassium phosphate (0.867 g) were added thereto, and then the mixture was heated at reflux for 4 hours. Thereafter the reaction mixture was poured into water, followed by extraction with ethyl acetate. The organic layer was washed with a saturated sodium chloride aqueous solution, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 10:0-0:10) to afford the title compound as a brown oil (1.47 g).
MS (m/z): 584[M]+

Reference Example 185
Preparation of (R)-1-[4-{4-(tert-butyl-dimethyl-silyloxy)-(1,4')-bipiperidinyl-1'-yl)phenoxy]-4-(2-chloro-4-
nitroimidazol-1-yl)butan-2-ol
Toluene-4-sulfonic acid (R)-4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutyl ester (848 mg) and 4-[4-(tert-butyl-dimethylsilanyloxy)[1,4']bipiperidinyl-1'-yl]phenol (850 mg) were suspended in ethanol (30 ml). Tripotassium phosphate (1.02 g) and sodium iodide (359 mg) were added to the suspension, and the mixture was stirred at 75°C for 3 hours under a nitrogen atmosphere. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure, and water was added to the resulting residue, followed by extraction with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. Insoluble matter that was precipitated by adding isopropyl ether to the residue was collected by filtration to afford the title compound as a pale brown powder (470 mg).

Reference Example 186
Preparation of 4-(4-hydroxyphenyl)piperazine-1-carboxylic acid tert-butyl ester
1-(4-Hydroxyphenyl)piperazine (5.0 g) was suspended in methanol (50 ml). Di-tert-butyl dicarbonate (6.8 ml) was added to the suspension, and stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (dichloromethane:methanol = 50:1) to afford the title compound as a white powder (7.88 g).
1H NMR (CDCl3) δ 1.49 (9H, s), 2.95-3.00 (4H, m), 3.55-3.60 (4H, m), 5.77 (1H, s), 6.74-6.86 (4H, m).

Reference Example 187
Preparation of 4-[4-(4-trifluoromethoxybenzyl)oxy)piperidin-1-yl]phenol
Pyridinium p-toluenesulfonate (81 mg) was added to an ethanol solution (3 ml) of 1-[4-(tetrahydropyran-2-yloxy)phenyl]-4-(4-trifluoromethoxybenzyl)oxy)piperidine (507 mg) and the
mixture was stirred at 70 to 80°C for 24 hours. After being
cooled to room temperature, the reaction mixture was concentrated
under reduced pressure, ethyl acetate and a saturated sodium
hydrogen carbonate aqueous solution were added to the residue,
and the result was separated into layers. The organic layer was
washed with a saturated sodium chloride aqueous solution and
dried over magnesium sulfate. After being concentrated under
reduced pressure, the residue was purified by silica gel column
chromatography (hexane:ethyl acetate = 2:1) to afford the title
compound as a pale purple solid (305 mg).

$^{1}H$ NMR (CDCl$_3$) $\delta$ 1.76-1.90 (2H, m), 2.00-2.10 (2H, m), 2.84 (2H,
m), 3.33-3.42 (2H, m), 3.51-3.60 (1H, m), 4.53 (1H, brs), 4.63
(2H, s), 6.74 (2H, d, $J = 9.0$ Hz), 6.87 (2H, d, $J = 9.0$ Hz), 7.48
(2H, d, $J = 8.1$ Hz), 7.60 (2H, d, $J = 8.2$ Hz).

Reference Example 188

Preparation of 4-[(4-
trifluoromethyl)benzyl]oxy)piperidin-1-yl]phenol

The title compound was prepared in the same manner as
in Reference Example 187 using suitable starting materials.

Colorless solid

$^{1}H$ NMR (CDCl$_3$) $\delta$ 1.71-1.93 (2H, m), 1.95-2.15 (2H, m), 2.71-2.93
(2H, m), 3.26-3.46 (2H, m), 3.46-3.63 (1H, m), 4.50 (1H, s), 4.57
(2H, s), 6.74 (2H, d, $J = 9.0$ Hz), 6.87 (2H, d, $J = 8.9$ Hz), 7.19
(2H, d, $J = 8.5$ Hz), 7.39 (2H, d, $J = 8.4$ Hz).

Reference Example 189

Preparation of 4-[(4-
trifluoromethyl)phenylamino)piperidin-1-yl]phenol

The title compound was prepared in the same manner as
in Reference Example 187 using suitable starting materials.

Colorless amorphous

$^{1}H$ NMR (CDCl$_3$) $\delta$ 1.56-1.72 (2H, m), 2.13-2.20 (2H, m), 2.77-2.88
(2H, m), 3.44-3.51 (3H, m), 3.92 (1H, d, $J = 7.94$ Hz), 4.86 (1H,
s), 6.59-6.63 (2H, m), 6.72-6.79 (2H, m), 6.85-6.92 (2H, m),
7.38-7.42 (2H, m).

Reference Example 190
Preparation of 4-[4-(4-
5 trifluoromethoxyphenoxymethyl)piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 187 using suitable starting materials.
Pale yellow solid
1H NMR (CDCl3) δ 1.48-1.63 (2H, m), 1.87-1.98 (3H, m), 2.62-2.72 (2H, m), 3.51-3.57 (2H, m), 3.83 (2H, d, J = 5.88 Hz), 4.50 (1H, brs), 6.73-6.78 (2H, m), 6.84-6.91 (4H, m), 7.12-7.16 (2H, m).

Reference Example 191
Preparation of 4-[4-(4-
15 trifluoromethoxybenzyl)piperidin-1-yl]phenol

10% palladium on carbon (64 mg) was added to an ethanol solution (13 ml) of 4-(4-trifluoromethoxybenzyl)piperidine (1.28 g) and 1,4-cyclohexanedione (1.19 g), and the mixture was stirred at 70 to 80°C for 8.5 hours. After being cooled to room temperature, the catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. After being dissolved in ethyl acetate, the residue was washed with a saturated sodium chloride aqueous solution and dried over magnesium sulfate. After being concentrated under reduced pressure, the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 10:0-6:4) to afford the title compound as a black oil (305 mg).
MS (m/z): 351[M]^+

Reference Example 192
Preparation of 4-[4-(3,4-dichlorobenzyl)piperidin-1-
30 5-yl]phenol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.
Brown oil
MS (m/z): 335[M]⁺

Reference Example 193
Preparation of 4-[4-(4-
trifluoromethylbenzyloxymethyl)piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 187 using suitable starting materials.
Pale yellow oil
1H NMR (CDCl₃) δ 1.37-1.54 (2H, m), 1.68-1.90 (3H, m), 2.57-2.68 (2H, m), 3.39 (2H, d, J = 6.29 Hz), 3.46-3.52 (2H, m), 4.57 (2H, s), 5.28 (1H, s), 6.67-6.74 (2H, m), 6.83-6.89 (2H, m), 7.33-7.47 (2H, m), 7.58-7.62 (2H, m).

Reference Example 194
Preparation of 4-[3-(4-trifluoromethoxyphenoxy)-8-
azabicyclo[3.2.1]oct-8-yl]phenol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.
Gray powder
MS (m/z): 379[M]⁺

Reference Example 195
Preparation of 1-(4-hydroxyphenyl)-4-(4-
trifluoromethoxyphenyl)piperidin-4-ol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.
Black powder
MS (m/z): 353[M]⁺

Reference Example 196
Preparation of 4-[4-[3-(4-
trifluoromethoxyphenyl)propyl]piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.
Black oil
MS (m/z): 379[M]+

Reference Example 197
Preparation of 4-[4-{2-(4-
trifluoromethoxybenzoyloxy)ethyl]piperdin-1-yl}phenol

6 N hydrochloric acid (1 ml) was added to an ethanol solution (15 ml) of 1-(4-methoxymethoxyphenyl)-4-{2-(4-
trifluoromethoxybenzoyloxy)ethyl]piperidine (1.51 g) and stirred at 60°C for 2 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. A saturated sodium hydrogen carbonate aqueous solution was added to the residue, followed by extraction with dichloromethane. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to afford the title compound as a pink solid (1.34 g).

1H NMR (CDCl3) δ 1.37-1.66 (5H, m), 1.75-1.81 (2H, m), 2.55-2.65 (2H, m), 3.44-3.50 (2H, m), 3.55 (2H, t, J = 6.3 Hz), 4.44 (1H, s), 4.50 (2H, s), 6.72-6.78 (2H, m), 6.83-6.89 (2H, m), 7.18-7.22 (2H, m), 7.35-7.39 (2H, m)

Reference Example 198
Preparation of 4-[4-{2-(4-
trifluoromethylbenzoyloxy)ethyl]piperdin-1-yl}phenol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.

Gray solid
1H NMR (CDCl3) δ 1.35-1.67 (5H, m), 1.76-1.82 (2H, m), 2.55-2.66 (2H, m), 3.44-3.50 (2H, m), 3.57 (2H, t, J = 6.3 Hz), 4.38 (1H, s), 4.57 (2H, s), 6.72-6.78 (2H, m), 6.84-6.89 (2H, m), 7.43-7.48 (2H, m), 7.39-7.62 (2H, m)

Reference Example 199
Preparation of 4-[4-(5-trifluoromethylbenzofuran-2-
ylmethyl)piperidin-1-yl]phenol

1 N hydrochloric acid was added to an ethanol solution of 1-[4-(tetrahydropropyran-2-yloxy)phenyl]-4-[5-
trifluoromethylbenzofuran-2-ylmethyl)piperidine (2.3 g) and stirred at 80°C for 1 hour. After being cooled to room temperature, a saturated sodium hydrogen carbonate aqueous solution was added to the mixture and concentrated under reduced pressure. The residue was subjected to extraction with ethyl acetate. The organic layer was dried over sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1) to afford the title compound as a pinkish white amorphous compound (1.15 g).

Reference Example 200
Preparation of 4-{4-{3-
trifluoromethylphenoxymethyl)piperidin-1-yl}phenol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials. Brown solid

Reference Example 201
Preparation of 4-{4-[2-{4-
trifluoromethylphenoxyl)ethyl)piperidin-1-yl}phenol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials. Brown solid

Reference Example 202
Preparation of 4-{4-[3-{4-
trifluoromethylphenoxyl)propyl)piperidin-1-yl}phenol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials. Brown solid

Reference Example 203
Preparation of 4-{2-{4-chlorophenoxymethyl)oxazol-4-
yl}phenol
2-Bromo-1-(4-hydroxyphenyl)ethanone (2.90 g) and 2-{4-chlorophenoxo}acetamide (5.0 g) were added to N-methylpyrrolidone (5 ml), and the mixture was stirred at 100 °C under a nitrogen atmosphere. After being cooled to room temperature, ethyl acetate and a saturated sodium hydrogen carbonate aqueous solution were added to the reaction mixture and separated into layers. The organic layer was washed with water, dried over sodium sulfate, and then concentrated under reduced pressure. Sodium acetate (11.1 g) in DMF (20 ml) were added to the residue and then stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate and the prepared insoluble matter was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1-1:1) and recrystallized from hexane-ethyl acetate to afford the title compound as a pale yellow powder (1.63 g).

Reference Example 204
Preparation of 4-{4-[2-{4-trifluoromethylphenyl}ethyl]piperidin-1-yl}phenol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.

White powder

Reference Example 205
Preparation of 4-{4-[4-{4-(4-trifluoromethoxybenzyloxy)benzyl]piperidin-1-yl}phenol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.

Brown powder

MS (m/z): 457[M]⁺
trifluoromethylphenyl)ethyl)piperazine (0.94 g) was dissolved in ethanol (19 ml) and THF (19 ml). 10% palladium on carbon (94 mg) was added to the mixture and stirred at 50 to 60°C under a hydrogen atmosphere for 8 hours. After being cooled to room temperature, the catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to afford the title compound as a gray powder (0.72 g).

MS (m/z): 349[M-H]

Reference Example 207
Preparation of 4-{4-[2-(4-trifluoromethoxyphenyl)ethyl)piperazin-1-yl)phenol
The title compound was prepared in the same manner as in Reference Example 206 using suitable starting materials.

Gray powder
MS (m/z): 366[M]+

Reference Example 208
Preparation of 4-{4-[4-(4-
trifluoromethylbenzyloxy)benzyl)piperidin-1-yl)phenol
The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.
Brown amorphous
MS (m/z): 411[M]+

Reference Example 209
Preparation of 3-fluoro-4-{4-(4-
trifluoromethoxyphenoxy)piperidin-1-yl)phenol
The title compound was prepared in the same manner as in Reference Example 206 using suitable starting materials.
Pale brown powder

Reference Example 210
Preparation of 4-{4-[4-(4-
trifluoromethoxyphenoxy)benzyl)piperidin-1-yl)phenol
The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Amorphous

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Reference Example 211
Preparation of 4-(3,5-dimethyl-4-(3-(4-
trifluoromethylphenyl)propyl)piperazin-1-yl)phenol
The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.

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Pale brown powder
MS (m/z): 392[M]⁺

Reference Example 212
Preparation of 4-((3R,5S)-3,5-dimethyl-4-(4-(4-
trifluoromethoxybenzyl)benzyl)piperazin-1-yl)phenol
The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.
Brown amorphous
MS (m/z): 486[M]⁺

Reference Example 213
Preparation of 4′-(4-(4-
trifluoromethoxyphenoxy)piperidin-1-ylmethyl)-biphenyl-4-ol
Sodium tricetoxysoborohydride (1.69 g) was added to a 1,2-dichloroethane solution (11 ml) of 4′-hydroxybiphenyl-4-
carbalddehyde (1.13 g) and 4-(4-trifluoromethoxyphenoxy)piperidine (1.78 g) and stirred at room temperature overnight. A potassium carbonate aqueous solution was added to the reaction mixture, followed by extraction with dichloromethane. The organic layer was washed with water, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 10:0-0:10) to afford the title compound as a yellow powder (1.73 g).

MS (m/z): 443[M]⁺
Reference Example 214
Preparation of 4-[(3,5-dimethyl-4-[4-(4-
trifluoromethylbenzyl)oxypiperazin-1-y1)]phenol

The title compound was prepared in the same manner as
in Reference Example 187 using suitable starting materials.
Brown powder
MS (m/z): 470[M]'

Reference Example 215
Preparation of 4-{(R)-3-methyl-4-[4-(4-
trifluoromethylbenzyl)piperazin-1-y1)]phenol

The title compound was prepared in the same manner as
in Reference Example 187 using suitable starting materials.
Brown amorphous
MS (m/z): 456[M]'  

Reference Example 216
Preparation of (R)-4-(4-hydroxyphenyl)-3-
methylpiperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as
in Reference Example 187 using suitable starting materials.
Yellow oil
MS (m/z): 292[M]'

Reference Example 217
Preparation of 4-{[(S)-3-methyl-4-[4-(4-
trifluoromethylbenzyl)piperazin-1-y1)]phenol

The title compound was prepared in the same manner as
in Reference Example 187 using suitable starting materials.
Brown amorphous
MS (m/z): 456[M]'  

Reference Example 218
Preparation of (S)-4-(4-hydroxyphenyl)-3-
methylpiperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 206 using suitable starting materials. Brown oil

5 \text{MS (m/z)}: \text{292[M]+}

Reference Example 219
Preparation of 1-(4'-hydroxybiphenyl-4-yl)-4-trifluoromethylpiperidin-4-ol

The title compound was prepared in the same manner as in Reference Example 206 using suitable starting materials. White powder

Reference Example 220
Preparation of 4-(4-[3-(3-trifluoromethylphenoxy)propyl]piperidin-1-yl)phenol

The title compound was prepared in the same manner as in Reference Example 187 using suitable starting materials. Yellow solid

Reference Example 221
Preparation of 4-(4-[3-(5-trifluoromethylpyridin-2-yloxy)propyl]piperidin-1-yl)phenol

The title compound was prepared in the same manner as in Reference Example 187 using suitable starting materials. White solid

Reference Example 222
Preparation of 4-(4-[4-(4-trifluoromethylbenzyloxy)benzyl]-3,6-dihydro-2H-pyridin-1-yl)phenol

The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials. Brown powder
Reference Example 223
Preparation of 4-[4-(4-trifluoromethoxyphenyl)-3,6-dihydro-2H-pyridin-1-yl]phenol
The title compound was prepared in the same manner as in Reference Example 187 using suitable starting materials. Pink powder

Reference Example 224
Preparation of 4-[4-(4-trifluoromethoxybenzyl)-3,6-dihydro-2H-pyridin-1-yl]phenol
The title compound was prepared in the same manner as in Reference Example 187 using suitable starting materials. Yellow oil

Reference Example 225
Preparation of 2-hydroxy-4-(4-trifluoromethylbenzyloxy)benzaldehyde
Potassium carbonate (16.51 g) and 4-trifluoromethylbenzylobromide (18.47 ml) were added to an acetone solution of 2,4-dihydroxybenzaldehyde (15 g). The mixture was stirred at room temperature for 15 hours and further stirred at 60°C for 7 hours. After being cooled to room temperature, the mixture was concentrated under reduced pressure. Water was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with water and a saturated sodium chloride aqueous solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 9:1) to afford the title compound as a white powder (12.76 g).

Reference Example 226
Preparation of 4-[4-[4-(4-trifluoromethylsulfanyl)phenoxy)piperidin-1-yl]phenol
The title compound was prepared in the same manner as in Reference Example 187 using suitable starting materials.
Yellow powder
MS (m/z): 369[M]+

Reference Example 227

Preparation of 4-(4-(5-trifluoromethylbenzofuran-2-ylmethoxy)piperidin-1-yl)phenol

p-Toluenesulfonic acid monohydrate (0.84 g) was added to an ethanol solution (40 ml) of 1-[4-(tetrahydropyran-2-yl-oxy)phenyl]-4-(5-trifluoromethylbenzofuran-2-ylmethoxy)piperidine (2.1 g) and the mixture was heated at reflux for 1 hour. After being cooled to room temperature, water was added to the reaction mixture and filtered through Celite, followed by extraction with ethyl acetate. The organic layer was washed with a saturated sodium chloride aqueous solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was washed with ether and dried to afford the title compound as a white powder (1.4 g).

1H NMR (CDCl3) δ 1.80-1.87 (2H, m), 2.03-2.09 (2H, m), 2.83 (2H, dt, J = 9.5, 2.9 Hz), 3.35-3.39 (2H, m), 3.60-3.66 (1H, m), 4.69 (2H, s), 5.23 (1H, brs), 6.70-6.76 (3H, m), 6.85-6.88 (2H, m), 7.52-7.56 (2H, m), 7.84 (1H, s).

Reference Example 228

Preparation of 4-[4-(4-trifluoromethoxyphenylsulfanyl)piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 227 using suitable starting materials. White powder

1H NMR (CDCl3) δ 1.76-1.84 (2H, m), 2.05-2.09 (2H, m), 2.74 (2H, dt, J = 9.5, 2.6 Hz), 3.13-3.19 (1H, m), 3.42-3.46 (2H, m), 5.23 (1H, brs), 6.70-6.76 (2H, m), 6.82-6.86 (2H, m), 7.15 (2H, d, J = 8.6 Hz), 7.44-7.47 (2H, m).

Reference Example 229

Preparation of 4-[4-[2-(4-
trifluoromethoxyphenyl)sulfanyl)ethyl)piperidin-1-yl)phenol

The title compound was prepared in the same manner as in Reference Example 227 using suitable starting materials. White powder

\[ \begin{align*}
\text{1H NMR (CDCl3)} & \quad \delta 1.36-1.46 (2H, m), 1.48-1.58 (1H, m), 1.64 (2H, dt, J = 7.0, 7.5 Hz), 1.76-1.83 (2H, m), 2.56-2.65 (2H, m), 2.96 (2H, t, J = 7.5 Hz), 3.43-3.49 (2H, m), 5.30 (1H, brs), 6.70 (2H, d, J = 9.0 Hz), 6.85 (2H, d, J = 9.0 Hz), 7.12-7.16 (2H, m), 7.31-7.35 (2H, m).
\end{align*} \]

Reference Example 230

Preparation of 4-{4-(3,4-dichlorophenoxy)piperidin-1-yl}phenol

10% palladium on carbon (350 mg) was added to an ethanol solution (50 ml) of 4-(3,4-dichlorophenoxy)piperidine (7.1 g) and 1,4-cyclohexanediol (6.47 g), and the mixture was stirred at 50 to 60°C for 5 hours. After being cooled to room temperature, the catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with a saturated sodium chloride aqueous solution, and dried over magnesium sulfate. After being concentrated under reduced pressure, the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 9:1-3:1) to afford the title compound as a pale brown powder (5.2 g).

\[ \begin{align*}
\text{1H NMR (CDCl3)} & \quad \delta 1.91-1.98 (2H, m), 2.05-2.13 (2H, m), 2.94-3.01 (2H, m), 3.29-3.34 (2H, m), 4.36-4.41 (1H, m), 5.25 (1H, brs), 6.72-6.79 (3H, m), 6.87-6.90 (2H, m), 7.02 (1H, d, J = 0.7 Hz), 7.31 (1H, d, J = 8.9 Hz).
\end{align*} \]

Reference Example 231

Preparation of 1-{(4-hydroxyphenyl)-4-(4-trifluoromethylphenyl)piperidin-4-ol

1-{(4-Benzylxyloxyphenyl)-4-{4-trifluoromethylphenyl)piperidin-4-ol (2 g) was dissolved in
ethanol (20 ml) and ethyl acetate (20 ml). 20% palladium hydroxide on carbon (0.2 g) was added to the mixture and stirred at room temperature under a hydrogen atmosphere for 1.5 hours. The mixture was filtered through Celite to remove the catalyst, and the filtrate was concentrated under reduced pressure. The residue was washed with an ether-hexane mixed solvent to afford the title compound as a pale pink powder (1.43 g).

Reference Example 232
Preparation of 4-[(4-methoxy-4-((4-
trifluoromethylphenyl)piperidin-1-yl)phenol
The title compound was prepared in the same manner as in Reference Example 231 using suitable starting materials.
White powder

Reference Example 233
Preparation of 4-[(4-methoxy-4-((4-
trifluoromethoxyphenyl)piperidin-1-yl)phenol
The title compound was prepared in the same manner as in Reference Example 231 using suitable starting materials.
Pale pink powder

Reference Example 234
Preparation of 4-[(4-hydroxybenzyl)piperidin-1-
yl]phenol
48% hydrobromic acid (300 ml) was added to 4-(4-
methoxybenzyl)-1-(4-methoxyphenyl)piperidine (10.58 g) and heated at 100°C for 21 hours. After being cooled to room temperature, the reaction mixture was diluted with water and neutralized by adding a sodium hydroxide aqueous solution and a sodium hydrogen carbonate aqueous solution. The insoluble matter formed was collected by filtration and dried to afford the title compound as a grayish brown powder (10.46 g).

Reference Example 235
Preparation of 4-(4-(1-methyl-1-(4-(4-trifluoromethylbenzyl)oxy)phenyl)-ethyl)piperazin-1-yl)phenol

The title compound was prepared in the same manner as in Reference Example 227 using suitable starting materials.

White powder

Reference Example 236
Preparation of 4-(4-(4-(4-trifluoromethyl)phenoxy)benzyl)piperidin-1-yl)phenol

The title compound was prepared in the same manner as in Reference Example 187 using suitable starting materials.

Pale red solid

Reference Example 237
Preparation of 4-[2-(4-trifluoromethoxyphenoxy)methyl]thiazol-4-yl)phenol

A solution of 2-Bromo-1-(4-hydroxyphenyl)ethanone (4.09 g) and 4-(4-trifluoromethoxyphenoxy)-thiobutyramid (5.31 g) in ethanol (100 ml) was heated at reflux overnight. The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane) to afford the title compound as a yellow oil (2.60 g, 6.57 mmol, 34.6%).

Reference Example 238
Preparation of 4-(4-hydroxyphenyl)piperidine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 206 using suitable starting materials.

Reference Example 239
Preparation of 4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 187 using suitable starting materials.
Reference Example 240
Preparation of 4-[(4-chlorophenoxy)piperidin-1-yl]phenol
The title compound was prepared in the same manner as in Reference Example 187 using suitable starting materials.

Reference Example 241
Preparation of 4-[(4-(4-trifluoromethylphenoxy)piperidin-1-yl]phenol
The title compound was prepared in the same manner as in Reference Example 187 using suitable starting materials.

Reference Example 242
Preparation of 4-[(4-chlorobenzylxoy)piperidin-1-yl]phenol
The title compound was prepared in the same manner as in Reference Example 187 using suitable starting materials.

Reference Example 243
Preparation of 4-[(4-(N-(4-chlorophenyl)-N-methylamino)piperidin-1-yl]phenol
The title compound was prepared in the same manner as in Reference Example 187 using suitable starting materials.

Reference Example 244
Preparation of 4-[(4-(4-trifluoromethoxybenzylxoy)methyl)piperidin-1-yl]phenol
The title compound was prepared in the same manner as in Reference Example 187 using suitable starting materials.

Reference Example 245
Preparation of 4-[(4-(4-trifluoromethylbenzyl)piperidin-1-yl]phenol
The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.
Reference Example 246
Preparation of 4-[4-(4-chlorobenzyl)piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.

Reference Example 247
Preparation of 4-[4-(4-trifluoromethylphenoxymethyl)piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 187 using suitable starting materials.

Reference Example 248
Preparation of 4-[4-(4-chlorobenzylxyloxymethyl)piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 187 using suitable starting materials.

Reference Example 249
Preparation of 4-[4-(4-trifluoromethoxyphenyl)piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.

Reference Example 250
Preparation of 4-[4-[N-methyl-N-(4-trifluoromethylphenyl)aminol]piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.

Reference Example 251
Preparation of 4-[1-(4-trifluoromethoxyphenyl)piperidin-4-yloxy]phenol

The title compound was prepared in the same manner as
in Reference Example 206 using suitable starting materials.

Reference Example 252
Preparation of 4-(4-hydroxyphenoxy)piperidine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 206 using suitable starting materials.

Reference Example 253
Preparation of 4-[1-(4-trifluoromethylphenyl)piperidin-4-yloxy]phenol

The title compound was prepared in the same manner as in Reference Example 206 using suitable starting materials.

Reference Example 254
Preparation of 4-[(N-methyl-N-(4-trifluoromethoxyphenyl)amino)piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.

Reference Example 255
Preparation of 4-\(\{N-(4\text{-}N\text{-}ethylamino)piperidin\text{-}1\text{-}yl\}\)phenol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.

Reference Example 256
Preparation of 4-(4'-hydroxybiphenyl-4-yl)piperazin-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 187 using suitable starting materials.

Reference Example 257
Preparation of 4-\(\{4\text{-}2\text{-}(4\text{-}\text{trifluoromethoxyphenyl})\text{ethyl}\}piperidin\text{-}1\text{-}yl\)phenol
The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.

Reference Example 258
Preparation of 4-\{(4-hydroxyphenyl)\}(1,4)diazepane-1-carboxylic acid tert-butyl ester
The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.

Reference Example 259
Preparation of 4-\{(4,4-dimethoxypiperidin-1-yl)\}phenol
The title compound was prepared in the same manner as in Reference Example 206 using suitable starting materials.

Reference Example 260
Preparation of 4-\{(4-(5-chlorobenzofuran-2-ylmethyl)piperidin-1-yl)\}phenol
The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.

Reference Example 261
Preparation of 4-\{(2-(4-trifluoromethoxyphenyloxazol-4-yl)\}phenol
2-Bromo-1-(4-hydroxyphenyl)ethanone (0.39 g) and 4-trifluoromethoxybenzamide (0.39 g) were dissolved in N,N-dimethylformamide (10 ml) and stirred at 140°C for 2 hours. After cooling the reaction mixture to room temperature, water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with water and a saturated sodium chloride aqueous solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 75:25). The result was concentrated to dryness under reduced pressure to afford the title compound as a pale yellow solid (70 mg).
Reference Example 262

Preparation of 4-[4-(4-trifluoromethoxyphenyl)oxazol-2-ylmethyl]phenol

The title compound was prepared in the same manner as in Reference Example 261 using suitable starting materials.

Reference Example 263

Preparation of [4-(4-hydroxyphenyl)piperazin-1-yl]carbamic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.

Reference Example 264

Preparation of 4-[2-(4-trifluoromethoxybenzyl)thiazol-4-yl]phenol

The title compound was prepared in the same manner as in Reference Example 237 using suitable starting materials.

Reference Example 265

Preparation of 4-[4-[2-(4-chlorophenoxy)ethyl]piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.

Reference Example 266

Preparation of 4-[4-[2-(4-trifluoromethoxyphenoxy)ethyl]piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.

Reference Example 267

Preparation of 4-[4-(5-trifluoromethylpyridin-2-yloxy methyl)piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 197 using suitable starting materials.
Reference Example 268
Preparation of 4-[(2-(4-
trifluoromethoxyphenoxymethyl)oxazol-4-yl)phenol

5 The title compound was prepared in the same manner as
in Reference Example 261 using suitable starting materials.

Reference Example 269
Preparation of 4-{4-[3-(4-
trifluoromethoxyphenoxy)propyl]piperidin-1-yl}phenol

10 The title compound was prepared in the same manner as
in Reference Example 197 using suitable starting materials.

Reference Example 270
Preparation of 4-{4-{5-trifluoromethylpyridin-2-
yloxy)piperidin-1-yl}phenol

15 The title compound was prepared in the same manner as
in Reference Example 199 using suitable starting materials.

Reference Example 271
Preparation of 4-{4-[(2-(5-trifluoromethylpyridin-2-
yloxy)ethyl]piperidin-1-yl}phenol

20 The title compound was prepared in the same manner as
in Reference Example 199 using suitable starting materials.

Reference Example 272
Preparation of 4-{4-[N-ethyl-N-(4-
trifluoromethylphenyl)amino]piperidin-1-yl}phenol

25 The title compound was prepared in the same manner as
in Reference Example 191 using suitable starting materials.

Reference Example 273
Preparation of 4-{4-[3-
trifluoromethylphenoxy)piperidin-1-yl}phenol

30 The title compound was prepared in the same manner as
in Reference Example 191 using suitable starting materials.

Reference Example 274
Preparation of 4-[4-{3,5-bis-
trifluoromethylphenoxy}piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.

Reference Example 275
Preparation of 4-{4-[N-ethyl-N-(4-
trifluoromethoxyphenyl)amino]piperidin-1-yl}phenol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.

Reference Example 276
Preparation of 4-[1-{4-trifluoromethoxyphenyl}piperidin-
4-yl]phenol

The title compound was prepared in the same manner as in Reference Example 234 using suitable starting materials.

Reference Example 277
Preparation of 4-[1-{4-trifluoromethylphenyl}piperidin-
4-yl]phenol

The title compound was prepared in the same manner as in Reference Example 234 using suitable starting materials.

Reference Example 278
Preparation of 1-(4-hydroxyphenyl)-4-
trifluoromethylpiperidin-4-ol

The title compound was prepared in the same manner as in Reference Example 206 using suitable starting materials.

Reference Example 279
Preparation of 4-[12-{4-trifluoromethoxyphenyl}thiazol-4-
yl]phenol
The title compound was prepared in the same manner as in Reference Example 237 using suitable starting materials.

Reference Example 280

Preparation of 4-(4-methoxy-4-trifluoromethylpiperidin-1-yl)phenol

Boron trichloride (1 M dichloromethane solution, 2.3 ml) was added to a solution (50 ml) of 1-(4-benzyloxyphenyl)-4-methoxy-4-trifluoromethylpiperidine (0.7 g) in dichloromethane (50 ml) at 0°C and stirred for 20 minutes. A sodium hydrogen carbonate aqueous solution was added to the reaction mixture, followed by extraction with dichloromethane. The organic layer was washed with water and dried over sodium sulfate. The result was concentrated under reduced pressure, and the residue was washed with diethylether and then dried to afford the title compound as a pale yellow powder (508 mg).

Reference Example 281

Preparation of 4-(4-propoxy-4-trifluoromethylpiperidin-1-yl)phenol

The title compound was prepared in the same manner as in Reference Example 206 using suitable starting materials.

Reference Example 282

Preparation of 4-[4-(3-chloro-5-trifluoromethylpyridin-2-yloxy)piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 283

Preparation of 4-[1-(4-trifluoromethoxyphenyl)piperidin-4-ylmethyl]phenol

The title compound was prepared in the same manner as in Reference Example 234 using suitable starting materials.
Reference Example 284
Preparation of 4-((4-hydroxybenzyl)piperidin-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 186 using suitable starting materials.

Reference Example 285
Preparation of 4-[[1-((4-trifluoromethylphenyl)piperidin-4-yl)methyl]phenol

The title compound was prepared in the same manner as in Reference Example 234 using suitable starting materials.

Reference Example 286
Preparation of 4-[[3-((4-

trifluoromethylphenyl)propyl]piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 287
Preparation of 4-[[2-((4-hydroxyphenyl)ethyl]piperidin-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 186 using suitable starting materials.

Reference Example 288
Preparation of 2-chloro-4-[[4-((4-

trifluoromethoxyphenoxo)piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 289
Preparation of 4-[[2-((4-chlorophenyl)ethyl]piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.
Reference Example 290
Preparation of 4-[4-(5-chlorobenzofuran-2-ylmethoxy)piperidin-1-yl]phenol

5 The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 291
Preparation of 4-{4-[3-(4-chlorophenoxo)propyl]piperidin-1-yl}phenol

10 The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 292
Preparation of 4-{4-[3-(4-chlorophenyl)propyl]piperidin-1-yl}phenol

15 The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 293
Preparation of 4-{4-[5-trifluoromethoxybenzofuran-2-ylmethyl]piperidin-1-yl}phenol

20 The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 294
Preparation of 4-{4-[5-chlorobenzofuran-2-ylmethoxymethyl]piperidin-1-yl}phenol

25 The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 295
Preparation of 4-{4-[4-(4-trifluoromethoxybenzyl)oxo]phenyl]piperazin-1-yl}phenol p-toluenesulfonate
The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.

Reference Example 296
Preparation of 4-(4-[2-(3,4-dichlorophenoxy)ethyl]piperidin-1-yl)phenol
The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 297
Preparation of 4-(4-[2-(3-chloro-5-trifluoromethyl)pyridin-2-yloxy)ethyl]piperidin-1-yl)phenol
The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 298
Preparation of 4-(4-[2-(3,5-dichloropyridin-2-yloxy)ethyl]piperidin-1-yl)phenol
The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 299
Preparation of 4-(4-[2-(4-chloro-3-trifluoromethylphenoxy)ethyl]piperidin-1-yl)phenol
The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 300
Preparation of 4-(4-[2-(2,4-dichlorophenoxy)ethyl]piperidin-1-yl)phenol
The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 301
Preparation of 4-(4-[2-(tetrahydropyran-2-yloxy)-2-(4-
trifluoromethoxypheny]ethyl]piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 206 using suitable starting materials.

Reference Example 302

Preparation of 4-[4-[2-(4-chloro-3-methylphenoxy)ethyl]piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 303

Preparation of 4-[4-[2-(3-trifluoromethylphenoxy)ethyl]piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 304

Preparation of 4-[4-[2-(3-chloro-4-fluorophenoxy)ethyl]piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 305

Preparation of 4-[4-[4-(4-trifluoromethoxyphenoxy)phenyl]piperazin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 191 using suitable starting materials.

Reference Example 306

Preparation of 4-[4-[4-(4-trifluoromethoxyphenoxy)butyl]piperidin-1-yl]phenol

The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 307
Preparation of \(4-\{4-\{4-\text{trifluoromethoxyphenoxymethyl}\text{-phenyl}\}\text{piperazin-1-yl}\}\text{phenol}

The title compound was prepared in the same manner as in Reference Example 197 using suitable starting materials.

Reference Example 308
Preparation of \(4-\{4-\{\text{N-methyl-N-}\text{-\{4-\text{trifluoromethylbenzyl}\text{-amino}\text{-phenyl}\}\text{piperazin-1-yl}\}\}\text{phenol}

The title compound was prepared in the same manner as in Reference Example 197 using suitable starting materials.

Reference Example 309
Preparation of \(4-\{4-\{4-\text{trifluoromethoxybenzoxyl}\text{-phenoxyl}\text{piperidin-1-yl}\}\text{phenol}

The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 310
Preparation of \(4-\{3\text{-trifluoromethyl-5,6-dihydro-5H-}\text{imidazo[1,2-a]pyrazin-7-yl}\}\text{phenol}

The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 311
Preparation of \(4-\{4-\{4-\text{trifluoromethylbenzoxyl}\text{-phenoxyl}\text{piperidin-1-yl}\}\text{phenol}

The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

Reference Example 312
Preparation of \(4-\{3\text{-trifluoromethyl-5,6-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl}\}\text{phenol}

The title compound was prepared in the same manner as in Reference Example 206 using suitable starting materials.
Reference Example 313
Preparation of 4\(-\{4-\{4-(4-
trifluoromethoxybenzoyloxy)phenoxymethyl\}piperidin-1-yl\}phenol\)
The title compound was prepared in the same manner as 5 in Reference Example 199 using suitable starting materials.

Reference Example 314
Preparation of 4'-diethoxymethylbiphenyl-4-ol
The title compound was prepared in the same manner as 10 in Reference Example 206 using suitable starting materials.

Reference Example 315
Preparation of (2R,5S)-4-(4-hydroxyphenyl)-2,5-
dimethylpiperazine-1-carboxylic acid tert-butyl ester
The title compound was prepared in the same manner as 15 in Reference Example 186 using suitable starting materials.

Reference Example 316
Preparation of (1R,4R)-5-(4-hydroxyphenyl)-2,5-diaza-
bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester
The title compound was prepared in the same manner as 20 in Reference Example 186 using suitable starting materials.

Reference Example 317
Preparation of 4-\{4-\{N-methyl-N-[4-(4-
trifluoromethoxybenzoyloxy)phenyl]amino\}methyl\}piperidin-1-
yl\}phenol\)
The title compound was prepared in the same manner as 25 in Reference Example 187 using suitable starting materials.

Reference Example 318
Preparation of 4-\{4-(4-trifluoromethylphenyl)piperidin-
1-yl\}phenol
The title compound was prepared in the same manner as 30 in Reference Example 187 using suitable starting materials.
Reference Example 319

Preparation of 4-(4-trifluoromethoxyphenoxy)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-ol

5'-Benzzyloxy-4-(4-trifluoromethoxyphenoxy)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl (0.93 g) and 10% palladium on carbon (93 mg) were added to ethanol (9.3 ml), and the mixture was stirred at room temperature under a hydrogen atmosphere (atmospheric pressure) for 1 hour. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 10:0-6:4). The result was concentrated to dryness under reduced pressure to afford the title compound as a pale yellow powder (0.55 g).

Reference Example 320

Preparation of 4-(4-trifluoromethoxybenzyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-ol

The title compound was prepared in the same manner as in Reference Example 319 using suitable starting materials.

Reference Example 321

Preparation of 4-(5-hydroxypyridin-2-y1)piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 319 using suitable starting materials.

Reference Example 322

Preparation of 4-(4-trifluoromethoxyphenoxy)methyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-ol

Pyridinium p-toluenesulfonate (PPTS) (0.917 g) was added to an ethanol solution (20 ml) of 5'-(tetrahydropyran-2-yloxy)-4-(4-trifluoromethoxyphenoxy)methyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl (1.65 g), and the mixture was stirred for 4 hours while heating under reflux. After cooling the reaction
mixture to room temperature, a sodium hydrogen carbonate aqueous solution was added thereto, and ethanol was distilled off under reduced pressure, followed by extraction with ethyl acetate. The organic layer was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. The solvent was distilled off and the precipitated solid was collected by filtration. The solid was then washed with diisopropyl ether and dried to afford the title compound as a yellow powder (0.94 g).

Reference Example 323
Preparation of 4-[(2-(4-trifluoromethoxyphenoxy)ethyl]-3,4,5,6-tetrahydro-2H-[1,2'']bipyridinyl-5'-ol

The title compound was prepared in the same manner as in Reference Example 322 using suitable starting materials.

Reference Example 324
Preparation of 4-[(4-chlorophenoxy)-3,4,5,6-tetrahydro-2H-[1,2'']bipyridinyl-5'-ol

The title compound was prepared in the same manner as in Reference Example 322 using suitable starting materials.

Reference Example 325
Preparation of 4-[(4-trifluoromethoxybenzyloxy)-3,4,5,6-tetrahydro-2H-[1,2'']bipyridinyl-5'-ol

The title compound was prepared in the same manner as in Reference Example 322 using suitable starting materials.

Reference Example 326
Preparation of 4-[(4-trifluoromethylphenoxy)-3,4,5,6-tetrahydro-2H-[1,2'']bipyridinyl-5'-ol

The title compound was prepared in the same manner as in Reference Example 322 using suitable starting materials.

Reference Example 327
Preparation of 4-{3-(4-trifluoromethoxyphenoxy)propyl}...
3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-ol

The title compound was prepared in the same manner as in Reference Example 322 using suitable starting materials.

Reference Example 328
Preparation of 6-(4-trifluoromethoxybenzyloxymethyl)pyridin-3-ol

2 N hydrogen chloride-ethyl acetate solution (20 ml) was added to an ethanol solution (20 ml) of 5-methoxymethoxy-2-(4-trifluoromethoxybenzyloxymethyl)pyridine (2.3 g) and stirred at room temperature for 16 hours. The reaction mixture was concentrated under reduced pressure and a sodium hydrogen carbonate aqueous solution was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with water and a saturated sodium chloride aqueous solution and dried over sodium sulfate. The result was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 4:1-2:1). The result was concentrated to dryness under reduced pressure to afford the title compound as a white solid (2.4 g).

Reference Example 329
Preparation of 2-(4-(4-trifluoromethoxybenzyl)piperazin-1-yl)benzothiazol-6-ol

Methanol (1 ml) and a catalytic amount of acetic acid and sodium triacetoxyborohydride (0.14 g) were added to a 1,2-dichloroethane solution (5 ml) of 2-piperazin-1-yl-benzothiazol-6-ol (0.1 g) and 4-trifluoromethoxybenzaldehyde (0.067 ml) and stirred at room temperature overnight. Water was added to the reaction mixture, followed by extraction with dichloromethane. The organic layer was washed with water, dried over sodium sulfate, and then concentrated under reduced pressure to afford the title compound as a colorless amorphous compound (80 mg).

Reference Example 330
Preparation of 4-((6-hydroxyquinolin-2-yl)piperazine-1-carboxylic acid tert-butyl ester
2-Chloro-6-((tetrahydro)pyran-2-yl)oxy)quinoline (1.00 g) and piperazine-1-carboxylic acid tert-butyl ester (0.76 g) were heated to 140°C in the absence of solvent under an argon atmosphere and stirred for 2 hours. After cooling the reaction mixture to room temperature, a sodium hydrogen carbonate aqueous solution was added thereto, followed by extraction with dichloromethane. The organic layer was washed with a saturated sodium chloride aqueous solution and dried over magnesium sulfate. The result was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 75:25-67:33). The result was concentrated to dryness under reduced pressure to afford the title compound as a pale yellow amorphous compound (0.55 g).

Reference Example 331
Preparation of 2-[(4-((4-trifluoromethoxy)phenoxy)piperidin-1-yl)quinolin-6-ol
The title compound was prepared in the same manner as in Reference Example 330 using suitable starting materials.

Reference Example 332
Preparation of 6-hydroxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester
1,2,3,4-Tetrahydro-isoquinolin-6-ol hydrobromide (8.3 g) and sodium hydroxide (4.35 g) were dissolved in a mixed solvent of 1,4-dioxane (50 mL) and water (50 mL). Under ice cooling, di-tert-butyl dicarbonate (Boc₂O) (8.7 g) was added thereto dropwise and stirred at 0 to 10°C for 2 hours. The result was made hydrochloric acidic, followed by extraction with dichloromethane. The organic layer was washed with a saturated sodium chloride aqueous solution, dried over sodium sulfate, and then concentrated under reduced pressure to afford the title compound as a brown oil (4.1 g).
Reference Example 333
Preparation of 5-hydroxy-1,3-dihydropyridoxindole-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 332 using suitable starting materials.

Reference Example 334
Preparation of 2-[4-({trifluoromethoxyphenoxyl)piperidin-1-yl]benzothiazol-5-ol

The title compound was prepared in the same manner as in Reference Example 330 using suitable starting materials.

Reference Example 335
Preparation of 1-{3-({4-trifluoromethoxyphenoxyl)propyl]-1,2,3,4-tetrahydroquinolin-6-ol

6-Benzyl oxy-1-{3-({4-trifluoromethoxy-phenoxyl)propyl]-1,2,3,4-tetrahydro-quinoline (2.13 g) was dissolved in ethanol (10 ml). 10% palladium on carbon (0.2 g) was added thereto and stirred at room temperature under a hydrogen atmosphere for 4 hours. The mixture was filtered through Celite to remove the catalyst, and then the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 4:1) and concentrated under reduced pressure to afford the title compound (1.45 g).

Reference Example 336
Preparation of 1-{3-({4-trifluoromethoxyphenoxyl)propyl]-1H-indol-5-ol

The title compound was prepared in the same manner as in Reference Example 335 using suitable starting materials.

Reference Example 337
Preparation of 1-{3-({4-trifluoromethoxyphenoxyl)propyl]-2,3,4,5-tetrahydro-1H-benzoz[b]azepin-7-ol
The title compound was prepared in the same manner as in Reference Example 335 using suitable starting materials.

Reference Example 338

Preparation of 1-{3-{4-trifluoromethoxyphenoxy}propyl}-1,2,3,4-tetrahydroquinolin-5-ol

A 1 N hydrochloric acid aqueous solution (10 ml) was added to an ethanol solution (15 ml) of 5-{tetrahydropyran-2-yloxy}-1-{3-{4-trifluoromethoxyphenoxy}propyl}-1,2,3,4-tetrahydroquinoline (1.71 g) and stirred at room temperature overnight. A saturated sodium hydrogen carbonate aqueous solution was added thereto, and the mixture was concentrated under reduced pressure. The residue was subjected to extraction with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 6:1) to afford the title compound as a colorless oil (0.62 g).

Reference Example 339

Preparation of 1-{4-{4-trifluoromethoxyphenoxy}benzyl}-1,2,3,4-tetrahydroquinolin-6-ol

The title compound was prepared in the same manner as in Reference Example 335 using suitable starting materials.

Reference Example 340

Preparation of 1-{4-{4-trifluoromethoxyphenoxy}benzyl}-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-ol

The title compound was prepared in the same manner as in Reference Example 335 using suitable starting materials.

Reference Example 341

Preparation of 4-{6-hydroxybenzothiazol-2-yl) piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 332 using suitable starting materials.
Reference Example 342
Preparation of 6-{4-[2-{4-
trifluoromethoxyphenyl}ethyl]piperidin-1-yl}naphthalen-2-ol

The title compound was prepared in the same manner as in Reference Example 338 using suitable starting materials.

Reference Example 343
Preparation of 2-{4-{4-
trifluoromethoxyphenoxy}piperidin-1-yl}benzooxazol-5-ol hydrochloride

The title compound was prepared in the same manner as in Reference Example 330 using suitable starting materials.

Reference Example 344
Preparation of 4-{5-hydroxybenzooxazol-2-yl}piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 332 using suitable starting materials.

Reference Example 345
Preparation of 7-hydroxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-tutyl ester

The title compound was prepared in the same manner as in Reference Example 332 using suitable starting materials.

Reference Example 346
Preparation of 2-{4-[4-{4-
trifluoromethoxybenzyloxy}benzyl]piperidin-1-yl}-benzothiazol-6-ol

Potassium carbonate (1.02 g) and 4-{4-{4-
trifluoromethoxybenzyloxy}benzyl]piperidine were added to an N,N-
dimethylformamide solution (10 mL) of 2-chlorobenzothiazol-6-ol (1.37 g) and the mixture was stirred at 80°C for 2 days. After being cooled to room temperature, the mixture was concentrated
under reduced pressure. Water was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with water and a saturated sodium chloride aqueous solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 4:1-2:1) to afford the title compound as a white powder (2.1 g).

Reference Example 347
Preparation of 7-hydroxy-1,3,4,5-tetrahydrobenzo[c]azepin-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 332 using suitable starting materials.

Reference Example 348
Preparation of 2-chloro-6-(tetrahydrofurano-2-yloxy)-quinoline

2-Chloroquinolin-6-ol (36 g, 0.20 mol) was dissolved in dichloromethane (500 ml) and tetrahydrofuran (500 ml). 3,4-dihydro-2H-pyran (74 ml, 0.81 mol) and p-toluenesulfonic acid (0.49 g, 0.005 mol) were added to the mixture in ice cooling water bath, followed by stirring at room temperature overnight. A 10% sodium hydroxide aqueous solution was added to the reaction mixture, followed by extraction with dichloromethane. The result was dried over potassium carbonate and subjected to filtration, and then the filtrate was concentrated under reduced pressure. The crude crystal thus obtained was recrystallized from ethanol to afford the title compound as a colorless granular compound (47 g, yield 89%).

Melting point: 122-124 °C

Reference Example 349
Preparation of (4-trifluoromethoxyphenoxy)acetic acid methyl ester

Bromoacetic acid methyl ester (8 ml, 84.2 mmol) was
added to a mixture of 4-(trifluoromethoxy)phenol (10 g, 56.1 mmol) and potassium carbonate (11.6 g, 84.2 mmol) in N,N-Dimethylformamide (50 ml) and stirred at room temperature overnight. The reaction mixture was poured into water and neutralized with a 1 N hydrochloric acid aqueous solution, followed by extraction with diethyl ether. The result was concentrated and used for the subsequent reaction.

1H NMR (CDCl₃) δ 3.80 (s, 3H), 4.63 (s, 2H), 6.89-6.92 (m, 2H), 7.15-7.16 (m, 2H).

Reference Example 350
Preparation of 2-(4-trifluoromethoxyphenoxy)acetamide

A 25% ammonia aqueous solution (20 ml) was added to (4-trifluoromethoxyphenoxy)acetic acid methyl ester in methanol (40 ml) and the mixture was stirred at room temperature overnight. After distilling the solvent off, the residue was washed with water and dried to afford the title compound as a white solid (12.1 g, yield 91%).

1H NMR (CDCl₃) δ 4.50 (s, 2H), 5.66 (br, 1H), 6.50 (br, 1H), 6.92-6.94 (m, 2H), 7.18-7.20 (m, 2H).

Reference Example 351
Preparation of 1-(3-chloropropoxy)-4-trifluoromethoxybenzene

1-Bromo-3-chloropropene (2.37 ml, 24 mmol), 4-(trifluoromethoxy)phenol (3.56 g, 20 mmol) and potassium carbonate (4.15 g, 30 mmol) were stirred in NMP (30 ml) overnight. After removing potassium carbonate by filtration, water was added to the mixture, followed by extraction with ethyl acetate. The organic layer was washed with water and dried over sodium sulfate. The solvent was distilled off, and the residue was fractionated and purified by silica gel column chromatography (hexane:ethyl acetate = 89:11) to afford the title compound as a colorless oil (5.09 g, yield 99%).

1H NMR (CDCl₃) δ 2.23-2.25 (m, 2H), 3.75 (t, J = 6.3 Hz, 2H), 4.11
-145-

\( \{t, J = 5.8 \text{ Hz}, 2H\}, 6.89 \{d, J = 9.1 \text{ Hz}, 2H\}, 7.14 \{d, J = 8.9 \text{ Hz}, 2H\}. \)

Reference Example 352

Preparation of 4'–[4-(4-

trifluoromethoxyphenoxy)piperidin-1-yl]biphenyl-4-ol

The title compound was prepared in the same manner as in Reference Example 199 using suitable starting materials.

\( ^1H \text{ NMR (CDCl}_3 \} \delta 1.85-2.04 \{m, 2H\}, 2.04-2.22 \{m, 2H\}, 3.07-3.23 \{m, 2H\}, 3.45-3.63 \{m, 2H\}, 4.38-4.53 \{m, 1H\}, 4.74 \{s, 1H\}, 6.81-6.96 \{m, 4H\}, 7.01 \{d, J = 8.8 \text{ Hz}, 2H\}, 7.08-7.20 \{m, 2H\}, 7.38-7.51 \{m, 4H\}. \)

Reference Example 353

Preparation of 4–[2–(4–

trifluoromethoxyphenoxy)ethyl]piperidine-1-carboxylic acid tert-

butyl ester

Sodium hydride (60% in oil, 2.12 g) was added to an N,N-dimethylformamide solution (100 ml) of 4-

trifluoromethoxyphenol (9.0 g) under ice cooling and stirred for 30 minutes. After adding 4–[2–(toluene-4-

sulfonyloxy)ethyl]piperidine-1-carboxylic acid tert-butyl ester (17.7 g), the mixture was heated to room temperature and stirred. The mixture was further stirred at 50°C for 1 hour. After cooling the reaction mixture to room temperature, water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. The result was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 67:33) to afford the title compound as a pale yellow oil (18.64 g).

Reference Example 354

Preparation of 4–[2–(4–

trifluoromethoxyphenoxy)ethyl]piperidine
Trifluoroacetic acid (40 ml) was added to a dichloromethane solution (40 ml) of 4-[2-(4-
trifluoromethoxyphenoxy)ethyl]piperidine-1-carboxylic acid tert-
butyl ester (18.6 g), and the mixture was stirred at room
temperature for 5 hours. The mixture was concentrated under
reduced pressure, and ice water was added to the resulting
residue. The result was treated with 6 N sodium hydroxide aqueous
solution, followed by extraction with ethyl acetate. The organic
layer was washed with a saturated sodium chloride aqueous
solution and dried over magnesium sulfate. The solvent was
concentrated to dryness under reduced pressure to afford the
title compound as a white powder (14 g).

Reference Example 355

Preparation of 6-(4-trifluoromethoxyphenoxy)nicotinic
acid ethyl ester

Ethyl 6-chloro nicotinate (5.00 g, 26.9 mmol), 4-
(trifluoromethoxy)phenol (5.28 g, 29.6 mmol), potassium carbonate
(4.84 g, 35.0 mmol) and N,N-dimethylformamide (50 ml) were mixed
and stirred at 100 to 110°C overnight. The reaction mixture was
poured into water, followed by extraction with ethyl acetate. The
organic layer was washed with a saturated sodium chloride aqueous
solution and dried over magnesium sulfate. The organic layer was
concentrated under reduced pressure. The residue was purified by
silica gel column chromatography (hexane:ethyl acetate =
100:0-70:30) to afford the title compound as a colorless oil
(7.48 g, 85%).
Mass: [M]+ = 327.

Reference Example 356

Preparation of [6-(4-trifluoromethoxyphenoxy)pyridin-3-
yl]methanol

6-(4-Trifluoromethoxyphenoxy)nicotinic acid ethyl ester
(7.48 g, 22.9 mmol) was dissolved in tetrahydrofuran (75 ml) and
cooled to -78°C. A toluene solution (100.6 ml, 100.6 mmol) of
diisobutylaluminium hydride was added thereto and the mixture was 
stirred at the same temperature for 1 hour. The reaction mixture 
was poured into a 1 N sodium hydroxide aqueous solution, followed 
by extraction with dichloromethane. The organic layer was washed 
with a saturated sodium chloride aqueous solution and dried over 
magnesium sulfate. The organic layer was concentrated and 
purified by silica gel column chromatography (hexane:ethyl acetate = 100:0-0:100) to afford the title compound as a 
colorless oil (6.15 g, 94%).

Reference Example 357
Preparation of 6-(4-trifluoromethoxyphenoxo)pyridine-3-
carbaldehyde

(6-[(4-Trifluoromethoxy)phenoxy]pyridine-3-yl)methanol 
(3.00 g, 10.5 mmol), dimethylsulfoxide (90 ml) and 2-
iodoxybenzoic acid (3.53 g, 12.6 mmol) were mixed and stirred at 
room temperature overnight. After adding water and ethyl acetate 
the reaction mixture, insoluble matter was removed and the 
filtrate was separated into layers. The organic layer was washed 
with water, dried over magnesium sulfate, and then concentrated. 
The residue was purified by silica gel column chromatography 
(hexane:ethyl acetate = 100:0-70:30) to afford the title compound 
as a colorless oil (2.96 g, 99%).
Mass: [M]+ = 283

Reference Example 358
Preparation of 5'-(tetrahydropyran-2-yloxy)-4-[2-(4-
trifluoromethoxyphenoxo)ethyl]-3,4,5,6-tetrahydro-2H-
[1,2']bipyridiny1

Toluene (15 ml) was added to a mixture of 2-bromo-5-
(tetrahydropyran-2-yloxy)pyridine (2.58 g, 10 mmol), 4-[2-(4-
trifluoromethoxyphenoxo)ethyl]piperidine (3.18 g, 11 mmol) and 
sodium tert-butoxide (1.35 g, 14 mmol), and then the atmosphere 
was replaced with nitrogen. Bis(dibenzylideneacetone)palladium
(Pd:(dba), complex) (0.23 g, 0.25 mmol) and 9,9-dimethyl-4,5-

bis(diphenylphosphino)xanthine (xantphos) (0.36 g, 0.63 mmol) were added to the mixture, and the reaction mixture was heated at 100°C for 3 hours under a nitrogen atmosphere. After being cooled to room temperature, the reaction mixture was poured into water, followed by extraction with ethyl acetate. The organic layer was washed with a saturated sodium chloride aqueous solution, dried over sodium sulfate, and concentrated. The result was purified by silica gel column chromatography (ethyl acetate:hexane = 10:90-25:75) to afford the title compound as a pale brown powder (4.45 g, 95%).

1H NMR (CDCl₃) δ 1.34-1.38 (m, 2H), 1.52-1.65 (m, 10H), 1.97-1.99 (m, 1H). 2.75-2.80 (m, 2H), 3.57-3.60 (m, 1H), 3.91-3.95 (m, 1H), 3.99-4.03 (m, 2H), 4.13-4.16 (m, 2H), 5.21 (s, 1H), 6.62-6.64 (m, 1H), 6.86-6.89 (m, 2H), 7.13-7.14 (m, 2H), 7.28 (m, 1H), 8.04-8.05 (m, 1H).

Reference Example 359

Preparation of 4-[(E)-3-(4-

trifluoromethylphenyl)allyl]piperidine-1-carboxylic acid tert-
butyl ester

Potassium tert-butoxide (5.76 g, 50.0 mmol) was added to a solution of 4-(trifluoromethyl)benzylphosphonic acid diethyl ester (14.8 g, 50.0 mmol) in tetrahydrofuran solution (40 ml) under ice cooling, and the mixture was stirred at the same temperature for 30 minutes. Subsequently, a tetrahydrofuran solution (10 ml) of 4-(2-oxoethyl)piperidine-1-carboxylic acid tert-butyl ester (11.4 g, 50.0 mmol) was added thereto dropwise at 0°C, warmed to room temperature, and then stirred overnight. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. After filtering, the filtrate was concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 86:14) to afford
the title compound as a colorless oil (8.6 g, yield 47%).
$\text{H NMR (CDCl}_3 \text{)} \delta$ 1.10-1.22 (m, 2H), 1.44 (s, 9H), 1.66-1.81 (m, 2H), 2.17-2.25 (m, 2H), 2.60-2.78 (m, 2H), 4.00-4.22 (m, 3H), 6.25-6.33 (m, 1H), 6.37-6.44 (m, 1H), 7.40-7.46 (m, 2H), 7.52-
5 7.56 (m, 2H)

Reference Example 360
Preparation of 4-{3-{4-
trifluoromethylphenyl)propyl}piperidine-1-carboxylic acid tert-
butyl ester

4-{3-{4-Trifluoromethylphenyl)allyl}piperidine-1-
carboxylic acid tert-butyl ester (13.4 g, 36.2 mmol) and 10% palladium on carbon (1.4 g, 1.3 mmol) were suspended in ethanol (120 ml), followed by stirring under a hydrogen atmosphere (atmospheric pressure) at room temperature for 5 hours.
Thereafter the insoluble matter was removed by filtration, and the resulting solution was concentrated to afford the title compound as a colorless oil (crude).
$\text{H NMR (CDCl}_3 \text{)} \delta$ 1.05-1.06 (m, 2H), 1.25-1.30 (m, 2H), 1.37-1.41 (m, 1H), 1.45 (s, 9H), 1.59-1.68 (m, 4H), 2.64-2.67 (m, 4H), 4.11-4.13 (m, 2H), 7.26-7.28 (d, J = 9.2 Hz, 2H), 7.52-7.54 (d, J = 8.1, 2H).

Reference Example 361
Preparation of 4-{3-{4-
trifluoromethylphenyl)propyl}piperidine

4-{3-{4-Trifluoromethylphenyl)propyl}piperidine-1-
carboxylic acid tert-butyl ester (13.45 g, 36.2 mmol) prepared in Reference Example 360 was dissolved in dichloromethane (50 ml).
Trifluoroacetic acid (25 ml, 324 mmol) was added thereto and stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and adjusted to a pH of 10 using a 5 N sodium hydroxide aqueous solution. The mixture was subjected to extraction with dichloromethane 4 times. The result was dried over anhydrous sodium sulfate and then concentrated to
afford the title compound as a pale brown oil (10.2 g, quant).

1H NMR (CDCl₃) δ 1.09-1.51 (m, 2H), 1.25-1.29 (m, 2H), 1.37 (m, 1H), 1.61-1.69 (m, 4H), 2.11 (br, 1H), 2.56-2.66 (m, 4H), 3.06-3.08 (m, 2H), 7.27-7.28 (d, J = 7.8 Hz, 2H), 7.52-7.53 (d, J = 8.1, 2H).

Reference Example 362

Preparation of 1-[4-(tetrahydrofuran-2-yloxy)phenyl]-4-[3-(4-trifluoromethylphenyl)propyl]piperidine

2-(4-Iodophenoxy)tetrahydropyran (1.12 g, 3.7 mmol) and 4-[3-(4-trifluoromethylphenyl)propyl]piperidine (1 g, 3.7 mmol) were dissolved in degassed anhydrous toluene (10 ml). Sodium tert-butoxide (0.50 g, 5.2 mmol), tri-tert-butylphosphine tetrafluoroborate (tBu₃P·HBF₄) (0.09 g, 0.3 mmol) and palladium acetate (0.03 g, 0.15 mmol) were added thereto, and the mixture was heated at reflux under a nitrogen atmosphere for 5 hours. After being allowed to cool to room temperature, water (10 ml) was added to the mixture, followed by extraction with ethyl acetate. The organic layers were combined and washed with water and a saturated sodium chloride aqueous solution, and dried over anhydrous sodium sulfate. After removing insoluble matter by filtration, the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane:ethyl acetate= 80 : 20) to afford the title compound as a pale yellow solid (1.42 g, 86%).

1H NMR (CDCl₃) δ 1.32-1.35 (m, 4H), 1.59-1.85 (m, 10H), 1.93-2.05 (m, 1H), 2.58 (t, J = 11.7 Hz, 2H), 2.65-2.68 (t, J = 7.7 Hz, 2H), 3.50-3.52 (d, J = 11.4 Hz, 2H), 3.57-3.59 (m, 1H), 3.92-3.96 (t, J = 9.3 Hz, 1H), 5.29-5.30 (m, 1H), 6.87-6.89 (d, J = 9.1 Hz, 2H), 6.96-6.97 (d, J = 9.1, 2H) 7.28-7.30 (d, J = 7.9 Hz, 2H), 7.52-7.54 (d, J = 8.05, 2H).

Reference Example 363

Preparation of 4-[4-(4-

trifluoromethylbenzylloxy)benzyl]piperidine-1-carboxylic acid
text-butyl ester
tert-Butyl 4-\{(4-hydroxybenzyl)piperidine-1-carboxylate (1.78 g, 6.1 mmol), potassium carbonate (1.27 g, 9.2 mmol), N,N-
dimethylformamide (18 ml) and 4-(trifluoromethyl)benzylbromide (1.75 g, 7.3 mmol) were mixed and stirred at room temperature overnight. The reaction mixture was poured into water, followed by extraction with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, and then concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0-60:40) to afford the title compound as a colorless powder (2.64 g, 96%).
Mass: [M]^+ = 449.

Reference Example 364
Preparation of 4-\{(4-
trifluoromethylbenzyloxy)benzyl\}piperidine
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as a pale yellow powder (2.32 g, 83%).

1H NMR (CDCl₃) δ 2.30 (t, J = 5.2 Hz, 2H), 2.44 (t, J = 5.2 Hz, 2H), 2.84 (t, J = 5.5 Hz, 2H), 2.94 (t, J = 5.5 Hz, 2H), 5.05 (s, 2H), 6.22 (s, 1H), 6.92-6.94 (m, 2H), 7.13 (d, J = 8.6 Hz, 2H).

7.32-7.44 (m, SH).

Reference Example 366

Preparation of 4-{4-benzylxoybenzylidene}-1-[4-(tetrahydrofuran-2-ylxoy)phenyl]piperidine

4-{4-(Benzylxoy)benzylidene}piperidine (2.32 g, 8.3 mmol), 1-bromo-4-(tetrahydrofuran-2H-pyran-2-ylxoy)benzene (2.35 g, 9.1 mmol), toluene (20 mL), sodium tert-butoxide (1.12 g, 11.6 mmol), palladium acetate (0.075 g, 0.3 mmol) and tri-tert-butylyphosphate tetrafluoroborate (0.19 g, 0.7 mmol) were mixed and stirred at 100°C overnight. Water was poured into the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 80:20-50:50) to afford the title compound as a colorless powder.

TLC: Rf = 0.6 (hexane:ethyl acetate = 1:1)

Reference Example 367

Preparation of 6-benzylxoy-1-[3-{4-trifluoromethoxyphenoxoy}propyl]-1,2,3,4-tetrahydro-quinoline

6-Benzylxoy-1,2,3,4-tetrahydro-quinoline (1.20 g, 5 mmol), 1-(3-chloroproproxy)-4-trifluoromethoxybenzene (1.42 g, 5.58 mmol), potassium carbonate (1.04 g, 7.5 mmol) and sodium iodide (0.90 g, 6 mmol) were heated and stirred at 90°C in NMP (10 mL) overnight. Water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with water and dried over sodium sulfate. The result was concentrated and purified by silica gel column chromatography (hexane:ethyl acetate = 75:25) to afford the title compound as a yellow oil (2.13 g, 93%).
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1H NMR (CDCl\textsubscript{3}) \(\delta\) 1.91-1.94 (m, 2H), 2.03-2.06 (m, 2H), 2.73 (t, \(J = 6.4\) Hz, 2H), 3.21 (t, \(J = 5.6\) Hz, 2H), 3.41 (t, \(J = 7.0\) Hz, 2H), 4.01 (t, \(J = 5.9\) Hz, 2H), 4.96 (s, 2H), 6.53-6.55 (m, 1H), 6.66-6.70 (m, 2H), 6.83-6.90 (m, 2H), 7.13-7.14 (m, 2H), 7.30-7.32 (m, 1H), 7.35-7.38 (m, 2H), 7.41-7.42 (m, 2H).

Reference Example 368

Preparation of 4-(1-4-(tetrahydropyran-2-yloxy)phenyl)piperidin-4-ylmethyl)phenol

Ethanol (20 ml) and ethyl acetate (10 ml) were added to 4-[4-(benzyloxy)benzylidene]-1-(4-(tetrahydro-2H-pyran-2-yloxy)phenyl)piperidine prepared in Reference Example 366. A palladium on carbon (0.378 g) was added to the mixture, and stirred at 50°C for 4 hours under a hydrogen atmosphere. The insoluble matter was removed by filtration, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 6:1-4:1) to afford the title compound as a colorless amorphous compound (1.10 g).

Reference Example 369

Preparation of 1-[4-(tetrahydropyran-2-yloxy)phenyl]-4-[4-(4-trifluoromethoxyphenoxy)benzyl]piperidine

4-(1-[4-(Tetrahydro-2H-pyran-2-yloxy)phenyl]piperidin-4-yl)methyl)phenol (1.10 g, 3.0 mmol), cesium carbonate (0.977 g, 3.0 mmol), N-methylpyrrolidinone (5 ml), 1-bromo-4-(trifluoromethoxy)benzene (0.723 g, 2.99 mmol) and dipivaloylmethane (0.3 g, 1.5 mmol) were mixed, and the atmosphere was replaced with nitrogen. Copper chloride (0.030 g, 0.3 mmol) was added thereto and stirred at 120°C for 24 hours. An ammonium chloride aqueous solution was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 75:25) to afford the title compound as a colorless powder (0.84 g, 53%).
TLC: Rf = 0.2 (hexane:ethyl acetate = 4:1)

Reference Example 370
Preparation of 6-(tetrahydrofuran-2-yl)oxy)-2-(4-
trifluoromethoxybenzyloxy)-quinoline

To a solution of (4-(trifluoromethoxy)phenyl)methanol
(1.65 ml, 11.4 mmol) in DMF (40 ml) was added 604 sodium hydride
(0.46 g, 11.4 mmol) at 0°C and further stirred for 20 minutes.
While stirring the resulting mixture under ice cooling, 2-chloro-
6-(tetrahydrofuran-2-yl)oxy)-quinoline (3.0 g, 11.4 mmol) was
added thereto and warmed to room temperature, followed by further
stirring for 5 hours. A saturated ammonium chloride aqueous
solution was added to the reaction mixture, followed by
extraction with ethyl acetate. The organic layer was washed with
a saturated sodium chloride aqueous solution and then dried over
sodium sulfate. After filtering, the filtrate was concentrated
under reduced pressure. The residue thus obtained was purified by
silica gel column chromatography (hexane:ethyl acetate = 80:20).
The resulting crude crystal was washed with hexane-diethyl ether
to afford the title compound as a white powder (3.84 g, yield
81%).

1H NMR (CDCl3) δ 1.65-1.94 (m, 6H), 3.45-3.58 (m, 1H), 3.86-3.94
(m, 1H), 5.51 (s, 2H), 5.51-5.53 (m, 1H), 6.92 (d, J = 9.0 Hz,
1H), 7.22 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 3.0 Hz, 1H), 7.39 (dd,
J = 9.0, 3.0 Hz, 1H), 7.55 (d, J = 8.5 Hz, 2H), 7.77 (d, J = 9.0
Hz, 1H), 7.92 (d, J = 9.0 Hz, 1H)

Reference Example 371
Preparation of 2-(4-trifluoromethoxybenzyloxy)-
quinolin-6-ol

A 1 N hydrochloric acid ethanol solution (40 ml) was
added to an ethanol (10 ml) solution of 6-(Tetrahydro-2H-pyran-2-
yloxy)-2-[4-(trifluoromethoxy)benzyloxy]quinoline (3.5 g, 8.3
mmol) and then stirred at room temperature for 2 hours. A
saturated sodium hydrogen carbonate aqueous solution was added to
the reaction mixture, followed by extraction with ethyl acetate.
The organic layer was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. After filtering, the filtrate was concentrated under reduced pressure, and the resulting crude crystal was washed with hexane-diethylether to afford the title compound as a white powder (2.52 g, yield 90%).

Reference Example 372
Preparation of 4-benzylxoy-1-bromo-2-fluorobenzene
The title compound was prepared in the same manner as in Example 363 using suitable starting materials.

Reference Example 373
Preparation of 1-(4-benzylxoy-2-fluoro-phenyl)-4-(4-trifluoromethoxyphenoxy)piperidine
4-Benzylxoy-1-bromo-2-fluorobenzene (3.55 g, 12.6 mmol), 4-(4-trifluoromethoxyphenoxy)piperidine (3.0 g, 11.5 mmol), sodium tert-butoxide (1.55 g, 16.1 mmol) and toluene (60 ml) were mixed. Palladium acetate (0.10 g, 0.46 mmol) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.57 g, 0.92 mmol) were added thereto. The mixture was heated and refluxed under a nitrogen atmosphere for 4 hours. A saturated ammonium chloride aqueous solution was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. After filtering, the filtrate was concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 80:20–60:40), and the resulting crude crystal was washed with hexane-diethylether to afford the title compound as a white powder (3.76 g, yield 71%).
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**Reference Example 374**

Preparation of **4-[(4-benzyl oxy-2-hydroxy-2-methylbutoxy)phenyl]piperazine-1-carboxylic acid tert-butyl ester**

2-[2-(Benzyl oxy)ethyl]-2-methyloxirane (2.60 g, 13.5 mmol), 4-(4-hydroxyphenyl)piperazine-1-carboxylic acid tert-butyl ester (4.14 g, 14.9 mmol), tripotassium phosphate (1.15 g, 5.4 mmol) and ethanol (26 ml) were mixed and stirred at 80 to 90°C overnight. The reaction mixture was poured into water, followed by extraction with ethyl acetate. The organic layer was washed with a saturated sodium chloride aqueous solution, dried over sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0-30:70) to afford the title compound as a pale yellow oil (6.16 g).

**Mass:** [M]" = 470.

**Reference Example 375**

Preparation of **4-[4-(2,4-dihydroxy-2-methylbutoxy)phenyl]piperazine-1-carboxylic acid tert-butyl ester**

4-[4-(4-Benzyl oxy-2-hydroxy-2-methylbutoxy)phenyl]piperazine-1-carboxylic acid tert-butyl ester (6.16 g, 13.1 mmol), palladium hydroxide on carbon (0.62 g) and ethanol (62 ml) were mixed and stirred at 50 to 60°C under a hydrogen atmosphere for 9 hours. The mixture was filtered through Celite to remove the catalyst, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0-0:100) to afford the title compound as a colorless powder (3.75 g).

**Mass:** [M]" = 380.
Reference Example 376

Preparation of 4-((4-[2-hydroxy-2-methyl-4-(toluene-4-sulfonyloxy)butoxy]phenyl)piperazine-1-carboxylic acid tert-butyl ester

4-[(4-[2,4-Dihydroxy-2-methylbutoxy]phenyl)piperazine-1-carboxylic acid tert-butyl ester (3.75 g, 9.9 mmol), tosyl chloride (2.07 g, 10.8 mmol), dichloromethane (38 ml) and triethylamine (2.75 ml, 19.7 mmol) were mixed and ice-cooled. 1,1,3,3,-Tetramethylpropanediamine (0.16 ml, 1.0 mmol) was added thereto and stirred at room temperature overnight. The reaction mixture was washed with a saturated sodium chloride aqueous solution and dried over magnesium sulfate. The organic layer was concentrated, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0-40:60) to afford the title compound as a colorless oil (4.69 g, 89%).
Mass: [M]+ = 534.

Reference Example 377

Preparation of 4'-(tetrahydropyran-2-yloxy)biphenyl-4-carbaldehyde

2-(4-Bromophenoxy)tetrahydropyran (3.0 g) was dissolved in N,N-dimethylformamide (30 ml). 4-Formylphenylboronic acid (2.1 g), tetrakis(triphenylphosphine)palladium(0) (1.35 g) and tripotassium phosphate (4.95 g) were added thereto, and the resulting mixture was heated at 90 to 100°C under a nitrogen atmosphere for 3 hours. After completion of the reaction, ethyl acetate was added to the reaction mixture and filtered through Celite. The filtrate was separated into layers. The organic layer was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0-50:50) to afford the title compound as a white powder (1.49 g).

Reference Example 378
Preparation of (R)-4-(4-benzylxoyphenyl)-3-methylpiperazine-1-carboxylic acid tert-butyl ester

(3R)-1-tert-Butyloxycarbonyl-3-methylpiperazine (3.0 g, 15.0 mmol), 4-benzylxoybromobenzene (4.73 g, 18.0 mmol), sodium tert-butoxide (2.02 g, 21.0 mmol) and toluene (30 ml) were mixed, and the atmosphere was replaced with nitrogen. tri-tert-Butylphosphine tetrafluoroborate (0.52 g, 1.8 mmol) and palladium acetate (0.34 g, 1.5 mmol) were added thereto and heated at 90 to 100°C for 4 hours. Water and ethyl acetate were added to the brown reaction mixture, and insoluble matter was removed by filtration. The filtrate was separated into layers. The organic layer was washed with a saturated sodium chloride aqueous solution, dried over magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0-50:50) to afford the title compound as a colorless oil (5.29 g, 92%).


Reference Example 379

Preparation of (R)-4-(4-benzylxoyphenyl)-2-methylpiperazine-1-carboxylic acid benzyl ester

(R)-2-Methylpiperazine-1-carboxylic acid benzyl ester (4.42 g, 18.9 mmol), 1-benzylxoy-4-bromobenzene (5.95 g, 22.6 mmol), cesium carbonate (8.60 g, 26.4 mmol) and toluene (49 ml) were mixed, and the atmosphere was replaced with nitrogen. Palladium acetate (0.42 g, 1.9 mmol) and tri-tert-butylphosphine tetrafluoroborate (0.66 g, 2.3 mmol) were added thereto and stirred at 90 to 100°C for 2 days. Water and ethyl acetate were added to the reaction mixture, the mixture was filtered through Celite to remove insoluble matter. The filtrate was separated into layers. The organic layer was washed with a saturated sodium chloride aqueous solution, dried over magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0-70:30) to afford the title compound as a brown oil (6.18 g, 79%).
Reference Example 380

Preparation of (R)-4-(4-hydroxyphenyl)-2-methylpiperazine-1-carboxylic acid tert-butyl ester

(R)-4-(4-Benzyloxyphenyl)-2-methylpiperazine-1-carboxylic acid benzyl ester (6.18 g, 14.8 mmol), acetic acid (62 ml) and 10% palladium on carbon (0.62 g) were mixed and stirred at room temperature under the hydrogen pressure of 1 atm for 8 hours. The mixture was filtered through Celite to remove the catalyst, and the filtrate was concentrated. Methanol (62 ml), triethylamine (10 ml) and di-tert-butyl dicarbonate (3.89 g, 17.8 mmol) were added to the residue and stirred at room temperature overnight. The reaction mixture was concentrated, and water was added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with a saturated sodium chloride aqueous solution, dried over sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0-60:40) to afford the title compound as a pale brown oil (4.65 g, 100%).

Mass: [M]’ = 292.

Reference Example 381

Preparation of 1’-[4-(tetrahydropyran-2-yloxy)phenyl]-4,4’bipiperidinyl-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 362 using suitable starting materials.

1H NMR (CDCl3) δ 1.11-1.32 (m, 4H), 1.38-1.52 (m, 2H), 1.46 (s, 9H), 1.55-1.74 (m, 5H), 1.75-1.89 (m, 4H), 1.95-2.05 (m, 1H), 2.56 (d, J = 12.0, 2.0 Hz, 2H), 2.60-2.75 (m, 2H), 3.52-3.63 (m, 3H), 3.91-4.01 (m, 1H), 4.02-4.22 (m, 2H), 5.31 (d, J = 2.0 Hz, 1H), 6.86-6.90 (m, 2H), 6.94-6.98 (m, 2H).

Reference Example 382

Preparation of 1’-(4-hydroxyphenyl)-
[4,4']bipiperidinyl-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Reference Example 187 using suitable starting materials. 1H NMR (CDCl₃) δ 1.08-1.30 (m, 4H), 1.46 (s, 9H), 1.54-1.69 (m, 4H), 1.77-1.85 (m, 2H), 2.59-2.72 (m, 2H), 2.72 (t, J = 12.0, 2H), 3.53 (d, J = 12.0, 2H), 4.00-4.25 (m, 2H), 6.79 (d, J = 9.0 Hz, 2H), 7.00 (d, J = 9.0 Hz, 2H).

Reference Example 383

Preparation of 4-trifluoromethylcyclohexane carbaldehyde

After dissolving [cis-4-(trifluoromethyl)cyclohexyl]methanol (2.04 g, 10.2 mmol) in dimethylsulfoxide (30 mL), 2-iodoxybenzoic acid (4.00 g, 14.3 mmol) was added thereto and stirred at room temperature overnight. Water and ethyl acetate were added to the reaction mixture, the insoluble matter was removed by filtration, and then the filtrate was separated into layers. The organic layer was washed with water and a saturated sodium chloride aqueous solution, dried over sodium sulfate, and concentrated to afford the title compound as a colorless oil (2.3 g, 100%). 1H NMR (CDCl₃) δ 1.28-1.39 (m, 2H), 1.53-1.65 (m, 2H), 1.78-1.88 (m, 2H), 1.95-2.10 (m, 1H), 2.30 (d, J = 14.1 Hz, 2H), 2.45-2.52 (m, 1H), 9.71 (s, 1H).

Reference Example 384

Preparation of 1-(4'-benzylxobyphenyl-4-yl)-4,4'-diethoxy-piperidine

4-(Benzyloxy)-4'-bromobiphenyl (10.0 g, 29.5 mmol), 4,4-diethoxy-piperidine (5.62 g, 32.4 mmol), sodium tert-butoxide (3.97 g, 41.3 mmol) and toluene (150 mL) were mixed. Palladium acetate (0.20 g, 0.88 mmol) and tri-tert-butylphosphine tetrafluoroborate (0.39 g, 1.33 mmol) were added thereto and heated and refluxed under a nitrogen atmosphere for 2 hours. A saturated ammonium chloride aqueous solution was added to the
reaction mixture, and the precipitated crystal was collected by filtration. The obtained crude crystal was washed with acetone-hexane to afford the title compound as a white powder (10.4 g, yield 82%).

Reference Example 385

Preparation of 1-(4′-benzylxybiphenyl-4-yl)piperidin-4-one

1-(4′-Benzylxybiphenyl-4-yl)-4,4-dioxy-piperidine

(10.0 g, 23.2 mmol), acetone (100 ml) and a 5 N hydrochloric acid aqueous solution (35 ml) were mixed and heated under reflux for 5 hours. 1 N sodium hydroxide was added to the residue obtained by removing the solvent by distillation, followed by extraction with dichloromethane. The organic layer was washed with water and then dried over sodium sulfate. After filtering, the filtrate was concentrated under reduced pressure. The resulting crude crystal was washed with diethylether to afford the title compound as a white powder (7.2 g, yield 87%).

1H NMR (CDCl₃) δ 2.57 (t, J = 6.1 Hz, 4H), 3.64 (t, J = 6.1 Hz, 4H), 5.10 (s, 2H), 7.00-7.06 (m, 4H), 7.33-7.39 (m, 1H), 7.40-7.45 (m, 2H), 7.46-7.52 (m, 6H).

Reference Example 386

Preparation of 4-benzyloxy-2-methyl-1-(4-(4-[2-(4-trifluoromethoxypheny)ethyl]piperidin-1-yl)phenoxy)butan-2-ol

A tripotassium phosphate (0.44 g, 2.1 mmol) was added to a solution of 2-[2-(Benzyloxy)ethyl]-2-methyloxirane (1.00 g, 5.2 mmol) and 4-[4-(trifluoromethoxy)phenethyl]piperidin-1-yl)phenol (2.28 g, 6.2 mmol) in ethanol (10 ml), and then the mixture was heated at reflux overnight. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated sodium chloride aqueous solution, dried over sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0-50:50) to afford the title compound.
as a brown powder (2.43 g, 85%).

1H NMR (CDCl₃) δ 1.32 (s, 3H), 1.34-1.49 (m, 3H), 1.53-1.65 (m, 3H), 1.78-1.89 (m, 2H), 1.89-2.08 (m, 2H), 2.53-2.63 (m, 2H), 2.63-2.70 (m, 2H), 3.42-3.55 (m, 2H), 3.66-3.83 (m, 4H), 4.51 (s, 2H), 6.81 (d, J = 9.1 Hz, 2H), 6.90 (d, J = 9.1 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.6 Hz, 2H), 7.27-7.41 (m, 5H).

Reference Example 387

Preparation of 3-methyl-4-{4-[2-{4-(trifluoromethoxy)phenyl}ethyl]piperidin-1-yl]phenoxy}butane-1,3-diol

4-Benzylxoy-2-methyl-1-(4-{4-[4-(trifluoromethoxy)phenethyl]piperidin-1-yl]phenoxy}butan-2-ol (2.43 g, 4.5 mmol), ethanol (24 ml) and 20% palladium hydroxide on carbon (0.24 g) were mixed and stirred at 50 to 60°C under the hydrogen pressure of 1 atm for 4 hours. The mixture was filtered through Celite to remove the catalyst, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0-0:100) to afford the title compound as a colorless powder (1.68 g, 80%).

Mass: [M]' = 467.

Reference Example 388

Preparation of toluene-4-sulfonic acid 3-hydroxy-3-methyl-4-{4-[2-(4-trifluoromethoxyphenyl)ethyl]piperidin-1-yl]phenoxy}butyl ester

3-Methyl-4-{4-[2-{4-(trifluoromethoxyphenyl)ethyl]piperidin-1-yl]phenoxy}butane-1,3-diol (1.68 g, 3.6 mmol), dichloromethane (17 ml), triethylamine (1.00 ml, 7.2 mmol) and p-toluenesulfonfyl chloride (0.82 g, 4.3 mmol) were mixed and ice-cooled. 1,1,3,3,-Tetramethylpropanediamine (0.12 ml, 0.7 mmol) was added thereto and stirred at room temperature for 1 hour. The reaction mixture was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. The organic layer was concentrated,
and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 100:0-50:50) to afford the title compound as a colorless powder (2.03 g, 91%).
Mass:[M]+ = 621.

Reference Example 389
Preparation of 4-[(3-(3-
trifluoromethylphenoxyl)propyl]piperidine-1-carboxylic acid tert-
butyl ester

4-(3-Hydroxypropyl]piperidine-1-carboxylic acid tert-
butyl ester (15.0 g, 61.6 mmol), 3-trifluoromethylphenol (19.4 g, 64.7 mmol), triphenylphosphine (1.40 g, 73.9 mmol) and tetrahydrofuran (200 ml) were mixed. While stirring the mixture at room temperature, DEAD (21.1 ml, 80.0 mmol) was added thereto dropwise and heated at reflux for 2 days. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. After filtering, the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane:ethyl acetate = 87:13) to afford the title compound as a pale yellow oil (20.5 g, yield 86%).

1H NMR (CDCl3) δ 1.05-1.21 (m, 2H), 1.40-1.57 (m, 3H), 1.46 (s, 9H), 1.65-1.76 (m, 2H), 1.81-1.89 (m, 2H), 2.65-2.80 (m, 2H),
3.98 (t, J = 6.4, 2H), 3.94-4.24 (m, 2H), 7.04 (dd, J = 8.3, 2.4 Hz, 1H), 7.11 (d, J = 2.4, 1H), 7.19 (d, J = 7.7, 1H), 7.38 (ddd, J = 8.3, 7.7, 2.4, 2H).

Reference Example 390
Preparation of 1-[(4'-benzylxoybiphenyl-4-y1)-4-
trifluoromethylpiperidin-4-ol

1-(4'-Benzylxoybiphenyl-4-y1)piperidin-4-one (7.1 g, 19.9 mmol), tetrabutylammonium acetate (0.3 g, 1.0 mmol) and 1,2-
dimethoxyethane (100 ml) were mixed. While stirring the mixture under ice cooling, trifluoromethyltrimethylsilane (4.11 ml, 27.8
mmol) was added to the mixture and warmed to room temperature, followed by stirring for 6 hours. The residue obtained by distilling off the solvent was dissolved in tetrahydrofuran (100 ml). While stirring at room temperature, 1 mol/l 5 tetrabutylammonium fluoride in tetrahydrofuran (23.8 ml, 23.8 mmol) was added thereto and stirred at room temperature overnight. Water was added to the residue obtained by distilling off the solvent, followed by extraction with dichloromethane. The organic layer was washed with water and dried over sodium sulfate. After filtering, the filtrate was concentrated under reduced pressure. The resulting crude crystal was washed with diethyl ether to afford the title compound as a white powder (7.6 g, yield 90%).

1H NMR (CDCl₃) δ 1.83 (dd, J = 14.0, 2.4 Hz, 2H), 2.08 (dt, J = 13.5, 4.5 Hz, 2H), 3.11 (dd, J = 12.6, 2.4 Hz, 2H), 3.60-3.66 (m, 2H), 5.10 (s, 2H), 6.99-7.05 (m, 4H), 7.34-7.39 (m, 3H), 7.40-7.45 (m, 2H), 7.47-7.54 (m, 6H).

Reference Example 391
Preparation of 4-[3-(3-
trifluoromethylphenoxy)propyl]piperidine
The title compound was prepared in the same manner as in Reference Example 354 using suitable starting materials.

1H NMR (CDCl₃) δ 1.42-1.63 (m, 5H), 1.80-1.90 (m, 4H), 2.75-2.83 (m, 2H), 3.24-3.33 (m, 2H), 3.98 (t, J = 6.3, 2H), 7.04 (dd, J = 8.2, 2.3 Hz, 1H), 7.10 (d, J = 2.3, 1H), 7.19 (d, J = 7.7, 1H), 7.39 (ddd, J = 6.2, 2.7, 2.3, 1H).

Reference Example 392
Preparation of 1-[4-(tetrahydroxyran-2-yl)oxy]phenyl]-4-
[3-(3-trifluoromethylphenoxy)propyl]piperidine
The title compound was prepared in the same manner as in Reference Example 362 using suitable starting materials.

1H NMR (CDCl₃) δ 1.37-1.55 (m, 5H), 1.60-1.75 (m, 3H), 1.83-1.90 (m, 6H), 1.95-2.08 (m, 1H), 2.63 (t, J = 10.0, 2H), 3.55-3.65 (m, 3H), 3.91-3.98 (m, 1H), 4.00 (t, J = 6.5, 2H), 5.31 (t, J = 2.0,
-165-

1H), 6.07-6.92 (m, 2H), 6.96-6.99 (m, 2H), 7.06 (d, J = 8.3, 2.4 Hz, 1H), 7.13 (d, J = 2.4, 1H), 7.20 (d, J = 7.7, 1H), 7.38 (d, J = 8.3, 7.7, 2.4, 1H).

5 Reference Example 393
Preparation of 1-[(4-tetrahydroxy-2-ylloxy)phenyl]-4-(4-trifluoromethylsulfanylphenoxy)piperidine

The title compound was prepared in the same manner as in Reference Example 379 using suitable starting materials.

Mass: [M]⁺ = 453.

Reference Example 394
Preparation of cis-(4-trifluoromethylcyclohexyl)methanol

cis-4-(Trifluoromethyl)cyclohexanecarboxylic acid (1.05 g, 5.4 mmol) and tetrahydrofuran (20 ml) were mixed and ica-cooled. A borane-tetrahydrofuran complex (10.71 ml, 10.7 mmol) was added to the mixture dropwise. After the completion of dropwise addition, the reaction mixture was stirred at room temperature overnight. 1 N hydrochloric acid was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with water and a saturated sodium chloride aqueous solution, dried over sodium sulfate, and concentrated to afford the title compound as a colorless oil

(0.92 g, 94%).

1H NMR (CDCl₃) δ 1.32 (t, J = 4.7 Hz, 1H), 1.48-1.62 (m, 4H), 1.64-1.74 (m, 4H), 1.76-1.82 (m, 1H), 2.05-2.17 (m, 1H), 3.62 (d, J = 4.5 Hz, 7.1 Hz, 2H).

30 Reference Example 395
Preparation of 1-(4-benzylxyloxyphenyl)-4-(4-trifluoromethylphenyl)piperidin-4-ol

Isopropylmagnesium chloride (2M tetrahydrofuran solution) (11.73 ml) was added to a tetrahydrofuran solution (20 ml) of 4-iodobenzotrifluoride (3.45 ml, 23.5 mmol) dropwise at
The mixture was stirred at the same temperature for 5 minutes and further stirred at room temperature for 2 hours. After cooling the mixture to -10°C, a tetrahydrofuran solution (40 ml) of 1-(4-benzylxoyphenyl)piperidin-4-one (6 g, 21.3 mmol) was added thereto dropwise. While gradually returning to room temperature, the mixture was stirred. After 10 hours, a saturated ammonium chloride aqueous solution/ice water was poured into the mixture, followed by extraction with ethyl acetate. The result was washed with water and a saturated sodium chloride aqueous solution and dried over sodium sulfate. After removing the desiccant by filtration, the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 75:25-66:34). The resultant was washed with a mixed solvent of isopropyl ether and hexane and filtered to afford the title compound as a white powder (6.69 g, 73%).

1H NMR (CDCl3) 5 = 1.65 (s, 1H), 1.82-1.88 (m, 2H), 2.31 (dt, J = 4.6 Hz, 13.3 Hz, 2H), 3.14 (dt, J = 2.5 Hz, 12.3 Hz, 2H), 3.40-3.47 (m, 2H), 5.03 (s, 2H), 6.92-6.96 (m, 2H), 6.96-7.01 (m, 2H), 7.30-7.35 (m, 1H), 7.36-7.41 (m, 2H), 7.42-7.45 (m, 2H), 7.63 (d, J = 8.6 Hz, 2H), 7.67 (d, J = 8.6 Hz, 2H).

Reference Example 396

Preparation of 1-(4-benzylxoyphenyl)-4-methoxy-4-(4-trifluoromethylphenyl)piperidine

60% sodium hydride (0.225 g, 5.2 mmol) was added to an N,N-dimethylformamide solution (20 ml) of 1-(4-benzylxoyphenyl)-4-(4-trifluoromethylphenyl)piperidin-4-ol (2 g, 4.7 mmol) and iodomethane (0.585 ml, 9.4 mmol) under an argon atmosphere while ice cooling, followed by stirring at the same temperature. After 2 hours, the mixture was poured into ice water, and the precipitate was collected by filtration. The resulting solid was dissolved in ethyl acetate/dichloromethane and dried over sodium sulfate. After removing the desiccant by filtration, the solvent was distilled off. The residue was purified by silica gel column.
chromatography (dichloromethane:ethyl acetate = 100:0-95:5) to afford the title compound as a white powder (1.64 g, 79%).

1H NMR (CDCl₃) δ = 2.10-2.18 (m, 4H), 3.02 (s, 3H), 3.05-3.15 (m, 2H), 3.35-3.43 (m, 2H), 5.03 (s, 2H), 6.91-6.94 (m, 2H), 6.94-6.98 (m, 2H), 7.29-7.34 (m, 1H), 7.36-7.41 (m, 2H), 7.42-7.45 (m, 2H), 7.56 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H).

Reference Example 397
Preparation of 2-methyl-2-[4-(4-

trifluoromethylbenzyl)oxy]phenyl]propionic acid

Iodomethane (4.63 ml, 74.0 mmol) was added to an N,N-
dimethylformamide solution (80 ml) of [4-(4-

trifluoromethylbenzyl)oxy]phenyl]acetic acid methyl ester (8 g, 24.7 mmol) under an argon atmosphere. Subsequently, sodium hydride (2.37 g, 54.3 mmol) was gradually added thereto under ice cooling. After stirring at the same temperature for 30 minutes, the mixture was further stirred at room temperature. After 2 hours, iodomethane (3.09 ml, 49.3 mmol) was added thereto, and sodium hydride (1.08 g, 24.7 mmol) was further added 1 hour later.

Thereafter, the mixture was stirred at room temperature overnight. Because a monomethylated compound still remained, the mixture was ice-cooled again. Sodium hydride (1.08 g, 24.7 mmol) was added thereto and stirred for 5 minutes. Iodomethane (3.09 ml, 49.3 mmol) was added to the mixture and stirred at room temperature.

The reaction mixture was poured into a mixture of ice water (500 ml) and acetic acid (6 ml), followed by stirring. Ethyl acetate was added thereto, and the mixture was neutralized with a saturated sodium hydrogen carbonate aqueous solution, followed by extraction with ethyl acetate. The result was washed with water and a saturated sodium chloride aqueous solution and dried over sodium sulfate. After distilling the solvent off, the residue was dissolved in an N,N-dimethylformamide solution (80 ml) again. Sodium hydride (1.08 g, 24.7 mmol) was added to the result under an argon atmosphere while ice cooling, followed by stirring at the same temperature for 30 minutes. Thereafter, iodomethane
(3.09 ml, 49.3 mmol) was added to the mixture and stirred while returning the mixture to room temperature. After 10 hours, the reaction mixture was poured into ice water/acetic acid (1.5 ml) and stirred for a while, and the precipitate was collected by filtration. The resulting solid was dissolved in ethyl acetate and dried over sodium sulfate. The solvent was then distilled off.

Because a monomethylated compound still remained, the mixture was dissolved in an N,N-dimethylformamide (80 ml) again, and sodium hydride (1.08 g, 24.7 mmol) was added thereto under an argon atmosphere while ice cooling. The mixture was stirred at the same temperature for 30 minutes, iodomethane (3.09 ml, 49.3 mmol) was added thereto and stirred while returning the mixture to room temperature. After 9 hours, the mixture was poured into ice water/acetic acid (1.5 ml) and stirred for a while. The precipitate was collected by filtration, and the resulting solid was dissolved in ethyl acetate and dried over sodium sulfate. Thereafter, the solvent was distilled off.

Because a monomethylated compound still remained, the mixture was dissolved in an N,N-dimethylformamide (80 ml) again, and sodium hydride (1.08 g, 24.7 mmol) was added thereto under an argon atmosphere while ice cooling. After stirring at the same temperature for 30 minutes, iodomethane (3.09 ml, 49.3 mmol) was added thereto and stirred while returning the mixture to room temperature. After 10 hours, the mixture was poured into ice water/acetic acid (1.5 ml) and the resulting mixture was stirred for a while. Thereafter, the precipitate was collected by filtration. The resulting solid was dissolved in ethyl acetate and dried over sodium sulfate. The solvent was then distilled off.

The resultant was dissolved in methanol (80 ml), and 5 N sodium hydroxide (25 ml) was added thereto and stirred under reflux. After 2 hours, the mixture was returned to room temperature, and the solvent was distilled off. The residue was dissolved in water and washed with hexane. The pH value of the water layer was adjusted to 1 to 2 using a concentrated hydrochloric acid under ice cooling, and the precipitate was
collected by filtration. The solid thus obtained was dissolved in ethyl acetate and dried over sodium sulfate. After removing the desiccant by filtration, the solvent was distilled off to afford the title compound as a white powder (7.03 g, 84%).

1H NMR (CDCl₃) δ = 1.59 (s, 6H), 5.11 (s, 2H), 6.91-6.95 (m, 2H), 7.32-7.36 (m, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.1 Hz, 2H).

Reference Example 398

Preparation of 1-{2-isocyanatopropan-2-yl}-4-{4-(trifluoromethyl)benzyl}oxybenzene

Triethylamine (2.90 ml, 20.8 mmol) and diphenylphosphorylazide (4.48 ml, 20.8 mmol) were added to a 1,4-dioxane solution (70 ml) of 2-methyl-2-{4-(trifluoromethyl)benzyl}oxyphenyl]propionic acid (7.03 g, 10.8 mmol) and heated at reflux. After 2 hours, the solvent was distilled off, and diethyl ether and water were added to the residue, followed by extraction with diethyl ether. The result was washed with water and a saturated sodium chloride aqueous solution and dried over sodium sulfate. After removing the desiccant by filtration, the solvent was distilled off to afford the title compound as a pale brown oil (6.89 g, 98%).

1H NMR (CDCl₃) δ = 1.70 (s, 6H), 5.13 (s, 2H), 6.90-6.96 (m, 2H), 7.33-7.39 (m, 2H), 7.55 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 8.1 Hz, 2H).

Reference Example 399

Preparation of 1-methyl-1-{4-{4-(trifluoromethyl)benzyl}oxyphenyl}ethyamine

Concentrated hydrochloric acid (18 ml) was added to an acetic acid solution (24 ml) of 1-{2-isocyanatopropan-2-yl}-4-{4-(trifluoromethyl)benzyl}oxybenzene (4.35 g, 13.0 mmol) and stirred at room temperature. After 2.5 hours, the mixture was heated to 80°C and stirred for 1 hour. The solvent was then distilled off. Ice and a 5 N sodium hydroxide aqueous solution
were sequentially added to the residue and stirred, followed by
extraction with ethyl acetate. The resultant was washed with a
saturated sodium chloride aqueous solution and dried over sodium
sulfate. After removing the desiccant by filtration, the solvent
was distilled off to afford the title compound as a brown solid
(3.3 g, 82%).
1H NMR (CDCl₃) δ = 1.48 (s, 6H), 1.76 (brs, 2H), 5.12 (s, 2H),
6.90-6.94 (m, 2H), 7.41-7.46 (m, 2H), 7.55 (d, J = 8.0 Hz, 2H),
7.64 (d, J = 8.0 Hz, 2H).

Reference Example 400
Preparation of 1-{1-methyl-1-[4-(4-
trifluoromethylbenzyloxy)phenyl]ethyl}-4-(toluene-4-
sulfonyl)piperazine

N,N-bis-2-{Chloro-ethyl}-4-methylbenzenesulfonamide
(4.74 g, 16.0 mmol) was added to a disopropylethylamine
suspension (40 ml) of 1-methyl-1-[4-(4-
trifluoromethylbenzyloxy)phenyl]ethylamine (3.3 g, 10.7 mmol) and
stirred at 130°C. After 24 hours, heating was stopped. The
solvent was distilled off, and a dilute sodium hydroxide aqueous
solution was added to the residue, followed by extraction with
ethyl acetate. The result was washed with water and a saturated
sodium chloride aqueous solution and dried over sodium sulfate
(30 g of silica gel was added at the same time). After removing
the desiccant and silica gel by filtration, the solvent was
distilled off. The residue was purified by silica gel column
chromatography (hexane:ethyl acetate = 90:10-85:15-80:20) to
afford the title compound as a white solid (2.67 g, 47%).
1H NMR (CDCl₃) δ = 1.29 (s, 6H), 2.45 (s, 2H), 2.54 (t, J = 4.7 Hz,
4H), 2.87-3.02 (m, 4H), 6.82-6.87 (m, 2H), 7.30-7.36 (m, 4H),
7.54 (d, J = 8.1 Hz, 2H), 7.60-7.66 (m, 4H).

Reference Example 401
Preparation of 1-{1-methyl-1-[4-(4-
trifluoromethylbenzyloxy)phenyl]ethyl)piperazine
Magnesium (1.83 g, 75.0 mmol) was added to a methanol solution (50 ml) of 1-[(1-methyl-1-[4-(4-trifluoromethylbenzyloxy)phenyl]ethyl)-4-(toluene-4-sulfonyl)piperazin-2-yl]phenyl)piperazine (2.67 g, 5.0 mmol) and stirred at 60°C. After 5 hours, magnesium (0.61 g, 25.1 mmol) was added thereto and further stirred. After 1 hour, heating was stopped and the solvent was distilled off. Ice and 10% hydrochloric acid (100 ml) were added to the residue and stirred. Ethyl acetate was added and further stirred. The mixture was separated into layers, and the water layer was made basic using a 25% sodium hydroxide aqueous solution. Ethyl acetate was added to the mixture, followed by stirring. The mixture was filtered through Celite to remove the insoluble matter. The filtrate was subjected to extraction with ethyl acetate. The organic layer was dried over sodium sulfate. After removing the desiccant by filtration, the solvent was distilled off to afford the title compound as a slightly yellow oil (1.05 g, 55%).

1H NMR (CDCl3) δ = 1.32 (s, 6H), 2.38-2.49 (m, 4H), 2.84 (t, J = 4.8 Hz, 4H), 5.11 (s, 2H), 6.87-6.92 (m, 2H), 7.42-7.48 (m, 2H). 7.56 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H).

Reference Example 402

Preparation of 1-[(1-methyl-1-[4-(4-trifluoromethylbenzyloxy)phenyl]ethyl)-4-[4-(tetrahydroxy-2-yloxy)phenyl)piperazine

The title compound was prepared in the same manner as in Reference Example 362 using suitable starting materials.

1H NMR (CDCl3) δ = 1.36 (s, 6H), 1.53-1.73 (m, 3H), 1.78-1.90 (m, 2H), 1.94-2.04 (m, 1H), 2.62 (t, J = 4.8 Hz, 4H), 3.05 (t, J = 4.8 Hz, 4H), 3.54-3.63 (m, 1H), 3.90-3.98 (m, 1H), 5.12 (s, 2H), 5.30 (t, J = 3.4 Hz, 1H), 6.83-6.88 (m, 2H), 6.89-6.93 (m, 2H), 6.95-6.99 (m, 2H), 7.45-7.50 (m, 2H), 7.56 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.2 Hz, 2H).

Example 1
Preparation of 2-nitro-7-(4-[4-(4-
trifluoromethoxyphenox)xy]piperidin-1-yl)phenoxy)methyl)-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

60% sodium hydride (70 mg) was added to an N,N-
dimethylformamide solution (10 ml) of 4-(2-chloro-4-
nitroimidazol-1-yl)-1-(4-[4-(4-trifluoromethoxyphenox)xy]piperidin-
1-yl)phenoxy)butan-2-ol (0.9 g) under ice cooling, and the
mixture was stirred at room temperature for 3 days. A saturated
ammonium chloride aqueous solution was added to the reaction
mixture, followed by extraction with ethyl acetate. The organic
layer was washed with a saturated sodium chloride aqueous
solution and dried over sodium sulfate. After filtering, the
filtrate was concentrated under reduced pressure. The residue
thus obtained was purified by silica gel column chromatography
(methylene chloride:ethyl acetate = 8:2-methylene chloride:ethyl
acetate = 2:8) and recrystallized from methylene chloride-ethyl
acetate-isopropyl ether to afford the title compound as a pale
yellow powder (158 mg).
Melting point: 186.8-187.8°C

Example 2

Preparation of 4-[4-(2-nitro-6,7-dihydro-5H-
imidazol-2,1-b)[1,3]oxazin-7-ylmethoxy)phenyl]piperazine-1-
carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
White powder
Melting point: 199.5-200.3°C

Example 3

Preparation of 2-nitro-7-(4-[4-(4-
trifluoromethoxybenzyl)piperazin-1-yl)phenoxy)methyl)-6,7-dihydro-
5H-imidazo[2,1-b][1,3]oxazine

Trifluoroacetic acid (6.0 ml) was added to 4-[4-(2-
nitro-6,7-dihydro-5H-imidazol-2,1-b)[1,3]oxazin-7-
ylmethoxy)phenyl)piperazine-1-carboxylic acid tert-butyl ester (200 mg), and the mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure, and methylene chloride (2.0 ml) and triethylamine (2.0 ml) were added to the residue, followed by stirring at room temperature for 5 minutes. The reaction mixture was reconcentrated under reduced pressure. 1,2-Dichloroethane (5 ml), 4-(trifluoromethoxy)benzaldehyde (124 µl) and sodium triacetoxycarbonylborohydride (185 mg) were added to the residue, and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the resulting mixture was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. After filtering, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride:methanol = 10:0-methylene chloride:methanol = 9:1) and recrystallized from methylene chloride-isopropyl ether to afford the title compound as a white powder (211 mg).

Example 4
Preparation of N-(4-chlorophenyl)-N-methyl-N-[1-(4-[2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperidin-4-yl]amine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 171.8-173.3°C

Example 5
Preparation of 2-nitro-7-(4-[4-(4-(trifluoromethyl)benzyl)oxy)methyl)piperidin-1-yl][phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 141-143°C

Example 6
Preparation of 2-nitro-7-(4-{4-[(4-
trifluoromethylphenoxymethyl)piperidin-1-yl]phenoxymethyl}-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Yellow solid
Melting point: 199.8-200.8°C

Example 7
Preparation of 7-(4-{4-[(4'-chlorobiphenyl-4-
yl)methyl]piperazin-1-yl]phenoxymethyl}-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 276.4-277.1°C

Example 8
Preparation of 2-nitro-7-(4-[(4-[(4-
trifluoromethoxyphenoxy)benzyl]piperazin-1-yl]phenoxymethyl}-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.
Pale brown powder
Melting point: 164.0-164.4°C

Example 9
Preparation of 2-nitro-7-(4-{4-[(4-
trifluoromethoxybenzyl)oxy]piperidin-1-yl]phenoxymethyl}-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

Pale yellow powder
Melting point: 189-190°C

Example 10
Preparation of N-methyl-N-(4-trifluoromethoxyphenyl)-1-[4-(2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]piperidin-4-yl)amine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

Pale yellow powder
Melting point: 188-189°C

Example 11
Preparation of 2-nitro-7-[4-[4-[4-(4-trifluoromethoxybenzyl)piperidin-1-yl]phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

White powder
Melting point: 174-175°C

Example 12
Preparation of 2-nitro-7-[4-[4-[2-(4-trifluoromethoxyphenyl)ethyl]piperidin-1-yl]phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

Pale yellow powder
Melting point: 204-205°C

Example 13
Preparation of (S)-2-nitro-7-[4-[4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxy)methyl]-6,7-
The title compound was prepared in the same manner as in Example 1 using suitable starting materials. White powder

5 Melting point: 165-166°C

Example 14

Preparation of 2-nitro-7-(4-{4-[4-(4-
trifluoromethoxybenzyl)oxy]methyl}piperidin-1-yl)phenoxymethyl)-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials. White powder

Melting point: 156-157°C

Example 15

Preparation of 2-nitro-7-{4-[4-{4-
trifluoromethoxyphenoxy]methyl}piperidin-1-yl}phenoxymethyl)-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials. Pale yellow powder

Melting point: 202-203°C

Example 16

Preparation of 7-{4-[4-(4-
chlorobenzyl)oxy]methyl}piperidin-1-yl)phenoxymethyl)-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials. Pale yellow powder

Melting point: 149-150°C

Example 17

Preparation of 7-{4-[4-(4-chlorobenzyl)oxy]piperidin-1-

yl]phenoxymethyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

White powder
Melting point: 200-201°C

Example 18
Preparation of (R)-2-nitro-7-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
White powder
Melting point: 163-164°C

Example 19
Preparation of 2-nitro-7-{4-[4-(4-trifluoromethylphenoxy)piperidin-1-yl]phenoxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 207-209°C

Example 20
Preparation of 7-{4-[4-(4-chlorophenoxy)piperidin-1-yl]phenoxymethyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 183-185°C

Example 21
Preparation of 2-nitro-7-{4-[4-(4-
-178-
trifluoromethoxyphenyl)piperidin-1-yl]phenoxy)methyl]-6,7-dihydro-
SH-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

5 Pale yellow powder
Melting point: 214-216°C

Example 22
Preparation of N-methyl-N-[4-(4-(3-
6 SH-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperidin-4-yl]-
N-(4-trifluoromethylphenyl)amine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 208-209°C

Example 23
Preparation of 2-nitro-7-(4-[4-(3-
8 trifluoromethylphenoxy)piperidin-1-yl]phenoxy)methyl]-6,7-dihydro-
5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 189-190°C

Example 24
Preparation of 7-(4-[4-(3,5-bis-
10 trifluoromethylphenoxy)piperidin-1-yl]phenoxy)methyl]-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 199-200°C

Example 25
Preparation of 2-nitro-7-\{4-[4-(4-trifluoromethoxybenzyl)benzyl]piperazin-1-yl|phenoxymethyl\}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Pale yellow powder
Melting point: 213.9-214.0°C

Example 26

Preparation of 2-nitro-7-(4-{1-(4-trifluoromethoxyphenyl)piperidin-4-yl|phenoxymethyl}]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

White powder
Melting point: 200-201°C

Example 27

Preparation of 2-nitro-7-(4-{1-(4-trifluoromethyl)phenyl)piperidin-4-yl|phenoxymethyl}]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

White powder
Melting point: 219-221°C

Example 28

Preparation of 2-nitro-7-(4-{4-[4-(4-trifluoromethyl)benzyl]benzyl)piperazin-1-yl|phenoxymethyl}]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Pale yellow powder
Melting point: 213.3-214.4°C
Example 29
Preparation of 4-[(4-(2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperidine-1-carboxylic acid tert-butyl ester
The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 182-183°C

Example 30
Preparation of 2-nitro-7-[(4-[(4-(4-trifluoromethyl)benzyl)piperidin-1-yl]phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
White powder
Melting point: 179-180°C

Example 31
Preparation of 7-[(4-[(4-(4-chlorobenzyl)piperidin-1-yl]phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 175-176°C

Example 32
Preparation of 7-[(4-[(4-(4-(4-chlorobenzyl)benzyl)piperazin-1-yl]phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 205.7-206.2°C
Example 33

Preparation of N-(4-chlorophenyl)-N-ethyl-N-{1-[4-(2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]piperidin-4-yl}amine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 195.2°C

Example 34

Preparation of N-ethyl-N-{1-[4-(2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]piperidin-4-yl}-N-(4-trifluoromethylphenyl)amine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 206.2°C

Example 35

Preparation of N-ethyl-N-{1-[4-(2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]piperidin-4-yl}-N-(4-trifluoromethoxyphenyl)amine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 184.8-185.3°C

Example 36

Preparation of 2-nitro-7-(4-[4-(4'-trifluoromethoxybiphenyl-4-ylmethyl)piperazin-1-yl]phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 236.0-236.8°C
Example 37
Preparation of 2-nitro-7-(4-(4-(4-(trifluoromethoxybenzyl)oxy)benzyl)piperazin-1-yl)phenoxyethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 196.3-196.8°C

Example 38
Preparation of 2-nitro-7-(4-(4-[4-(4-trifluoromethylbenzyl)oxy]benzyl)piperazin-1-yl)phenoxyethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 205.2-205.4°C

Example 39
Preparation of 2-nitro-7-(4-(4-[3-(4-trifluoromethylphenyl)propyl)piperazin-1-yl)phenoxyethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 172.5-173.2°C

Example 40
Preparation of 2-nitro-7-(4-[4-[[3-(4-trifluoromethoxyphenyl)allyl]piperazin-1-yl)phenoxyethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 203.6-204.3°C

Example 41
Preparation of 7-(4-(4-[4-(4-chlorobenzoxyl)benzyl]piperazin-1-yl)phenoxy)methyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 231.3-232.2°C

Example 42
Preparation of 2-nitro-7-(4-(4-[4-(4-trifluoromethyl)phenyl]propyl)[1,4]diazepan-1-yl)phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 157.8-158.0°C

Example 43
Preparation of 2-nitro-7-(4-(4-[2-(4-trifluoromethoxy)phenoxy]ethyl)piperidin-1-yl)phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
White powder
Melting point: 167-168°C

Example 44
Preparation of 2-nitro-7-(4-(4-[3-(4-trifluoromethoxy)phenoxy]propyl)piperidin-1-yl)phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
White powder
Melting point: 180-181°C

Example 45
Preparation of 4-(4-(2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperazin-1-ylmethyl)piperidine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Pale yellow powder
Melting point: 217.5-217.8°C

Example 46
Preparation of 4-(4-(2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)-(1,4)diazepane-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

Pale yellow powder
Melting point: 176.7-177.1°C

Example 47
Preparation of 2-nitro-7-(4-[2-(4-trifluoromethoxy)phenyl]oxazol-4-yl)phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

Pale yellow powder
Melting point: 238-239°C

Example 48
Preparation of 2-nitro-7-(4-(4-[3-(4-trifluoromethoxy)phenyl]propyl)piperidin-1-yl)phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
White powder
Melting point: 172-174°C

Example 49
Preparation of 1-(4-(2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)-4-trifluoromethylpiperidin-4-ol
The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
White powder
Melting point: 209-211°C

Example 50
Preparation of 2-nitro-7-(4-(4-[1-(4-trifluoromethylbenzyl)piperidin-4-ylmethyl)piperazin-1-yl)phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
Trifluoroacetic acid (1.5 ml) was added to a methylene chloride solution (1.5 ml) of 4-[4-[4-(2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperazin-1-ylmethyl)piperidine-1-carboxylic acid tert-butyl ester (300 mg), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, methylene chloride (1.5 ml) and triethylamine (1.5 ml) were added to the residue, and the result was stirred at room temperature for 5 minutes. After concentrating the reaction mixture under reduced pressure, methanol (3 ml), 4-(trifluoromethyl)benzaldehyde (130 mg), sodium cyanoborohydride (160 mg) and acetic acid (1 ml) were added to the residue in this order, and the mixture was stirred at room temperature overnight. The resulting reaction mixture was added to a potassium carbonate aqueous solution, followed by extraction with methylene chloride. The organic layer was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. After filtering, the filtrate was concentrated under reduced pressure, the residue
was purified by silica gel column chromatography (methylene chloride:methanol = 1:0-methylene chloride:methanol = 9:1) and recrystallized from methanol to afford the title compound as a pale yellow powder (50 mg).

Melting point: 214.3-217.2°C

Example 51

Preparation of 7-(4-(4-[1-(4-chlorobenzyl)piperidin-4-ylmethyl]piperazin-1-yl)phenoxy)methyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 50 using suitable starting materials.
Pale yellow powder
Melting point: 211.1-213.2°C

Example 52

Preparation of 2-nitro-7-(4-(4-[1-(4-trifluoromethoxybenzyl)piperidin-4-ylmethyl]piperazin-1-yl)phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 50 using suitable starting materials.
Pale yellow powder
Melting point: 207.6°C

Example 53

Preparation of 2-nitro-7-(4-[2-(4-trifluoromethoxyphenoxy)methyl]oxazol-4-yl)phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 171-172°C

Example 54

Preparation of 2-nitro-7-(4-(4-[6-(4-
-187-

trifluoromethoxyphenoxy)pyridin-3-ylmethyl)piperazin-1-yl)phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Pale yellow powder
Melting point: 190.7°C

Example 55
Preparation of 2-nitro-7-[(4-[2-(4-

trifluoromethoxyphenoxy)methyl]thiazol-4-yl)phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 219-220°C

Example 56
Preparation of 2-nitro-7-[(4-[2-(4-

trifluoromethoxyphenyl]thiazol-4-yl)phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Slightly yellow powder
Melting point: 235-236°C

Example 57
Preparation of 2-nitro-7-[(4-[2-(5-

trifluoromethylpyridin-2-yl)oxy)ethyl)piperidin-1-yl)phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
White powder
Melting point: 156-158°C

Example 58
Preparation of 2-nitro-7-[4-{4-(5-
trifluoromethyl)pyridin-2-yl氧methyl)piperidin-1-yl]
phenoxy methyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 206-207°C

Example 59
Preparation of 7-[4-{4-methoxy-4-
trifluoromethyl)piperidin-1-yl]phenoxy methyl}-2-nitro-6,7-dihydro-
5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
White powder
Melting point: 167-168°C

Example 60
Preparation of 2-nitro-7-[4-{4-(4-
trifluoromethoxyphenyl)oxazol-2-yl)methyl]phenoxy methyl}-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 87-89°C

Example 61
Preparation of 2-nitro-7-[4-{4-(5-
trifluoromethyl)pyridin-2-yl oxy)piperidin-1-yl]phenoxy methyl}-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
White powder
Melting point: 186-187°C
Example 62

Preparation of 2-nitro-7-{4-{4-[6-(4-trifluoromethylphenoxy)pyridin-3-ylmethyl]piperazin-1-yl}phenoxy)methyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder
Melting point: 197.5-197.9°C

Example 63

Preparation of 7-{4-{4-[6-(4-chlorophenoxy)pyridin-3-ylmethyl]piperazin-1-yl}phenoxy)methyl}-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder
Melting point: 199.1-200.6°C

Example 64

Preparation of 2-nitro-7-[4-(4-{3-[4-{4-(trifluoromethoxy)phenoxy]phenyl}propyl]piperazin-1-yl}phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Pale yellow powder
Melting point: 140.6-142.4°C

Example 65

Preparation of 2-nitro-7-{6-[4-{4-{4-(trifluoromethoxy)benzyl}piperazin-1-yl}pyridin-3-yloxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder
Melting point: 167.0-167.1°C
Example 66
Preparation of 2-nitro-7-{6-[6-{4-[4-
trifluoromethoxyphenoxy]pyridin-3-ylmethyl}piperazin-1-
yl}pyridin-3-yloxy)methyl]-6,7-dihydro-5H-imidazo[2,1-
b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.
White powder
Melting point: 186.0-186.1°C

Example 67
Preparation of 2-nitro-7-{4-{4-[2-{4-
trifluoromethylbenzoyloxy]ethyl}piperazin-1-yl}phenoxy)methyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 156.0-158.2°C

Example 68
Preparation of 4-{5-(2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)pyridin-2-yl}piperazine-1-
carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 205.4-205.7°C

Example 69
Preparation of 2-nitro-7-{4-[2-{4-
trifluoromethoxybenzyl}thiazol-4-yl]phenoxy)methyl]-6,7-dihydro-
5H-imidazo[2,1-b][1,3]oxazine

Sodium tert-butoxide (62 mg) was added to a dimethyl
formaldehyde solution (5 ml) of 4-{2-chloro-4-nitroimidazol-1-
yl)-1-(4-[2-(4-trifluoromethoxybenzyl)thiazol-4-yl]phenoxy)butan-2-ol (334 mg), and the mixture was stirred at room temperature. While confirming the progress of the reaction, sodium tert-butoxide (62 mg) was added 3 times, and the resulting mixture was stirred overnight. A saturated ammonium chloride aqueous solution was added to the reaction mixture, and the precipitated solid was sequentially washed with water and diisopropyl ether. The residue was purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:1-ethyl acetate) to afford the title compound as a pale brown powder (69 mg).

Melting point: 222-224°C

Example 70
Preparation of 2-nitro-7-{6-[4-(4-
trifluoromethoxyphenoxy)piperidin-1-yl]pyridin-3-yloxyethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.

White powder

Melting point: 181-182°C

Example 71
Preparation of 2-nitro-7-{4-(4-[3-{5-
trifluoromethyl]pyridin-2-yl}propyl)piperazin-1-yl}phenoxyethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Pale yellow powder

Melting point: 173.3-173.4°C

Example 72
Preparation of 2-nitro-7-{6-[4-(4-
trifluoromethoxybenzyl)piperidin-1-yl]pyridin-3-yloxyethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 69 using suitable starting materials.
Pale yellow powder
Melting point: 184-185°C

Example 73
Preparation of 2-nitro-7-{6-(4-[3-(5-trifluoromethyl)pyridin-2-yl]propyl)piperazin-1-yl)pyridin-3-yloxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 164.2-164.7°C

Example 74
Preparation of 2-nitro-7-{4-(4-[3-(5-trifluoromethyl)pyridin-2-yl]propyl)\{1,4\}diazepan-1-yl)phenoxy)methyl]5,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 177.4°C

Example 75
Preparation of 7-{4-(4-[5-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)thiophen-2-yl)methyl)piperazin-1-yl)phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 204.6°C

Example 76
Preparation of 2-nitro-7-{6-(4-[4-(4-trifluoromethoxyphenoxy)methyl)piperidin-1-yl)pyridin-3-
-193-
yloxyethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.
White powder

5 Melting point: 181-182°C

Example 77

Preparation of 7-(4-[4-(4-benzylloxybenzyl)piperazin-1-yl]phenoxyethyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 219.5-220.5°C

15 Example 78

Preparation of 2-nitro-7-(4-[4-(2-(4-
trifluoromethylphenoxy)ethyl)piperazin-1-yl]phenoxyethyl)-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 166.5-168.8°C

25 Example 79

Preparation of 2-nitro-7-[6-(4-[2-(4-
trifluoromethoxyphenoxy)ethyl]piperidin-1-yl)pyridin-3-
yloxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.
White powder
Melting point: 140-141°C

Example 80

Preparation of 2-nitro-7-[4-(4-propoxy-4-
trifluoromethyl)piperidin-1-yl)phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

Pale yellow powder
Melting point: 157-158°C

Example 81

Preparation of 4-[(S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]piperazine-1-carboxylic acid tert-butyl ester

An ethanol solution (25.00 ml) of 20% sodium ethoxide was added to an ethanol solution (250 ml) of toluene-4-sulfonic acid (S)-4-(2-chloro-4-nitro-imidazol-1-yl)-2-hydroxybutyl ester (25.00 g), and the mixture was stirred at room temperature for 30 minutes. 4-(4-Hydroxyphenyl)piperazine-1-carboxylic acid tert-butyl ester (19.63 g) and tripotassium phosphate (13.61 g) were added to the reaction mixture, followed by heating under reflux for 4 hours. The reaction mixture was then concentrated under reduced pressure, and water was added to the residue, followed by extraction with methylene chloride. The organic layer was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. After filtering, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride:ethyl acetate = 1:1) and concentrated under reduced pressure. Sodium hydride (3.08 g) was added to a dimethylformamide solution (269 ml) of residue and the mixture was stirred at room temperature for 1 hour. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried over magnesium sulfate. After filtering, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride:ethyl acetate = 1:0-methylene chloride:ethyl acetate = 0:1) to afford the title compound as a yellow powder (16.57 g).
Example 82
Preparation of (S)-2-nitro-7-(4-(4-[(2-(4-
trifluoromethoxyphenyl)ethyl]piperidin-1-yl)phenoxymethyl)-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 69 using suitable starting materials.
Pale yellow powder

Melting point: 201-202°C

Example 83
Preparation of N-methyl-N-(1-[4-([(S)-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-
yl]methoxy)phenyl)piperidin-4-yl]-N-(4-
trifluoromethoxyphenyl)amine

The title compound was prepared in the same manner as
in Example 69 using suitable starting materials.
Pale yellow powder

Melting point: 186-187°C

Example 84
Preparation of 7-{4-[4-[(3-chloro-5-
trifluoromethyl)pyridin-2-yloxy)piperidin-1-yl]phenoxymethyl]-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 185-186°C

Example 85
Preparation of 7-{4-[(5-(2-methyl-5-trifluoromethyl-
2H-pyrazol-3-yl)thiophen-2-yl)methyl)piperazin-1-
yl)phenoxymethyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-
b][1,3]oxazine
The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder (acetone-methanol)
Melting point: 180.3-180.8°C

Example 86
Preparation of 4-[(4-[(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy]phenyl)piperazine-1-carboxylic acid tert-butyl ester

An ethanol solution (3.02 ml) of 20% sodium ethoxide was added to an ethanol solution (30 ml) of toluene-4-sulfonic acid (R)-4-[(2-chloro-4-nitroimidazo[1-yl]-2-hydroxybutyl ester (3.00 g), and the mixture was stirred at room temperature for 30 minutes. 4-[(4-Hydroxyphenyl)piperazine-1-carboxylic acid tert-butyl ester (2.36 g) and tripotassium phosphate (1.80 g) were added to the reaction mixture and heated under reflux for 4 hours. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with water and dried over sodium sulfate. After filtering, the filtrate was concentrated under reduced pressure. The residue thus obtained was dissolved in dimethylformamide (46 ml), sodium hydride (0.31 g) was added thereto, and the resulting mixture was stirred at room temperature for 30 minutes. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried over magnesium sulfate. After filtering, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride:ethyl acetate = 1:0-methylene chloride:ethyl acetate = 0:1) and recrystallized from acetone to afford the title compound as a yellow powder (0.72 g).
Melting point: 206.7-208.0°C

Example 87
Preparation of (5)-2-nitro-7-[(4-[(4-[(4-(trifluoromethoxy)phenacyl)piperazin-1-yl)phenoxymethyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder

5 Melting point: 161.2-163.8°C

Example 88

Preparation of (R)-2-nitro-7-(4-[(4-4-(4-
trifluoromethoxyphenoxy)benzyl)piperazin-1-yl]phenoxy)methyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 162.6-163.2°C

15

Example 89

Preparation of (R)-2-nitro-7-(4-[(4-2-[4-
trifluoromethoxyphenyl)ethyl)piperidin-1-yl]phenoxy)methyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.
Pale yellow needle
Melting point: 201-202°C

25 Example 90

Preparation of N-methyl-N-[1-4-[(R)-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-
ylmethoxy)phenyl)piperidin-4-yl]-N-(4-
trifluoromethoxyphenyl)amine

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.
Yellow needle
Melting point: 186-187°C

35 Example 91
-198-

Preparation of 2-nitro-7-{6-[4-(4-
chlorophenoxypiperidin-1-yl)pyridin-3-yloxy]methyl}-6,7-dihydro-
5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 69 using suitable starting materials.

White powder

Melting point: 171-172°C

Example 92

Preparation of 2-nitro-7-{4-[1-(4-
trifluoromethoxyphenyl)piperidin-4-y1methyl]phenoxy}methyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.

White powder

Melting point: 193-194°C

Example 93

Preparation of 7-{4-[4-(5-chlorothiophen-2-yl
methyl)piperazin-1-yl]phenoxy}methyl]-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.

Pale yellow powder

Melting point: 182.5-183.3°C

Example 94

Preparation of 2-nitro-7-{6-[4-(4-
trifluoromethoxybenzyl)oxy)piperidin-1-yl]pyridin-3-yloxy]methyl}]-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 69 using suitable starting materials.

Pale yellow powder

Melting point: 168-169°C
Example 95
Preparation of 2-nitro-7-(6-[4-{4-
trifluoromethylphenoxy]piperidin-1-yl]pyridin-3-yloxymethyl}-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 69 using suitable starting materials.
Pale yellow powder
Melting point: 199-200°C

Example 96
Preparation of 2-nitro-7-(4-[1-{4-
trifluoromethylphenyl]piperidin-4-ylmethyl}phenoxy)methyl}-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 186-188°C

Example 97
Preparation of 7-[4-{4-[2,2-difluorobenzo(1,3)dioxol-5-
ylmethyl]piperazin-1-yl}phenoxy)methyl}-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 195.8-196.5°C

Example 98
Preparation of 2-nitro-7-(4-{1-{4-
trifluoromethoxybenzyl]piperidin-4-ylmethyl}phenoxy)methyl}-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.
White powder
Melting point: 185-186°C
Example 99

Preparation of 2-nitro-7-(4-(4-(4-trifluoromethyl)benzyl)piperazin-1-yl)phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 170.7-171.0°C

Example 100

Preparation of 7-(4-(4-(4-chlorobenzyl)piperazin-1-yl)phenoxy)methyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Yellow powder
Melting point: 188.8-189.5°C

Example 101

Preparation of 2-nitro-7-(4-[1-(4-trifluoromethyl)benzyl]piperidin-4-yl)methyl)phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
White powder
Melting point: 180-181°C

Example 102

Preparation of 2-nitro-7-(4-(1-[4-(4-trifluoromethoxy)phenoxy)benzyl]piperidin-4-yl)methyl)phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
White powder
Melting point: 197-198°C

Example 103
Preparation of 7-{4-[1-{4-chlorobenzyl}piperidin-4-ylmethyl]phenoxyethyl}-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder
Melting point: 194-195°C

Example 104
Preparation of 2-nitro-7-{6-[4-[3-{4-trifluoromethoxyphenyl}propyl]piperidin-1-yl]pyridin-3-yloxyethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.

Pale yellow powder
Melting point: 162-163°C

Example 105
Preparation of 7-{4-[4-{4-methylsulfanylbenzyl}piperazin-1-yl]phenoxyethyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Pale yellow powder
Melting point: 191.1-191.5°C

Example 106
Preparation of 2-nitro-7-{4-[4-[5-trifluoromethylbenzofuran-2-ylmethyl]piperazin-1-yl]phenoxyethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 181.0-181.6°C

Example 107
Preparation of 2-nitro-7-(4-(4-[3-(4-
trifluoromethoxyphenyl)propyl]piperazin-1-yl)phenoxymethyl)-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.
Yellow powder
Melting point: 168.5-168.8°C

Example 108
Preparation of 2-nitro-7-[4-(4-
trifluoromethoxybenzoyloxymethyl)pyridin-3-ylcyclohexyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 105-106°C

Example 109
Preparation of 2-nitro-7-(4-(4-[2-(4-
trifluoromethylphenyl)ethyl]piperidin-1-yl)phenoxymethyl)-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 210-211°C

Example 110
Preparation of 2-nitro-7-(4-(4-[2-(4-
trifluoromethylphenoxy)ethyl]piperidin-1-yl)phenoxymethyl)-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 69 using suitable starting materials.
Pale yellow powder
Melting point: 171-172°C

Example 111
Preparation of 7-(4-(4-[2-(4-chlorophenoxy)ethyl]piperidin-1-yl)phenoxymethyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.
Pale yellow powder
Melting point: 174-175°C

Example 112
Preparation of 2-[4-(2-[2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy]phenyl)piperazin-1-yl]-1-(4-trifluoromethylphenyl)ethanol

1) Trifluoroacetic acid (1.5 ml) and methylene chloride (1.5 ml) were added to 4-[4-(2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperazine-1-carboxylic acid tert-butyl ester (300 mg), and the mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. Methylene chloride (1.5 ml) and triethylamine (1.5 ml) were added to the residue, and the mixture was stirred at room temperature for 5 minutes. The reaction mixture was reconcentrated under reduced pressure.

2) 2,2,6,6-Tetramethyl-1-piperidinyloxy radical (TEMPO) (13 mg) and trichloroisocyanuric acid (1.93 g) were added to a methylene chloride solution (15 ml) of 4-trifluoromethyl phenethyl alcohol (1.5 g) under ice cooling and the mixture was stirred at the same temperature for 1 hour. After removing insoluble matter by filtration, the filtrate was washed with water, dried over magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 1:0-1:1) and then
concentrated under reduced pressure.

3) The residues obtained in Step 1) and Step 2) above were dissolved in 1,2-dichloroethane (5 ml). Sodium triacetoxyborohydride (0.39 g) was added thereto, and the mixture was stirred at room temperature overnight. After adding methylene chloride, the reaction mixture was washed with a potassium carbonate aqueous solution and water, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:methanol = 1:0-9:1) and concentrated under reduced pressure. The residue was recrystallized from methanol to afford the title compound as a pale yellow powder (69 mg).

Melting point: 223.8-225.3°C

Example 113
Preparation of 2-nitro-7-(4-{4-[4-(4-
trifluoromethyl)phenoxo]benzyl}piperazin-1-yl)phenoxy)methyl)-6,7-
dihydro-5H-imidazoo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Pale yellow powder
Melting point: 149.9-151.9°C

Example 114
Preparation of 7-(4-{4-[4-(4-
chlorophenoxy)benzyl}piperazin-1-yl)phenoxy)methyl)-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Pale yellow powder
Melting point: 134.7°C

Example 115
Preparation of 2-nitro-7-(4-{4-[4-(4-
trifluoromethoxyphenyl)butyl}piperazin-1-yl)phenoxy)methyl)-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Yellow powder

Melting point: 186.3-186.5°C

Example 116
Preparation of 7-[[2-chloro-4-[4-(4-
trifluoromethoxyphenoxoy)piperidin-1-yl]phenoxy)methyl]-2-nitro-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 108-110°C

Example 117
Preparation of 7-[[4-(4-[[2-(4-
chlorophenyl)ethyl]piperidin-1-yl]phenoxy)methyl]-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 212-214°C

Example 118
Preparation of 2-nitro-7-[[4-[4-[4-
trifluoromethylphenyl)propyl]piperidin-1-yl]phenoxy)methyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.
Pale yellow powder
Melting point: 180-181°C

Example 119
Preparation of 2-nitro-7-[[4-[4-[4-
trifluoromethylphenoxy)propyl)piperidin-1-yl)phenoxy)methyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.

5 Pale yellow powder
Melting point: 184-185°C

Example 120
Preparation of 7-{4-{4-(5-chlorobenzofuran-2-yl)methyl)piperidin-1-yl)phenoxy)methyl}-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.

White powder
15 Melting point: 157-158°C

Example 121
Preparation of 7-{4-{4-(5-chlorobenzofuran-2-yl)methoxy)piperazin-1-yl)phenoxy)methyl}-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.

Pale yellow powder
Melting point: 198-200°C

Example 122
Preparation of 7-{4-{4-(4-fluoro-naphthalen-1-yl)methyl)piperazine-1-yl)phenoxy)methyl}-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Pale yellow powder
Melting point: 182.9-184.4°C

Example 123
Preparation of 2-nitro-7-(4-{4-[2-(4-
trifluoromethylphenyl)ethyl]piperazin-1-yl}phenoxy)methyl)-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

Toluene-4-sulfonic acid 4-{2-chloro-4-nitroimidazol-1-
yl}-2-hydroxybutyl ester (1.12 g) was suspended in an ethanol (14
ml). An ethanol solution (1.13 ml) of 20% sodium ethoxide was
added to the suspension, and the mixture was stirred at room
temperature for 30 minutes. 4-{4-{2-(4-
Trifluoromethylphenyl)ethyl]piperazin-1-yl}phenol (0.72 g) and
tripotassium phosphate (0.61 g) were added to the reaction
mixture and heated for 4 hours under reflux. After the reaction
mixture was cooled to room temperature, water was added thereto,
followed by extraction with methylene chloride. The organic layer
was washed with water, dried over sodium sulfate, and
concentrated under reduced pressure. The residue was purified by
silica gel column chromatography (hexane:ethyl acetate =
1:0-hexane:ethyl acetate=0:1) and recrystallized from methanol to
afford the title compound as a pale yellow powder (0.72 g).
Melting point: 213.6-213.7°C

Example 124

Preparation of 7-(4-{4-[3-(4-
chlorophenoxy)propyl]piperidin-1-yl}phenoxy)methyl)-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 69 using suitable starting materials.
White powder
Melting point: 196-198°C

Example 125

Preparation of 2-nitro-7-[4-{4-
trifluoromethoxyphenoxo}]-8-azabicyclo[3.2.1]oct-8-
yl]phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 123 using suitable starting materials.
Pale brown powder
Melting point: 220.5-222.6°C

Example 126
Preparation of 2-nitro-7-{4-{4-{4-{4-
trifluoromethoxybenzyl}oxybenzyl}piperidin-1-yl}phenoxymethyl}-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 123 using suitable starting materials.

Yellow powder
Melting point: 214.5°C

Example 127
Preparation of 2-nitro-7-{4-{4-{5-
trifluoromethylbenzofuran-2-ylmethyl}piperidin-1-yl}phenoxymethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 69 using suitable starting materials.
White powder
Melting point: 171-172°C

Example 128
Preparation of 7-{4-{4-{4-{3-{4-
chlorophenyl}propyl}piperidin-1-yl}phenoxymethyl}-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 69 using suitable starting materials.
Pale yellow powder
Melting point: 170-171°C

Example 129
Preparation of 2-nitro-7-{4-{4-{2-{4-
trifluoromethoxyphenyl}ethyl}piperazin-1-yl}phenoxymethyl}-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 123 using suitable starting materials.
White powder
Melting point: 206.0-206.1°C

Example 130

Preparation of \((R)-2\text{-nitro-7-}(4\text{-}(4\text{-}(4\text{-trifluoromethoxybenzyl)oxy}benzyl)piperidin-1-yl)phenoxymethyl)-6.7\text{-dihydro-5H-imidazo}[2.1-b][1.3]oxazine

The title compound was prepared in the same manner as in Example 123 using suitable starting materials.
Pale yellow powder
Melting point: 209.5-210.4°C

Example 131

Preparation of \((R)-2\text{-nitro-7-}(4\text{-}(4\text{-}(4\text{-trifluoromethoxybenzyl)oxy}benzyl)piperazin-1-yl)phenoxymethyl)-6.7\text{-dihydro-5H-imidazo}[2.1-b][1.3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
White powder
Melting point: 194.0-194.4°C

Example 132

Preparation of 2\text{-nitro-7-}(4\text{-}(4\text{-}(5\text{-trifluoromethoxybenzofuran-2-ylmethyl)piperidin-1-yl)phenoxymethyl)-6.7\text{-dihydro-5H-imidazo}[2.1-b][1.3]oxazine

Sodium tert-butoxide (81 mg) was added to an N-methylpyrrolidone solution (5 mL) of 4\text{-}(2-chloro-4\text{-nitroimidazol-1-yl})-1\text{-}(4\text{-}(5\text{-trifluoromethoxybenzofuran-2-ylmethyl)piperidin-1-yl)phenoxy)butan-2-ol (469 mg), and the mixture was stirred at room temperature for 1 hour. A saturated ammonium chloride aqueous solution was added to the reaction mixture, and precipitated solid was sequentially washed with water and diisopropyl ether. The crude product formed was purified by silica gel column chromatography (ethyl acetate:n-hexane =
1:1-3:1) to afford the title compound as a white powder (181 mg).
Melting point: 142-143°C

Example 133

Preparation of (R)-2-nitro-7-(4-{4-[4-{4-
trifluoromethylbenzyloxy}benzyl]piperidin-1-yl}phenoxy)methyl)-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 123 using suitable starting materials.
Pale yellow powder
Melting point: 217.0-220.3°C

Example 134

Preparation of 2-nitro-7-(4-{4-[4-(4-
trifluoromethylbenzyloxy)benzyl]piperidin-1-yl}phenoxy)methyl)-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 123 using suitable starting materials.
Pale yellow powder
Melting point: 217.2-217.3°C

Example 135

Preparation of 7-{4-[4-{(5-chlorobenzofuran-2-
yl)methoxy}methyl]piperidin-1-yl}phenoxy)methyl)-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 132 using suitable starting materials.
Pale yellow powder
Melting point: 130-132°C

Example 136

Preparation of 7-{4-[4-{4'-fluoro-3'
trifluoromethylbiphenyl-4-ylmethyl]piperazin-1-yl}phenoxy)methyl}-
2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.
Yellow powder
Melting point: 187.4-187.7°C

Example 137
Preparation of 7-(4-{4-(4'-fluorobiphenyl-4-
ylmethyl)piperazin-1-yl}phenoxy)methyl)-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 232.4-233.0°C

Example 138
Preparation of 7-{4-{4-(4'-methylsulfanylbiphenyl-4-
ylmethyl)piperazin-1-yl}phenoxy)methyl)-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.
Pale brown powder
Melting point: 258.2-259.1°C

Example 139
Preparation of 2-nitro-7-{4-{4-(5-
trifluoromethyl)pyridin-2-yl}benzyl)piperazin-1-yl}phenoxy)methyl)-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 243.0-243.9°C

Example 140
Preparation of 7-{4-{4-(3-fluoro-4'-
trifluoromethoxybiphenyl-4-ylmethyl)piperazin-1-
yl}phenoxy)methyl}-2-nitro-6,7-dihydro-5H-imidazo[2,1-
b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 179.0-180.4°C

Example 141
Preparation of 7-{4-[4-(3-fluoro-4′-trifluoromethyl)biphenyl-4-ylmethyl]piperazin-1-yl}phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 211.6-212.9°C

Example 142
Preparation of 7-{4-[4-(4′-chloro-3-fluorobiphenyl-4-ylmethyl)piperazin-1-yl]phenoxy)methyl}-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 234.5-235.1°C

Example 143
Preparation of 6-(2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-1-[3-{4-trifluoromethoxyphenoxyl}propyl]-1,2,3,4-tetrahydroquinoline

The title compound was prepared in the same manner as in Example 132 using suitable starting materials.
Pale yellow powder
Melting point: 175-176°C

Example 144
Preparation of 2-nitro-7-(4-{4-[(E)-3-}
-213-

trifluoromethylbenzofuran-2-yl)allyl)piperazin-1-yl)phenoxyethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

5 Pale yellow powder
Melting point: 196.6-197.4°C

Example 145

Preparation of 2-nitro-7-(4-[4-(5-
trifluoromethoxybenzofuran-2-yl)methyl)piperazin-1-yl)phenoxyethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Yellow powder
Melting point: 185.5-185.6°C

Example 146

Preparation of 2-nitro-7-(4-{4-[[((E)-3-{4-
trifluoromethylphenyl)allyl]piperazin-1-yl)phenoxyethyl})-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 206.0-206.4°C

Example 147

Preparation of 7-{3-fluoro-4-[4-(4-
trifluoromethoxyphenoxy)piperidin-1-yl)phenoxyethyl)-2-nitro-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.
White powder
Melting point: 186-187°C

Example 148
Preparation of 7-(3-chloro-4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

White powder

Melting point: 143-144°C

Example 149

Preparation of 7-(3-methyl-4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

White powder

Melting point: 199-200°C

Example 150

Preparation of 7-(2-methyl-4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

White powder

Melting point: 156-157°C

Example 151

Preparation of 6-[(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-2-[2-(4-trifluoromethoxy)ethoxy]quinoline

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

White powder

Melting point: 156-157°C
Example 152
Preparation of 6-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-2-{3-{4-trifluoromethoxyphenoxy}propoxy}quinoline

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
White powder
Melting point: 172-173°C

Example 153
Preparation of 6-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-2-{4-trifluoromethoxybenzyl}oxy}quinoline

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
White powder
Melting point: 203-204°C

Example 154
Preparation of 6-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-1-{3-{4-trifluoromethoxyphenoxy}propyl}-1,2,3,4-tetrahydroquinoline

The title compound was prepared in the same manner as in Example 132 using suitable starting materials.
Pale yellow powder
Melting point: 183-185°C

Example 155
Preparation of (R)-2-nitro-7-{1-{3-4-trifluoromethoxyphenoxy}propyl]-1H-indol-5-yloxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 132 using suitable starting materials.
Pale yellow powder
Melting point: 129-131°C
Example 156
Preparation of 7-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-1-[4-(4-
trifluoromethoxyphenoxo)propyl]-2,3,4,5-tetrahydro-1H-benzo[b]azepine

The title compound was prepared in the same manner as in Example 132 using suitable starting materials.
White powder
Melting point: 159-160°C

Example 157
Preparation of 6-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-1-[4-((4-
trifluoromethoxyphenoxo)benzyl]-1,2,3,4-tetrahydraquinolone

The title compound was prepared in the same manner as in Example 132 using suitable starting materials.
Pale brown powder
Melting point: 194-196°C

Example 158
Preparation of 7-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-1-[4-((4-
trifluoromethoxyphenoxo)benzyl]-2,3,4,5-tetrahydro-1H-benzo[b]azepine

The title compound was prepared in the same manner as in Example 132 using suitable starting materials.
Powder
Melting point: 133-134°C

Example 159
Preparation of 6-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-2-[4-((4-
trifluoromethoxyphenoxo)piperidin-1-yl]quinoline

The title compound was prepared in the same manner as
-217-

in Example 132 using suitable starting materials.
Yellow powder
Melting point: 193-195°C

5 Example 160
Preparation of (R)-7-{2-methyl-4-{4-[2-(4-
trifluoromethoxyphenyl)ethyl]piperidin-1-yl}phenoxymethyl}-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
White powder
Melting point: 181-182°C

Example 161
Preparation of (R)-7-{2-chloro-4-{4-[2-(4-
trifluoromethoxyphenyl)ethyl]piperidin-1-yl}phenoxymethyl}-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
White powder
Melting point: 160-162°C

Example 162
Preparation of (R)-2-nitro-7-{6-{4-[2-(4-
trifluoromethoxyphenyl)ethyl]piperidin-1-yl}naphthalen-2-
yloxymethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 234-235°C

Example 163
Preparation of 2-nitro-7-{4-[4-(4'-(4-
trifluoromethylbiphenyl-4-yl)methyl)piperazin-1-yl]phenoxymethyl}-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 256.9-257.9°C

Example 164
Preparation of 2-nitro-7-(4-(4-[6-(4-
trifluoromethoxyphenyl)pyridin-3-ylmethyl]piperazin-1-
yl)phenoxymethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
White powder
Melting point: 201.2-203.7°C

Example 165
Preparation of 6-((R)-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-2-(4-(4-
trifluoromethoxybenzyl)piperazin-1-yl)quinoline
The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Yellow powder
Melting point: 218-221°C

Example 166
Preparation of 6-((R)-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-2-(4-[4-(4-
trifluoromethoxyphenoxy)benzyl]piperazin-1-yl)quinoline
The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
White powder
Melting point: 208-211°C

Example 167
Preparation of 6-((R)-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-2-(4-[4-(4-

1904
trifluoromethoxybenzyl)piperazin-1-yl)quinoline

The title compound was prepared in the same manner as in Example 3 using suitable starting materials. Yellow powder

Melting point: 226-230°C

Example 168

Preparation of (R)-2-nitro-7-{2-[4-(4-
trifluoromethoxyphenox) piperidin-1-yl]benzothiazol-6-
yloxy methyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 132 using suitable starting materials. Yellow powder
Melting point: 189-191°C

Example 169

Preparation of (R)-2-nitro-7-{2-[4-(4-
trifluoromethoxybenzyl)piperazin-1-yl]benzothiazol-6-
yloxy methyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

Sodium tert-butoxide (112 mg) was added to a dimethylsulfoxide solution (6 ml) of (R)-4-(2-chloro-4-
nitroimidazol-1-yl)-1-{2-[4-(4-trifluoromethoxybenzyl)piperazin-
1-yl]benzothiazol-6-yloxy}butan-2-ol (662 mg), and the mixture was stirred at room temperature for 3 hours. A saturated ammonium chloride aqueous solution was added to the reaction mixture, and precipitated solid was sequentially washed with water and diisopropyl ether. The crude product was purified by silica gel column chromatography (ethyl acetate:n-hexane = 2:1-ethyl acetate) to afford the title compound as a pale yellow powder (60 mg).

Melting point: 157-159°C

Example 170

Preparation of (R)-2-nitro-7-{4-[4-(4-[2-(4-
trifluoromethoxyphenyl)ethoxy]benzyl)piperazin-1-
yl)phenoxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder

Melting point: 157.7°C

Example 171

Preparation of (S)-2-nitro-7-(4-{4-[4-(4-trifluoromethoxybenzyloxy)benzyl]piperazin-1-yl}phenoxymethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder

Melting point: 193.4-193.9°C

Example 172

Preparation of (R)-2-nitro-7-(4-{4-[2-{4-(trifluoromethoxyphenoxy)ethyl]piperidin-1-yl}phenoxymethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

White powder

Melting point: 152-153°C

Example 173

Preparation of 2-nitro-7-(2-{4-[4-{4-(trifluoromethoxybenzyloxy)benzyl]piperazin-1-yl}benzothiazol-6-yloxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Pale yellow powder

Melting point: 203-205°C

Example 174

Preparation of (R)-2-nitro-7-(4-{4-[4-{3-[4-
trifluoromethoxyphenyl)propoxy]benzyl)piperazin-1-yl)phenoxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

5 Yellow powder
Melting point: 158.2-158.4°C

Example 175
Preparation of (R)-2-nitro-7-[4-[(4-[(4-[(E)-3-(4-
trifluoromethoxyphenyl)allyloxy]benzyl)piperazin-1-
yl)phenoxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine.

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder
Melting point: 183.0-183.9°C

Example 176
Preparation of (R)-7-[4-[(4-[(2-(4-chlorophenyl)ethoxy]benzyl)piperazin-1-yl)phenoxymethyl]-2-nitro-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine.

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder
Melting point: 150.0-152.2°C

Example 177
Preparation of (R)-2-nitro-7-[4-[(4-[(3-(4-
trifluoromethylphenyl)propoxy]benzyl)piperazin-1-
yl)phenoxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine.

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder
Melting point: 155.0-155.9°C

Example 178
Preparation of (R)-2-nitro-7-[4-{4-[(4-{4-[(4-
trifluoromethyl)phenyl]allyloxy}benzyl)piperazin-1-
yl]phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder
Melting point: 196.1-199.1°C

Example 179

Preparation of (R)-2-nitro-7-[4-{4-[(4-
trifluoromethoxyphenoxo)piperidin-1-yl]benzyl)piperazin-1-
yl]phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow solid
Melting point: 168.3-169.5°C

Example 180

Preparation of N-{1-[(4-[(R)-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazin-7-ylmethoxy]phenyl)piperidin-4-yl}-N-
[4-((4-trifluoromethoxyphenoxy)phenyl)amine

1-[4-[(R)-2-Nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy]phenyl)piperidin-4-one (700 mg) and 4-
(4-trifluoromethoxyphenoxy)phenylamine (559 mg) were suspended in 1,2-dichloroethane (20 ml) and tetrahydrofuran (20 ml). Sodium triacetoxylborohydride (558 mg) and acetic acid (0.13 ml) were added to the suspension, and stirred at room temperature for 20 hours. The reaction mixture was concentrated under reduced pressure and the remaining water layer was ice-cooled. A 20% sodium carbonate aqueous solution was added thereto, followed by extraction with methylene chloride. The organic layer was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. After filtering, the filtrate was concentrated under reduced pressure. The residue was then purified by silica gel column chromatography (methylene chloride:methanol =
100:1-methylene chloride:methanol=40:1) and recrystallized from isopropyl alcohol-isopropyl ether to afford the title compound as a yellow solid (226 mg).

Melting point: 119.6-121°C

Example 181

Preparation of N-(4'-chlorobiphenyl-4-ylmethyl)-N-methyl-N-{1-[4-{(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy]phenyl)piperidin-4-yl}amine

The title compound was prepared in the same manner as in Example 180 using suitable starting materials.

Colorless solid

Melting point: 256.5-258°C

Example 182

Preparation of (R)-2-nitro-7-(4-{4-{4-[(4-trifluoromethyl)benzyl]piperazin-1-yl}phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder

Melting point: 196.8-200.8°C

Example 183

Preparation of (R)-7-{4-{4-{4-(4-chlorobenzyl)oxy}benzyl)piperazin-1-yl}phenoxy)methyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder

Melting point: 225.5-229.0°C

Example 184

Preparation of (R)-7-{4-{4-(2-(3,4-dichlorophenoxy)ethyl)piperidin-1-yl}phenoxy)methyl)-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 132 using suitable starting materials.

Yellow powder

5 Melting point: 152-153°C

Example 185

Preparation of (R)-7-\{(4-\{(4-\{3-chloro-5-
trifluoromethylpyridin-2-yloxy\}ethyl\}piperidin-1-yl\}
phenoxy)methyl\}-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 132 using suitable starting materials.

Yellow powder

Melting point: 140-143°C

Example 186

Preparation of (R)-2-nitro-7-\{(4-\{(4-
trifluoromethoxyphenyl)propyl\}piperidin-1-yl\}phenoxy)methyl\}-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

White powder

Melting point: 171-172°C

Example 187

Preparation of (R)-2-nitro-7-\{(4-\{2-(tetrahydropyran-
2-yloxy)\}-2\{(4-trifluoromethoxyphenyl)ethyl\}piperidin-1-yl\}
phenoxy)methyl\}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

Pale yellow powder

Melting point: 172-175°C

Example 188

Preparation of 2-\{(1-\{4-\{(R)-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]piperidin-4-yl]-1-(4-trifluoromethoxyphenyl)ethanol.

A 1 M HCl ethanol solution (6 mL) was added to (R)-2-nitro-7-(4-{4-[2-(tetrahydrofuran-2-yl)oxy]-2-(4-trifluoromethoxyphenyl)ethyl]piperidin-1-yl}phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine (0.20 g), and the mixture was stirred at room temperature for 3 hours. A saturated sodium hydrogen carbonate aqueous solution was added to the residue obtained by distilling the solvent off, followed by extraction with ethyl acetate. The organic layer was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. After filtering, the filtrate was concentrated under reduced pressure. The crystal thus obtained was washed with methylene chloride-ether and dried to afford the title compound as a white powder (0.16 g).

Melting point: 186-187°C

Example 189

Preparation of (R)-7-(4-{4-[2-(3,5-dichloropyridin-2-yloxy)ethyl]piperidin-1-yl}phenoxy)methyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 69 using suitable starting materials. Yellow powder
Melting point: 143-145°C

Example 190

Preparation of N-[1-{4-(4-{(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]piperidin-4-yl}]N-[4-(4-trifluoromethoxybenzyloxy)phenyl]amine

Sodium trisacetoxyborohydride (0.32 g) and acetic acid (1 mL) were added to a 1,2-dichloroethane solution (8 mL) of 1-[4-{(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]piperidin-4-one (0.40 g) and 4-{4-(4-trifluoromethoxybenzyloxy)phenyl}amine (0.33 g), and the mixture
was stirred at room temperature for 5 days. The reaction mixture was diluted with methylene chloride. The result was washed with a potassium carbonate aqueous solution and water in this order, and then dried over magnesium sulfate. After filtering, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride:methanol = 1:0-methylene chloride:methanol = 9:1) to afford the title compound as a yellow powder (0.46 g).

Melting point: 226.9-228.6°C

Example 191

Preparation of (R)-7-{4-[4-{2-{4-chloro-3-trifluoromethylphenoxy}ethyl]piperidin-1-yl}phenoxy)methyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.

Yellow powder
Melting point: 116-118°C

Example 192

Preparation of (R)-2-nitro-7-{4-[4-{3-{4-trifluoromethoxybenzyl}oxy]benzyl}piperazin-1-yl}phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder
Melting point: 155.6-156.5°C

Example 193

Preparation of (R)-7-{4-[4-{2-{2,4-dichlorophenoxy}ethyl]piperidin-1-yl}phenoxy)methyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.

Pale yellow powder
Melting point: 164-166°C

Example 194
Preparation of (R)-7-\{4-\{4-\{2-\{(4-chloro-3-
methylphenoxy)ethyl\}piperidin-1-yl\}phenoxy)methyl\}-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 69 using suitable starting materials.
Pale yellow powder

Melting point: 166-168°C

Example 195
Preparation of (R)-2-nitro-7-\{4-\{4-\{2-(3-
trifluoromethylphenoxy)ethyl\}piperidin-1-yl\}phenoxy)methyl\}-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 69 using suitable starting materials.
Yellow powder
Melting point: 148-149°C

Example 196
Preparation of (R)-2-nitro-7-\{4-\{4-(3-(4-
trifluoromethoxyphenoxy)propyl\}piperidin-1-yl\}phenoxy)methyl\}-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 176-177°C

Example 197
Preparation of (R)-2-nitro-7-\{4-\{4-\{(2-(5-
trifluoromethyl)pyridin-2-yloxy)ethyl\}piperidin-1-yl\}
phenoxy)methyl\}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
White powder
Melting point: 162-163°C

Example 198

Preparation of (R)-2-nitro-7-(4-(4-[4-(4-
trifluoromethoxybenzoyloxy)phenyl]piperazin-1-yl)phenoxy)methyl)-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.

Yellow solid
Melting point: 261-262°C

Example 199

Preparation of (R)-7-(4-[4-(2-(3-chloro-4-
fluorophenoxy)ethyl]piperidin-1-yl)phenoxy)methyl)-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 69 using suitable starting materials.

Yellow powder
Melting point: 144-145°C

Example 200

Preparation of (R)-2-nitro-7-(2-[4-[4-
trifluoromethoxyphenoxy]piperidin-1-yl]benzoxazol-5-
yloxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine hydrochloride

The title compound was prepared in the same manner as
in Example 69 using suitable starting materials.

Pale yellow powder
Melting point: 146-149°C

Example 201

Preparation of (R)-2-nitro-7-(4-(4-[4-(4-
trifluoromethoxyphenoxy)phenyl]piperazin-1-yl)phenoxy)methyl)-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

Colorless solid
Melting point: 207.6-208.2°C

Example 202
Preparation of (R)-2-nitro-7-(4-[(4-[(3-(4-
trifluoromethylphenyl)propyl)piperazin-1-yl]phenoxy)methyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale brown powder
Melting point: 190.9°C

Example 203
Preparation of (R)-7-[4-[(4-[(4-[(3-(4-
chlorophenyl)allyloxy]benzyl)piperazin-1-yl]phenoxy)methyl]-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 210.6-213.6°C

Example 204
Preparation of N-{4-[(4-[(R)-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazin-7-ylmethoxy]phenyl)piperazin-1-yl]-N-
(4'-trifluoromethylbiphenyl-4-yl)methy]amine

Trifluoroacetic acid (3.0 ml) was added to a mixture of (4-[(4-[(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-
yl]methoxy]phenyl)piperazin-1-yl)carbonic acid tert-butyl ester (600 mg) and methylene chloride (3.0 ml), and the mixture was stirred at room temperature for 40 minutes. The reaction mixture was concentrated under reduced pressure, and methylene chloride (3.0 ml) and triethylamine (3.0 ml) were added to the residue, followed by stirring at room temperature for 5 minutes. The
reaction mixture was concentrated under reduced pressure, and the resulting residue was dissolved in acetic acid (8 ml). 4′-Trifluoromethylbiphenyl-4-carbaldehyde (316 mg) and sodium cyanoborohydride (239 mg) were added thereto, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was added to a 20% sodium carbonate aqueous solution, followed by extraction with methylene chloride. The organic layer was washed with a saturated sodium chloride aqueous solution and then dried over sodium sulfate. After filtering, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride:methanol = 100:1-methylene chloride:methanol = 40:1) and washed with ethyl acetate-isopropyl ether to afford the title compound as a colorless solid (265 mg).

Melting point: 294-295°C

Example 205

Preparation of (R)-2-nitro-7-(4-{1-[4-trifluoromethoxybenzyl]piperidin-4-yloxy[phenoxy-methyl]}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder
Melting point: 151-152°C

Example 206

Preparation of (R)-2-nitro-7-(4-{1-[4-({4-trifluoromethoxybenzyl]oxy}benzyl]piperidin-4-yloxy[phenoxy-methyl]}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder
Melting point: 163-164°C

Example 207
Preparation of (R)-2-nitro-7-(4-{1-[4-(4-
trifluoromethoxyphenoxyl)benzyl]piperidin-4-yloxy)phenoxy)methyl}-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.
White powder
Melting point: 127-128°C

Example 208
Preparation of N-methyl-N-{1-[4-{((R)-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-
ylmethoxy)phenyl]piperidin-4-yl}-N-[4-(4-
trifluoromethoxybenzyl)oxy]phenyl]amine
N-{1-[4-{((R)-2-Nitro-6,7-dihydro-5H-imidazo[2,1-
b][1,3]oxazin-7-yilmethoxy)phenyl]piperidin-4-yl}-N-[4-(4-
trifluoromethoxybenzyl)oxy]phenyl]amine (0.30 g) was suspended in
methanol (3 ml). A 37% formaldehyde aqueous solution (0.11 g),
sodium cyanoborohydride (89 mg) and acetic acid (1 ml) were added
to the suspension and stirred at room temperature for 1 day. A
37% formaldehyde aqueous solution (0.22 g), sodium
cyanoborohydride (178 mg) and acetic acid (2 ml) were further
added to the mixture and stirred at room temperature for 1 day.
The reaction mixture was gradually added to a potassium carbonate
aqueous solution, followed by extraction with methylene chloride.
The organic layer was washed with a saturated sodium chloride
aqueous solution and dried over sodium sulfate, and the filtrate
was concentrated under reduced pressure. The resulting residue
was purified by medium pressure silica gel column chromatography
(methylene chloride:methanol = 10:0-methylene chloride:methanol =
9:1) and recrystallized from methanol to afford the title
compound as a pale brown powder (0.20 g).
Melting point: 142.0-143.7°C

Example 209
Preparation of (R)-2-nitro-7-(4-{4-[4-(4-4-
trifluoromethoxyphenoxy)butyl]piperidin-1-yl]phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.

White powder
MELTING POINT: 160-162°C

Example 210
Preparation of (R)-7-[4-(4-(4-[3-(4-chlorophenyl)propoxy]benzyl)piperazin-1-yl]phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Yellow powder
MELTING POINT: 200.7-200.9°C

Example 211
Preparation of (R)-2-nitro-7-[4-(4-[2-(4-trifluoromethoxyphenyl)ethyl]benzyl)piperazin-1-yl]phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Gray powder
MELTING POINT: 147.3-150.0°C

Example 212
Preparation of N-[1-[4-[(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy]phenyl]piperidin-4-yl]-N-[4-(4-trifluoromethylbenzyl)oxy]phenyl]amine

The title compound was prepared in the same manner as in Example 190 using suitable starting materials.
Yellow powder
MELTING POINT: 233.2-235.6°C

Example 213
Preparation of N-methyl-N-{1-[4-{(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy}phenyl]piperidin-4-yl}-N-[4-(4-trifluoromethylbenzoxloxy)phenyl]amine

N-{1-[4-{(R)-2-Nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy}phenyl]piperidin-4-yl}-N-[4-(4-trifluoromethylbenzoxloxy)phenyl]amine (0.40 g) and methanol (3 ml) were mixed. A 37% formaldehyde aqueous solution (0.47 g), sodium cyanoborohydride (0.36 g) and acetic acid (3 ml) were added to the mixture and stirred at room temperature overnight. The reaction mixture was added to a potassium carbonate aqueous solution, followed by extraction with methylene chloride. The organic layer was washed with water and dried over sodium sulfate. After filtering, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride:methanol = 1:0-methylene chloride:methanol = 9:1) to afford the title compound as a yellow powder (0.26 g).

Melting point: 170.6°C

Example 214

Preparation of N-[4-(4-chlorobenzoxloxy)phenyl]-N-{1-[4-{(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy}phenyl]piperidin-4-yl}amine

The title compound was prepared in the same manner as in Example 190 using suitable starting materials.

Yellow powder

Melting point: 236.5-237.1°C

Example 215

Preparation of N-[4-(4-chlorobenzoxloxy)phenyl]-N-methyl-N-{1-[4-{(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy}phenyl]piperidin-4-yl}amine

The title compound was prepared in the same manner as in Example 213 using suitable starting materials.
Yellow powder
Melting point: 205.6-206.5°C

Example 216
Preparation of (R)-2-nitro-7-{4-[4-(3-(4-
trifluoromethyl)benzyl)benzyl]piperazin-1-yl}phenoxy(methyl)-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.

Example 217
Preparation of (R)-7-{4-[4-(3-(4-
chlorobenzyl)benzyl]piperazin-1-yl}phenoxy(methyl)-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.

Example 218
Preparation of (R)-2-nitro-7-{4-[3-(trifluoromethyl)-5,6-
dihydro-8H-imidazo[1,2-a]pyrazin-7-yl]phenoxy(methyl)-6,7-dihydro-
5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.

Pale yellow powder
Melting point: 167.8-167.9°C

Example 219
Preparation of (R)-2-nitro-7-[4-[4-[(4-(4-
trifluoromethoxyphenoxy(methyl)benzyl]piperazin-1-
yl)phenoxy(methyl)]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.

Yellow powder

Melting point: 174.2-174.4°C

Example 220

Preparation of (R)-2-nitro-7-[4-{4-[4-(4-
trifluoromethylphenoxymethyl)benzyl]piperazin-1-
yl]phenoxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as

in Example 3 using suitable starting materials.

Yellow powder

Melting point: 207.2-208.2°C

Example 221

Preparation of 4-{4-(4-(7-methyl-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperazine-1-
carboxylic acid tert-buty1 ester

4-{4-[4-(2-Chloro-4-nitroimidazol-1-yl)-2-hydroxy-2-
methylbutoxy)phenyl)piperazine-1-carboxylic acid tert-buty1 ester

(2.12 g) was dissolved in dimethylformamide (21 ml), 60% sodium
hydride (0.24 g) was added thereto, and the mixture was stirred
at room temperature for 3 hours. Water was added to the reaction
mixture, the mixture was subjected to extraction with methylene
chloride, and then dried over sodium sulfate. After filtering,
the filtrate was concentrated under reduced pressure. The residue
was purified by silica gel column chromatography (methylene
chloride:ethyl acetate = 1:0-methylene chloride:ethyl acetate =
1:1) to afford the title compound as a colorless powder (1.05 g).

Melting point: 208.2-208.8°C

Example 222

Preparation of (R)-2-nitro-7-[4-{4-[4-{2-[4-
trifluoromethyl]ethoxy}benzyl]piperazin-1-
yl]phenoxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials. Yellow powder
Melting point: 149.1°C

Example 223
Preparation of (R)-7-(4-(4-[3-{4-chlorophenoxy}benzyl]piperazin-1-yl)phenoxy)methyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as in Example 3 using suitable starting materials. Yellow powder
Melting point: 185.2-186.1°C

Example 224
Preparation of (R)-2-nitro-7-(4-{4-[4-{4-trifluoromethylbenzyloxy}benzyl]piperidin-4-yloxy]phenoxy)methyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as in Example 3 using suitable starting materials. White powder
Melting point: 177-178°C

Example 225
Preparation of 7-{4-{(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy}phenyl}-3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine
The title compound was prepared in the same manner as in Example 1 using suitable starting materials. Pale yellow powder
Melting point: 145-146°C

Example 226
Preparation of 7-methyl-2-nitro-7-(4-{4-[4-{4-trifluoromethoxybenzyloxy}benzyl]piperazin-1-yl)phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder
Melting point: 178.7-178.8°C

Example 227
Preparation of 7-methyl-2-nitro-7-(4-(4-(4-(trifluoromethoxyphenoxy)benzyl)piperazin-1-yl)phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder
Melting point: 162.1-162.7°C

Example 228
Preparation of (R)-2-nitro-7-(4-(4-(4-(trifluoromethoxyphenoxy)benzyl)piperidin-1-yl)phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.

Pale grey powder
Melting point: 143.2-144.9°C

Example 229
Preparation of (S)-2-nitro-7-(4-(4-(4-(trifluoromethoxyphenoxy)benzyl)piperidin-1-yl)phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.

Pale grey powder
Melting point: 143.5-146.9°C

Example 230
Preparation of (S)-2-nitro-7-(4-(4-(4-(trifluoromethoxybenzyl)oxy)phenoxy)piperidin-1-yl)phenoxy)methyl)-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 69 using suitable starting materials. White powder

Melting point: 189-191°C

Example 231
Preparation of (R)-2-nitro-7-{4-[(4-(4-(4-
trifluoromethoxybenzyl)oxy)phenoxyl)piperidin-1-yl)phenoxymethyl]-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 169 using suitable starting materials. White powder

Melting point: 190-191°C

Example 232
Preparation of (S)-2-nitro-7-{4-[4-{3-
trifluoromethylphenoxy}benzyl]piperazin-1-yl)phenoxymethyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials. Yellow powder

Melting point: 155.5-156.4°C

Example 233
Preparation of (S)-7-{4-{4-[4-(4-
chlorophenoxy)benzyl]piperazin-1-yl)phenoxymethyl}]-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials. Yellow powder

Melting point: 135.7-138.7°C

Example 234
Preparation of (S)-2-nitro-7-{4-{4-[4-[2-[4-
trifluoromethoxyphenyl)ethoxy]benzyl)piperazin-1-yl)phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

**Example 235**

Preparation of (S)-2-nitro-7-[4-(4-[2-(4-
trifluoromethyl)phenyl)ethoxy]benzyl)piperazin-1-
yl)phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder

**Melting point: 169.8-170.6°C**

**Example 236**

Preparation of (S)-7-[4-(4-[4-[2-(4-
chlorophenyl)ethoxy]benzyl)piperazin-1-yl)phenoxy)methyl]-2-nitro-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder

**Melting point: 153.6°C**

**Example 237**

Preparation of (S)-2-nitro-7-[4-(4-[4-(4-
trifluoromethoxyphenoxy)methyl)benzyl)piperazin-1-
yl)phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder

**Melting point: 174.1-174.5°C**

**Example 238**
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Preparation of (S)-2-nitro-7-(4-{4-[4-(4-
trifluoromethylphenoxymethyl)benzyl]piperazin-1-
yl)phenoxymethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.

Yellow powder
Melting point: 208°C

Example 239

Preparation of (S)-7-(4-{4-[4-{4-
chlorophenoxymethyl)benzyl]piperazin-1-yl)phenoxymethyl}-2-nitro-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.

Yellow powder
Melting point: 228.6°C

Example 240

Preparation of (S)-2-nitro-7-(4-{4-{3-{4-
trifluoromethoxybenzyl)oxy}benzyl]piperazin-1-yl)phenoxymethyl}-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.

Yellow powder
Melting point: 156.6-158.3°C

Example 241

Preparation of (S)-2-nitro-7-(4-{4-{3-{4-
trifluoromethylbenzyl)oxy}benzyl]piperazin-1-yl)phenoxymethyl}-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.

Yellow powder
Melting point: 188.0-188.5°C
Example 242
Preparation of (R)-7-(4-{1-[4-(4-
chlorobenzyl oxy) benzyl] piperidin-4-yloxy} phenoxy)methyl)-2-nitro-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
White powder
Melting point: 176-177°C

Example 243
Preparation of (S)-2-nitro-7-(4-{1-[4-{4-
trifluoromethoxy benzyl oxy} benzyl] piperidin-4-
yloxy} phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
White powder
Melting point: 162-164°C

Example 244
Preparation of (S)-2-nitro-7-(4-{1-[4-{4-
trifluoromethyl benzyl oxy} benzyl] piperidin-4-yloxy} phenoxy)methyl)-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
White powder
Melting point: 156-158°C

Example 245
Preparation of (S)-7-(4-{1-[4-{4-
chlorobenzyl oxy} benzyl] piperidin-4-yloxy} phenoxy)methyl)-2-nitro-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
White powder
Melting point: 146-148°C
Example 246

Preparation of (S)-2-nitro-7-(4-{4-[4-(4-
trifluoromethylbenzyloxy)phenoxy]piperidin-1-yl}phenoxy)methyl)-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 69 using suitable starting materials.
White powder
Melting point: 187-188°C

Example 247

Preparation of (R)-2-nitro-7-(4-{4-[4-{4-
trifluoromethylbenzyloxy)phenoxy]piperidin-1-yl}phenoxy)methyl)-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 69 using suitable starting materials.
White powder
Melting point: 187-189°C

Example 248

Preparation of (R)-2-nitro-7-(4-{4-[4-[4-
trifluoromethoxyphenoxy)methyl]phenyl}piperazin-1-
yl)phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Pale brown solid
Melting point: 199-201°C

Example 249

Preparation of N-methyl-N-(4-{4-[4-(R)-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-
ylmethoxy)phenyl}piperazin-1-yl)phenyl)-N-(4-
trifluoromethylbenzyl)amine

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Colorless solid
Melting point: 229-230°C

Example 250

Preparation of (S)-7-(4-(4-[3-(4-chlorobenzyl)oxy]benzyl)piperazin-1-yl)phenoxy)methyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Pale yellow powder
Melting point: 186.1-186.2°C

Example 251

Preparation of (S)-2-nitro-7-(2-{4-[4-(4-trifluoromethoxy)phenoxy]benzyl}piperazin-1-yl)benzooxazol-5-yloxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder
Melting point: 165-167°C

Example 252

Preparation of (S)-2-nitro-7-(2-{4-[4-(4-trifluoromethoxy)benzyl]oxy}benzyl)piperazin-1-yl)benzooxazol-5-yloxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder
Melting point: 174-176°C

Example 253

Preparation of (R)-2-nitro-7-(2-{4-[4-(4-trifluoromethoxy)benzyl]oxy}benzyl)piperazin-1-yl)benzooxazol-5-yloxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.  
White powder
Melting point: 175-176°C

Example 256  
Preparation of (R)-7-(4-((3R,5S)-3,5-dimethyl-4-[4-(4- 
25 trifluoromethoxybenzyl)oxy]benzyl)piperazin-1-yl)phenoxyethyl)-2- 
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 86 using suitable starting materials.
Pale brown powder
Melting point: 125.1°C

Example 257  
Preparation of (S)-2-nitro-7-[4-(4-[2-(4- 
35 trifluoromethoxyphenyl)ethy]benzyl)piperazin-1- 
yl)phenoxyethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

Example 255  
Preparation of (S)-7-(4-((3R,5S)-3,5-dimethyl-4-[4-(4- 
15 trifluoromethoxybenzyl)oxy]benzyl)piperazin-1-yl)phenoxyethyl)-2- 
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 86 using suitable starting materials.
Pale brown powder
Melting point: 122.1-122.6°C

Example 254  
Preparation of (S)-2-nitro-7-(4-[4-{4-(4- 
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 86 using suitable starting materials.
Brown powder
Melting point: 217.9-220.1°C
The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 178.0-178.6°C

Example 258
Preparation of (S)-2-nitro-7-[4-{4-[2-{4-trifluoromethylphenyl}ethyl]benzyl}piperazin-1-yl]phenoxyethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 193.6°C

Example 259
Preparation of (S)-2-nitro-7-[4-{4-{4-[3-(4-trifluoromethylphenyl)propoxy]benzyl}piperazin-1-yl}phenoxyethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 164.7-164.8°C

Example 260
Preparation of (S)-7-[4-{4-{3-[4-chlorophenyl]propoxy}benzyl}piperazin-1-yl]phenoxyethyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 200.2-200.6°C

Example 261
Preparation of (S)-2-nitro-7-{4-{4-[4-(4-(4-trifluoromethylbenzyloxy)benzyl}piperazin-1-yl}phenoxyethyl]-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 208°C

Example 262

Preparation of (S)-7-[(4-{4-[(4-chlorobenzyl)oxy]benzyl}piperazin-1-yl)phenoxy)methyl]-3-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 229.9°C

Example 263

Preparation of N-{1-[4-{{(S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy}phenyl}piperidin-4-yl}-N-[4-(4-trifluoromethoxybenzyl)oxy]phenyl]amine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Powder
Melting point: 228-229°C

Example 264

Preparation of (S)-2-nitro-7-[(4-{4-[3-(4-trifluoromethoxyphenyl)propoxy]benzyl}piperazin-1-yl)phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Yellow powder
Melting point: 159.4-161.7°C

Example 265

Preparation of (4-{4-{{(S)-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]piperazin-1-ylmethyl)phenyl]carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder

Melting point: 191.4-191.9°C

Example 266

Preparation of N-methyl-N-(1-[4-[(S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy]phenyl]piperidin-4-yl)-N-[4-(4-trifluoromethoxybenzyl)oxy]phenyl]amine

N-(1-[4-[(S)-2-Nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy]phenyl]piperidin-4-yl)-N-[4-(4-trifluoromethoxybenzyl)oxy]phenyl]amine (0.30 g) was suspended in 1.2-dichloroethane (2 ml). A 37% formaldehyde aqueous solution (0.362 ml) and sodium triacetoxyborohydride (149 mg) were added to the suspension and stirred at room temperature overnight. A 37% formaldehyde aqueous solution (0.362 ml) and sodium triacetoxyborohydride (149 mg) were further added thereto and stirred at room temperature for 1 day. A sodium hydrogen carbonate aqueous solution was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under reduced pressure.

The residue was purified by silica gel column chromatography (ethyl acetate:hexane = 2:1-methylene chloride:methanol = 4:1) and crystallized from ether to afford the title compound as a pale yellow powder (130 mg).

Melting point: 143-145°C

Example 267

Preparation of N-ethyl-N-(1-[4-[(S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy]phenyl]piperidin-4-yl)-N-[4-(4-trifluoromethoxybenzyl)oxy]phenyl]amine
The title compound was prepared in the same manner as in Example 226 using suitable starting materials.
Pale yellow powder
Melting point: 147-150°C

Example 268
Preparation of (R)-7-{4-((3R,5S)-3,5-dimethyl-4-[3-(4-
trifluoromethylphenyl)propyl]piperazin-1-yl)phenoxy)methyl}-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.
Yellow powder
Melting point: 190.6-191.4°C

Example 269
Preparation of (S)-7-{4-((3R,5S)-3,5-dimethyl-4-[3-(4-
trifluoromethylphenyl)propyl]piperazin-1-yl)phenoxy)methyl}-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.
Yellow powder
Melting point: 190.6-191.5°C

Example 270
Preparation of (S)-2-nitro-7-{4-4-[5-(4-
trifluoromethoxyphenyl)pentyl]piperazin-1-yl)phenoxy)methyl}-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 165-168°C

Example 271
Preparation of (R)-2-nitro-7-{4-4-[5-(4-
trifluoromethoxyphenyl)pentyl]piperazin-1-yl)phenoxy)methyl}-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Example 272
Preparation of (S)-2-nitro-7-{2-[4-(4-
trifluoromethoxyphenoxo)benzyl]-2,3-dihydro-1H-isooindol-5-
yloxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder
Melting point: 160-162°C

Example 273
Preparation of (S)-2-nitro-7-{2-[4-(4-
trifluoromethoxybenzyl)oxy)benzyl]-2,3-dihydro-1H-isooindol-5-
yloxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder
Melting point: 161-163°C

Example 274
Preparation of (S)-2-nitro-7-{4-[4-(4-
trifluoromethoxybenzyl)oxy)piperidin-1-yl]phenoxymethyl]-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 36 using suitable starting materials.

Yellow powder
Melting point: 210.2-212.2°C

Example 275
Preparation of N-ethyl-N-{1-[4-((R)-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperidin-4-yl]-N-[4-((4-
trifluoromethoxybenzyloxy)phenyl)amine

N-[1-[4-((R)-2-Nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperidin-4-yl]-N-[4-((4-
trifluoromethoxybenzyloxy)phenyl)amine (0.47 g) was suspended in 1,2-dichloroethane (5 ml). Acetaldheyde (0.41 ml) and sodium triacetoxyborohydride (0.46 g) were added to the suspension, and the mixture was stirred at room temperature for 3 days. A potassium carbonate aqueous solution was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated sodium chloride aqueous solution, dried over sodium sulfate, and then concentrated under reduced pressure. The residue was purified by medium pressure silica gel column chromatography (methylene chloride:methanol = 10:0-methylene chloride:methanol = 9:1) and recrystallized from methanol to afford the title compound as a yellow powder (0.25 g). Melting point: 95.2-97.0°C

Example 276
Preparation of N-ethyl-N-[1-[4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperidin-4-yl]-N-[4-((4-
trifluoromethoxybenzyloxy)phenyl)amine

The title compound was prepared in the same manner as in Example 275 using suitable starting materials. Brown solid Melting point: 88.7-90.2°C

Example 277
Preparation of (R)-2-nitro-7-(2-[4-((4-
trifluoromethoxyphenoxy)benzyl]-2,3-dihydro-1H-isocindol-5-
yloxy methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
White powder
Melting point: 161-164°C

Example 278

Preparation of (R)-2-nitro-7-{2-[4-(4-
trifluoromethoxybenzyl)oxy]benzyl}-2,3-dihydro-1H-isocindol-5-
yloxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.

White powder
Melting point: 160-163°C

Example 279

Preparation of (R)-2-nitro-7-{4-{4-[4-(4-
trifluoromethoxybenzyl)oxy]phenoxymethyl}piperidin-1-yl} 
phenoxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 69 using suitable starting materials.

Pale yellow powder
Melting point: 210-215°C

Example 280

Preparation of (R)-2-nitro-7-{4-[4-{4-[2-(4-
trifluoromethyl)phenyl]ethyl}benzyl)piperazin-1-yl]phenoxymethyl]-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.

Yellow powder
Melting point: 187.6-188.8°C

Example 281

Preparation of (R)-2-nitro-7-{4'-[4-{4-
trifluoromethoxyphenoxy)piperidin-1-ylmethyl]biphenyl-4-
yloxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 86 using suitable starting materials.
Pale brown powder
Melting point: 200.4-201.4°C

Example 282
Preparation of (S)-2-nitro-7-{4'-(4-(4-trifluoromethoxyphenoxy)piperidin-1-ylmethyl)benzyl-4-yloxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 86 using suitable starting materials.
Pale brown powder
Melting point: 196.9-198.0°C

Example 283
Preparation of (S)-2-nitro-7-{4-{4-[4-(4-trifluoromethoxybenzyl)oxy)methyl]piperidin-1-yl}phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 69 using suitable starting materials.
Brown powder
Melting point: 193-196°C

Example 284
Preparation of (R)-7-{4-{((3R,5S)-3,5-dimethyl-4-{4-(4-trifluoromethyl)benzyl]piperazin-1-yl)phenoxy)methyl}-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 86 using suitable starting materials.
Brown powder
Melting point: 112.8°C

Example 285
Preparation of (S)-7-{4-{((3R,5S)-3,5-dimethyl-4-{4-(4-trifluoromethyl)benzyl]piperazin-1-yl)phenoxy)methyl}-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as in Example 86 using suitable starting materials.
Brown powder
Melting point: 111.5°C

Example 286
Preparation of (S)-2-nitro-7-{2-[4-[4-(4-trifluoromethoxybenzyl)oxy]benzyl]piperidin-1-yl}benzothiazol-6-yloxyethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.
Pale yellow powder
Melting point: 190-191°C

Example 287
Preparation of (R)-2-nitro-7-{2-[4-[4-(4-trifluoromethoxybenzyl)oxy]benzyl]piperidin-1-yl}benzothiazol-6-yloxyethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.
Pale yellow powder
Melting point: 190-191°C

Example 288
Preparation of 7-((S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-2-[4-(4-trifluoromethoxyphenoxyl)benzyl]-1,2,3,4-tetrahydriodisoquinoline

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
White powder
Melting point: 147-150°C

Example 289
Preparation of 7-((S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-2-[4-(4-
trifluoromethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Pale yellow powder

Melting point: 150-154°C

Example 290

Preparation of N-(4-(4-((S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperazin-1-ylmethyl)phenyl)-N-(4-trifluoromethylbenzyl)amine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder

Melting point: 215.8-217.1°C

Example 291

Preparation of 7-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-2-[4-(4-trifluoromethoxybenzylxy)benzyl]-1,2,3,4-tetrahydroisoquinoline

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder

Melting point: 149-151°C

Example 292

Preparation of 7-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-2-[4-(4-trifluoromethoxybenzylxy)benzyl]-1,2,3,4-tetrahydroisoquinoline

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Pale yellow powder

Melting point: 149-152°C

Example 293

Preparation of N-methyl-N-(4-(4-((S)-2-nitro-6,7-
-255-

dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-
ylethoxy)phenyl)piperazin-1-ylmethyl)phenyl)-N-(4-
trifluoromethylbenzyl)amine

The title compound was prepared in the same manner as
in Example 213 using suitable starting materials.
White powder
Melting point: 168.5-169.0°C

Example 294

Preparation of (R)-7-(4-(4-(4-(2,4-bis-
trifluoromethylbenzyl)oxy)benzyl)piperazin-1-yl)phenoxy)methyl)-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.
Yellow powder
Melting point: 185.4-186.3°C

Example 295

Preparation of (S)-7-(4-(4-(4-(2,4-bis-
trifluoromethylbenzyl)oxy)benzyl)piperazin-1-yl)phenoxy)methyl)-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.
Yellow powder
Melting point: 184.5-185.8°C

Example 296

Preparation of (R)-2-nitro-7-(4-(4-(4-(4-
trifluoromethoxybenzyl)oxy)phenyl)piperazin-1-
ylmethyl)phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 190 using suitable starting materials.
Yellow powder
Melting point: 212-214°C
Example 297

Preparation of (R)-2-nitro-7-(4-((4-(4-(trifluoromethoxy)phenoxyl)piperazin-1-yl)methyl)phenoxymethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 190 using suitable starting materials.
Yellow powder
Melting point: 140-142°C

Example 298

Preparation of (4-((4-(2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperazin-1-yl)methyl)phenyl)carbamic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 190.5-190.7°C

Example 299

Preparation of (R)-7-(4-((R)-3-methyl-4-(4-(trifluoromethyl)benzoxyl)benzyl)piperazin-1-yl)phenoxymethyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.
Pale brown powder
Melting point: 151.0-152.2°C

Example 300

Preparation of (S)-7-(4-((R)-3-methyl-4-(4-(trifluoromethyl)benzoxyl)benzyl)piperazin-1-yl)phenoxymethyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.
Pale brown powder
Melting point: 156.8-158.3°C
Example 301
Preparation of 6-((S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-2-[(4- 
trifluoromethoxyphenoxo)benzyl]-1,2,3,4-tetrahydroisoquinoline

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
White powder
Melting point: 196-198°C

Example 302
Preparation of (R)-3-methyl-4-[(4-((R)-2-nitro-6,7- 
dihydro-5H-imidazo[2,1-b][1,3]oxazin-7- 
ylmethoxy)phenyl)piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.
Brown powder
Melting point: 196.4°C

Example 303
Preparation of 6-((R)-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-2-[(4- 
trifluoromethoxybenzylxy)benzyl]-1,2,3,4-tetrahydroisoquinoline

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
White powder
Melting point: 212-215°C

Example 304
Preparation of 6-((R)-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-2-[(4- 
trifluoromethoxybenzylxy)benzyl]-1,2,3,4-tetrahydroisoquinoline

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
White powder
Melting point: 209-211°C

Example 305

Preparation of 7-((S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-2-[4-(4-trifluoromethoxyphenoxo)benzyl]-2,3,4,5-tetrahydro-1H-benzo[c]azepine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder
Melting point: 196-198°C

Example 306

Preparation of 7-((S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-2-[4-(4-trifluoromethoxybenzyloxy)benzyl]-2,3,4,5-tetrahydro-1H-benzo[c]azepine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder
Melting point: 216-218°C

Example 307

Preparation of N-((4-((4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperazin-1-yl)methyl)phenyl)-N-(4-trifluoromethylbenzyl)amine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder
Melting point: 216.0-217.7°C

Example 308

Preparation of (R)-7-((S)-3-methyl-4-[4-(4-trifluoromethylbenzyloxy)benzyl)piperazin-1-yl)phenoxymethyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as in Example 86 using suitable starting materials. Pale brown powder
Melting point: 155.9°C

Example 309
Preparation of (S)-7-(4-((S)-3-methyl-4-[4-(4-
trifluoromethylbenzyloxy)benzyl]piperazin-1-yl)phenoxy)methyl)-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials. Pale brown powder Melting point: 150.6°C

Example 310
Preparation of (R)-7-(4-((R)-2-methyl-4-[4-(4-
trifluoromethoxybenzyloxy)benzyl]piperazin-1-yl)phenoxy)methyl)-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials. Pale yellow powder Melting point: 164.5°C

Example 311
Preparation of (R)-7-(4-((R)-2-methyl-4-[4-(4-
trifluoromethylbenzyloxy)benzyl]piperazin-1-yl)phenoxy)methyl)-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials. Pale yellow powder Melting point: 154.3°C

Example 312
Preparation of (R)-7-(4-[4-[(2-fluoro-4-
trifluoromethylbenzyloxy)benzyl]piperazin-1-yl)phenoxy)methyl]-2-
-260-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale brown powder

5 Melting point: 166.4-167.2°C

Example 313
Preparation of (S)-7-[(4-[(4-[(2-fluoro-4-trifluoromethylbenzyloxy)benzyl]piperazin-1-yl)phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale brown powder
Melting point: 166.4-167.8°C

Example 314
Preparation of N-[4-{4-[4-{[(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy]phenyl]piperazin-1-ylmethyl}phenyl]-N-{4-trifluoromethoxybenzyl}amine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Yellow powder
Melting point: 226.3-228.2°C

Example 315
Preparation of N-methyl-N-[4-{4-{[(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy]phenyl]piperazin-1-ylmethyl}phenyl]-N-{4-trifluoromethylbenzyl}amine

The title compound was prepared in the same manner as in Example 313 using suitable starting materials.
Yellow powder
Melting point: 179.6-179.7°C

Example 316
Preparation of 7-{((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy}-2-[4-(4-
trifluoromethoxyphenoxy)benzyl]-2,3,4,5-tetrahydro-1H-
benzo[c]azepine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
White powder
Melting point: 195-196°C

Example 317
Preparation of 7-{((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-2-[4-(4-
trifluoromethoxybenzyl)oxy]benzyl]-2,3,4,5-tetrahydro-1H-
benzo[c]azepine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
White powder
Melting point: 215-217°C

Example 318
Preparation of (S)-3-methyl-4-{((R)-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-
ylmethoxy)phenyl)piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 36 using suitable starting materials.
Yellow powder
Melting point: 167.6°C

Example 319
Preparation of (S)-3-methyl-4-{((S)-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-
ylmethoxy)phenyl)piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 36 using suitable starting materials.

Yellow powder
Melting point: 195.0-195.4°C

Example 320
Preparation of N-methyl-N-(4-(4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperazin-1-ylmethyl)phenyl)-N-(4-trifluoromethoxybenzyl)amine

The title compound was prepared in the same manner as in Example 213 using suitable starting materials.

Yellow powder
Melting point: 184.8-184.9°C

Example 321
Preparation of (R)-7-(4-((S)-2-methyl-4-[(4-(4-trifluoromethoxybenzyl)oxy)phenyl)piperazin-1-yl)phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder
Melting point: 132.5-132.6°C

Example 322
Preparation of (R)-7-(4-((S)-2-methyl-4-[(4-(4-trifluoromethoxybenzyl)oxy)phenyl)piperazin-1-yl)phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder
Melting point: 155.6-155.8°C

Example 323
Preparation of (S)-7-(4-((S)-2-methyl-4-[(4-(4-trifluoromethoxybenzyl)oxy)phenyl)piperazin-1-yl)phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.

White powder
Melting point: 148.0-148.3°C

Example 324
Preparation of (S)-7-(4-{(S)-2-methyl-4-[4-(4-
trifluoromethylbenzoyl)benzyl]piperazin-1-yl}phenoxy)methyl)-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.

Yellow powder
Melting point: 163.7-164.2°C

Example 325
Preparation of (R)-2-nitro-7-(4-{4-[4-(2,3,5,6-
tetrafluoroo-4-trifluoromethylbenzoyl)benzyl]piperazin-1-
yl]phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.

Yellow powder
Melting point: 172.0-172.5°C

Example 326
Preparation of (S)-2-nitro-7-(4-{4-[4-(2,3,5,6-
tetrafluoroo-4-trifluoromethylbenzoyl)benzyl]piperazin-1-
yl]phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.

Yellow powder

Melting point: 171.9-172.2°C

Example 327
Preparation of (R)-2-nitro-7-(4-{4-[4-(4-
trifluoromethylphenoxy)benzyl]piperazin-1-yl]phenoxy)methyl)-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder
Melting point: 184.6-184.9°C

Example 328
Preparation of (R)-7-(4-(((S)-2-methyl-4-[4-(4-trifluoromethoxyphenoxy)benzyl]piperazin-1-yl)phenoxy)methyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder
Melting point: 147.0-147.4°C

Example 329
Preparation of (R)-7-(4-(((S)-2-methyl-4-[4-(4-trifluoromethylphenoxy)benzyl]piperazin-1-yl)phenoxy)methyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder
Melting point: 158.8°C

Example 330
Preparation of (R)-3-methyl-4-[4-(((S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethyl)phenyl)piperazin-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.

Yellow powder
Melting point: 164.3-164.9°C

Example 331
Preparation of N-methyl-N-{1-[4-(((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-
-285-
ylmethoxy)phenyl)piperidin-4-yl)-N-[4-(4-
trifluoromethoxybenzyl)oxy]benzyl]amine

The title compound was prepared in the same manner as
in Example 180 using suitable starting materials.

Example 332

Preparation of N-methyl-N-[4-[(S)-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-
ylmethoxy)phenyl)piperidin-4-yl]-N-[4-(4-
trifluoromethoxybenzyl)oxy]benzyl]amine

The title compound was prepared in the same manner as
in Example 180 using suitable starting materials.

Example 333

Preparation of (S)-7-[(S)-2-methyl-4-[4-(4-
trifluoromethoxyphenoxy)benzyl)piperazin-1-yl]phenoxymethyl]-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.

Yellow powder

Melting point: 150.0-150.3°C

Example 334

Preparation of (S)-7-[(S)-2-methyl-4-[4-(4-
trifluoromethylphenoxy)benzyl)piperazin-1-yl]phenoxymethyl]-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.

Yellow powder

Melting point: 158.0-159.1°C
Example 335
Preparation of (R)-7-{4-{(R)-2-methyl-4-[4-(4-
trifluoromethoxyphenoxo)benzyl]piperazin-1-yl]phenoxymethyl}-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder
Melting point: 150.2-150.6°C

Example 336
Preparation of (R)-7-{4-{(R)-2-methyl-4-[4-(4-
trifluoromethylphenoxy)benzyl]piperazin-1-yl]phenoxymethyl}-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder
Melting point: 158.6-160.6°C

Example 337
Preparation of (R)-2-nitro-7-{6-[4-[4-(4-
trifluoromethoxybenzyl oxy)benzyl]piperazin-1-yl]pyridin-3-
yloxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Pale brown solid
Melting point: 197.7-198.0°C

Example 338
Preparation of (S)-2-nitro-7-{6-[4-[4-(4-
trifluoromethoxybenzyl oxy)benzyl]piperazin-1-yl]pyridin-3-
yloxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Pale brown solid
Melting point: 197-198°C
Example 339
Preparation of (S)-7-(4-((2S,5R)-2,5-dimethyl-4-[4-(4-
itro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 95-97°C

Example 340
Preparation of (S)-7-(4-((2S,5R)-2,5-dimethyl-4-[4-(4-
trifluoromethoxybenzyloxy)benzyl]piperazin-1-yl)phenoxymethyl)-2-
5
These title compounds were prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 127.6-129.8°C

Example 341
Preparation of (S)-7-(4-((2S,5R)-2,5-dimethyl-4-[4-(4-
trifluoromethoxyphenoxo)benzyl]piperazin-1-yl)phenoxymethyl)-2-
10
These title compounds were prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 124.2-125.2°C

Example 342
Preparation of (S)-7-(4-((R)-2-methyl-4-[4-(4-
trifluoromethoxyphenoxo)benzyl]piperazin-1-yl)phenoxymethyl)-2-
15
These title compounds were prepared in the same manner as in Example 3 using suitable starting materials.
Pale yellow powder
Melting point: 102-103.5°C
Melting point: 145.7-146.3°C

Example 343
Preparation of (S)-7-(4-{{(R)-2-methyl-4-[4-(4-
trifluoromethylenoxy)benzyl]piperazin-1-yl}phenoxymethyl}-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder

Melting point: 153.5-154.3°C

Example 344
Preparation of (S)-7-(4-{{(R)-2-methyl-4-[4-(4-
trifluoromethoxybenzyl)oxy)benzyl]piperazin-1-yl}phenoxymethyl}-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder

Melting point: 151.0-151.7°C

Example 345
Preparation of (S)-7-(4-{{(R)-2-methyl-4-[4-(4-
trifluoromethylbenzyl)oxy)benzyl]piperazin-1-yl}phenoxymethyl}-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Yellow powder

Melting point: 155.1-157.2°C

Example 346
Preparation of (R)-7-(4-{{(3-methyl-4-[4-(4-
trifluoromethoxybenzyl)oxy)benzyl]piperazin-1-yl}phenoxymethyl}-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
White powder  
Melting point: 172.9-173.8°C

Example 347

Preparation of (R)-7-(4-(4-{3-methyl-4-(4-trifluoromethylbenzoxyl)benzyl)piperazin-1-yl)phenoxymethyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder  
Melting point: 199.4-206.5°C

Example 348

Preparation of (S)-7-(4-(4-{3-methyl-4-(4-
trifluoromethoxybenzoxyl)benzyl)piperazin-1-yl)phenoxymethyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder  
Melting point: 169.8-170.2°C

Example 349

Preparation of (S)-7-(4-(4-{3-methyl-4-(4-
trifluoromethylbenzoxyl)benzyl)piperazin-1-yl)phenoxymethyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

White powder  
Melting point: 161.2-162.8°C

Example 350

Preparation of (R)-7-(4-{(2S,5R)-2,5-dimethyl-4-(4-(4-trifluoromethoxyphenoxy)benzyl)piperazin-1-yl)phenoxymethyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

Potassium carbonate (135 mg) and sodium iodide (146 mg)
were added to an N-methylpyrrolidone solution (6 ml) of (R)-7-[4-((2S,5R)-2,5-dimethyl-piperazin-1-yl)phenoxymethyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine trifluoroacetate (343 mg) and 1-(chloromethyl)-4-[4-(trifluoromethoxy)phenoxymethyl]benzene (269 mg), and the mixture was stirred at 60°C for 3 hours. Sodium tert-butoxide (112 mg) was added to the mixture and stirred at room temperature for 3 hours. Water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with a saturated sodium chloride aqueous solution and then dried over sodium sulfate. After filtering, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:1—ethyl acetate:n-hexane = 3:1) to afford the title compound as a pale brown amorphous compound (200 mg).

1H NMR (CDC13) δ 0.83 (d, J = 6.1 Hz, 3H), 1.14 (d, J = 6.3 Hz, 3H), 2.04 (t, J = 8.9 Hz, 1H), 2.26-2.54 (m, 2H), 2.55-2.73 (m, 2H), 2.62 (dd, J = 12.0 Hz, 2.9 Hz, 1H), 2.93-3.17 (m, 2H), 3.22 (d, J = 13.4 Hz, 1H), 4.02 (d, J = 13.4 Hz, 1H), 4.06-4.35 (m, 4H), 4.65-4.78 (m, 1H), 6.84 (d, J = 8.9 Hz, 2H), 6.90-7.11 (m, 6H), 7.18 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.44 (s, 1H).

Example 351
Preparation of (R)-7-[4-((2S,5R)-2,5-dimethyl-4-[4-(4-
trifluoromethoxybenzoyl)piperazin-1-yl)phenoxymethyl]-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 350 using suitable starting materials.
Pale brown amorphous

Melting point: 119.5-121.5°C
1H NMR (CDCl3) δ 0.81 (d, J = 6.1 Hz, 3H), 1.13 (d, J = 5.9 Hz, 3H), 1.91-2.06 (m, 1H), 2.22-2.54 (m, 2H), 2.54-2.83 (m, 3H), 2.94-3.10 (m, 2H), 3.19 (d, J = 13.1 Hz, 1H), 3.89-4.34 (m, 5H), 4.62-4.77 (m, 1H), 5.06 (s, 2H), 6.84 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 8.6 Hz, 2H), 7.04 (d, J = 8.9 Hz, 2H), 7.18-7.32 (m, 4H).
Example 352

Preparation of (R)-7-4-((2S,5R)-2,5-dimethyl-4-(4-(4-
trifluoromethylenbenzyl)oxybenzyl)piperazin-1-yl)phenoxymethyl)-2-
nitro-6,7-dihydro-3H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 350 using suitable starting materials.

Pale brown amorphous

10 Melting point: 108-110°C

1H NMR (CDCl3) δ 0.91 (d, J = 6.1 Hz, 3H), 1.13 (d, J = 6.8 Hz,
3H), 1.93-2.07 (m, 1H), 2.26-2.52 (m, 2H), 2.56-2.83 (m, 3H),
2.92-3.14 (m, 2H), 3.19 (d, J = 13.2 Hz, 1H), 3.99 (d, J = 13.2
Hz, 1H), 4.05-4.34 (m, 4H), 4.66-4.79 (m, 1H), 5.13 (s, 2H), 6.83
(d, J = 8.9 Hz, 2H), 6.93 (d, J = 8.6 Hz, 2H), 7.04 (d, J = 8.9
Hz, 2H), 7.18-7.28 (m, 2H), 7.45 (s, 1H), 7.56 (d, J = 8.2 Hz,
2H), 7.65 (d, J = 8.2 Hz, 2H).

Example 353

Preparation of (R)-2-nitro-7-(4'-4-(4-
trifluoromethoxybenzyl)oxybenzyl)piperazin-1-yl)biphenyl-4-
yloxymethyl)-6,7-dihydro-3H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.

25 Pale yellow solid

Melting point: 249.6-252.8°C

Example 354

Preparation of (S)-2-nitro-7-(4'-4-(4-
trifluoromethoxybenzyl)oxybenzyl)piperazin-1-yl)biphenyl-4-
yloxymethyl)-6,7-dihydro-3H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 3 using suitable starting materials.

Pale yellow solid

35 Melting point: 222.6-222.9°C
Example 355
Preparation of N-methyl-N-[1-{4-[(R)-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-
ylmethoxy]phenyl}piperidin-4-ylmethyl]-N-[4-(4-
trifluoromethoxybenzyloxy)phenyl]amine

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Pale yellow solid
Melting point: 167.0-170.1°C

Example 356
Preparation of N-methyl-N-[1-{4-[(S)-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-
ylmethoxy]phenyl}piperidin-4-ylmethyl]-N-[4-(4-
trifluoromethoxybenzyloxy)phenyl]amine

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Pale yellow solid
Melting point: 170-171°C

Example 357
Preparation of (S)-2-nitro-7-(4-[(5-4-{4-
trifluoromethoxyphenoxy}benzyl]-2,5-diazabicyclo[2.2.1]hept-2-
yl)phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 350 using suitable starting materials.
Pale brown powder
Melting point: 127-129°C

Example 358
Preparation of (S)-2-nitro-7-(4-[(5-4-{4-
trifluoromethoxybenzyloxy}benzyl]-2,5-diazabicyclo[2.2.1]hept-2-
yl)phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 350 using suitable starting materials.

Powder
Melting point: 142-145°C

Example 359

Preparation of (R)-2-nitro-7-(4-[(5-[4-(4-
trifluoromethoxyphenoxy)benzyl]-2,5-diazabicyclo[2.2.1]hept-2-
yl]phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as

in Example 350 using suitable starting materials.
Pale brown powder
Melting point: 165-168°C

Example 360

Preparation of (R)-2-nitro-7-(4-[(5-[4-(4-
trifluoromethoxybenzyl)oxy]benzyl]-2,5-diazabicyclo[2.2.1]hept-2-
yl]phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as

in Example 350 using suitable starting materials.
Pale brown powder
Melting point: 172-174°C

Example 361

Preparation of 7-[(4-[2-(4-chlorophenoxy)methyl]oxazol-4-
yl]phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-
b][1,3]oxazine

An ethanol solution (0.45 ml) of 20% sodium ethoxide was added to an ethanol solution (10 ml) of toluene-4-sulfonic acid 4-(2-chloro-4-nitroimidazol-1-yl)-2-hydroxybutyl ester (0.52 g), and the mixture was stirred at room temperature for 30 minutes. 4-[2-(4-Chlorophenoxy)methyl]oxazol-4-yl]phenol (0.40 g) and tripotassium phosphate (0.34 g) were added to the reaction mixture, and the resulting mixture was heated under reflux for 2 hours. Water was added thereto and the precipitated solid was collected by filtration and dried at 60°C. The residue thus
obtained was dissolved in dimethylformamide (3 mL), and sodium hydride (53 mg) was added thereto, followed by stirring at room temperature for 1 hour. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried over magnesium sulfate. After filtering, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride:methanol = 10:0, methylene chloride:methanol = 9:1) to afford the title compound as a pale yellow powder (0.34 g).

Melting point: 199-200°C

Example 362
Preparation of (R)-7-[(4-[(2-[(4-chlorophenoxymethyl)oxazol-4-yl]phenoxy)methyl])]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 361 using suitable starting materials.
Pale yellow powder
Melting point: 214-215°C

Example 363
Preparation of (R)-2-nitro-7-[(4-[(4-trifluoromethoxybenzyl)piperidin-4-yl]phenoxy)methyl])]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

Trifluoroacetic acid (6 mL) was added to 4-[(4-[(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperidine-1-carboxylic acid tert-butyl ester (2.0 g), and the mixture was stirred at room temperature for 40 minutes. The reaction mixture was concentrated under reduced pressure. Methylene chloride (6 mL) and triethylamine (6 mL) were added to the residue, and the mixture was stirred at room temperature for 10 minutes. The reaction mixture was reconstituted under reduced pressure. N-Methylpyrrolidone (5 mL), 4-(trifluoromethoxy)benzaldehyde (0.93 mL) and sodium triacetoxycobaltetrachloride (1.39 g) were added to the residue, and the
mixture was stirred at room temperature for 3 hours. A 20% sodium carbonate aqueous solution (20 ml) and water (20 ml) were added to the reaction mixture, followed by stirring. The insoluble matter generated was collected by filtration. The residue thus obtained was washed with water and hexane, and then dried. Subsequently, the residue was suspended in ethyl acetate-isopropyl ether (1:1), and the suspension was stirred at room temperature, followed by collection by filtration. The residue was then dried to afford the title compound as a reddish brown solid (2.39 g).
Melting point: 183-184°C

Example 364
Preparation of 2-nitro-7-(4-1-(4-
trifluoromethoxybenzyl)piperidin-4-yl)phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 363 using suitable starting materials.
Pale yellow solid
Melting point: 178.6-180.2°C

Example 365
Preparation of N-{1-[4-{(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxatin-7-ylmethoxy}phenyl]piperidin-4-yl}-N-
(4-trifluoromethylphenyl)amine

The title compound was prepared in the same manner as in Example 366 using suitable starting materials. Yellowish orange powder
Melting point: 214-216°C

Example 366
Preparation of (R)-2-nitro-7-(4-[4-2-(4-
trifluoromethylphenoxy)ethyl]piperidin-1-yl)phenoxy)methyl)-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 36 using suitable starting materials.

Yellow solid
Melting point: 172.9-173.1°C

5 Example 367

Preparation of (R)-2-nitro-7-{4-[4-(4-trifluoromethylbenzyloxy)piperidin-1-yl]phenoxymethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 36 using suitable starting materials.

Yellow solid
Melting point: 186.6-197.0°C

Example 368

15 Preparation of (R)-2-nitro-7-{4-[4-(4-trifluoromethylbenzyl)piperazin-1-yl]phenoxymethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 363 using suitable starting materials.

20 Slightly yellow powder
Melting point: 162-164°C

Example 369

Preparation of (R)-2-nitro-7-{4-[4-(4-trifluoromethoxybenzyl)piperazin-1-yl]phenoxymethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 363 using suitable starting materials.

Pale yellow powder
Melting point: 188-189°C

Example 370

Preparation of N-ethyl-N-{1-[(4-(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]piperidin-4-yl}-N-(4-trifluoromethylphenyl)amine
Acetaldehyde (2.2 ml) was added to an acetic acid solution (11 ml) of N-[1-{4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]piperidin-4-yl]-N-(4-trifluoromethylphenyl)amine (2.2 g). Subsequently, sodium triacetoxoborohydride (2.52 g) was added thereto, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into ice water, and neutralized with a 5 % sodium hydroxide aqueous solution and a saturated sodium hydrogen carbonate aqueous solution. The resulting precipitate was collected by filtration and dried. The solid thus obtained was purified by silica gel column chromatography (methylene chloride:ethyl acetate = 50:50) and recrystallized from acetone-ethyl acetate to afford the title compound as a yellow powder (1.96 g).

Melting point: 206°C

Example 371
Preparation of N-methyl-N-[1-{4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]piperidin-4-yl]-N-(4-trifluoromethylphenyl)amine

The title compound was prepared in the same manner as in Example 370 using suitable starting materials.

Yellow powder
Melting point: 208-209°C

Example 372
Preparation of (R)-2-nitro-7-(4-{4-{(E)-3-{(4-trifluoromethylphenyl)allyl}piperazin-1-yl}phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 363 using suitable starting materials.

White powder
Melting point: 207-210°C

Example 373
Preparation of N-[1-[4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-yl)methoxy]phenyl]piperidin-4-yl]-N-(4-trifluoromethoxyphenyl)amine

4-(Trifluoromethoxy)aniline (1.271 ml) was added to a 1,2-dichloroethane solution (50 ml) of 1-[4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-yl)methoxy]phenyl]piperidin-4-one (2.5 g). Subsequently, sodium triacetoxyborohydride (1.992 g) and acetic acid (0.538 ml) were added thereto and the mixture was stirred at room temperature for 21 hours. A saturated sodium hydrogen carbonate aqueous solution was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated sodium chloride aqueous solution and dried over anhydrous sodium sulfate. Thereafter, the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:1) and recrystallized from ethyl acetate to afford the title compound as a yellow powder (2.55 g).

Melting point: 189-190°C

Example 374

Preparation of N-ethyl-N-[1-[4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-yl)methoxy]phenyl]piperidin-4-yl]-N-(4-trifluoromethoxyphenyl)amine

The title compound was prepared in the same manner as in Example 370 using suitable starting materials. Yellow powder

Melting point: 184-185°C

Example 375

Preparation of (R)-2-nitro-7-[4-4-((E)-3-(4-trifluoromethoxyphenyl)allyl]piperazin-1-yl]phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 363 using suitable starting materials.
Slightly yellow powder
Melting point: 208-209°C

Example 376

Preparation of (R)-2-nitro-7-{4-[4-(4-
trifluoromethylbenzyl)oxy)methyl]piperidin-1-yl}phenoxymethyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 86 using suitable starting materials.
Yellow solid
Melting point: 137.7-139.8°C

Example 377

Preparation of (R)-2-nitro-7-{4-[4-(4-
trifluoromethylphenoxymethyl]piperidin-1-yl}phenoxymethyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Yellow solid
Melting point: 198.5-200°C

Example 378

Preparation of (R)-2-nitro-7-{4-[4-(4-
trifluoromethoxybenzyl)oxy)methyl]piperidin-1-yl}phenoxymethyl]-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Orange solid
Melting point: 123-127°C

Example 379

Preparation of 1-{4'-(R)-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazin-7-yl(methoxy)biphenyl-4-yl]-4-
trifluoromethyl)piperidin-4-ol
The title compound was prepared in the same manner as in Example 86 using suitable starting materials.

Pale yellow powder

Melting point: 225-230°C

Example 380

Preparation of (R)-2-nitro-7-{4-[4-(nonafluorobutane-1-sulfonyl)piperazin-1-yl]phenoxyethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

Triethylamine (0.35 ml) was added to a methylene chloride suspension (6 ml) of (R)-2-nitro-7-{4-piperazin-1-ylphenoxyethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine (0.30 g). Subsequently, bis(nonafluoro-1-butanesulfonic)anhydride (0.31 ml) was added thereto dropwise under ice cooling. The mixture was stirred for 7.5 hours while it gradually returned to room temperature. A saturated sodium hydrogen carbonate aqueous solution was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was washed with a saturated sodium chloride aqueous solution and dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (methylene chloride:ethyl acetate = 1:1) and recrystallized from acetone-water to afford the title compound as a pale orange powder (0.19 g).

Melting point: 235-236°C

Example 381

Preparation of (R)-2-nitro-7-{4-[4-trifluoromethanesulfonylpiperazin-1-yl]phenoxyethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 380 using suitable starting materials.

Beige needle

Melting point: 225-227°C
Example 382
Preparation of 7-methyl-2-nitro-7-{4-[4-[(4-
trifluoromethoxyphenyl)ethyl]piperidin-1-yl]phenoxy)methyl}-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine
5
The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Yellow powder
Melting point: 216.6-218.2°C

Example 383
Preparation of (R)-2-nitro-7-{4-[4-[(4-
trifluoromethoxybenzyl)piperidin-1-yl]phenoxy)methyl]-6,7-dihydro-
5H-imidazo[2,1-b][1,3]oxazine
10
The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Pale yellow solid
Melting point: 172-173°C

Example 384
Preparation of (R)-2-nitro-7-{4-[4-[(4-
trifluoromethylbenzyl)piperidin-1-yl]phenoxy)methyl]-6,7-dihydro-
5H-imidazo[2,1-b][1,3]oxazine
20
The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Pale yellow solid
Melting point: 178-179°C

Example 385
Preparation of (R)-7-{4-[4-((4-chlorobenzyl)piperidin-1-
yl)phenoxy)methyl}-2-nitro-6,7-dihydro-5H-imidazo[2,1-
b][1,3]oxazine
30
The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Colorless solid
Melting point: 176.5-178°C
Example 386

Preparation of (R)-2-nitro-7-{4-[4-(4-
trifluoromethoxyphenoxy)methyl]piperidin-1-yl}phenoxy)methyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 86 using suitable starting materials.
Orange solid
Melting point: 199.3-199.5°C

Example 387

Preparation of (R)-2-nitro-7-{4-[4-(4-
trifluoromethoxyphenyl)piperidin-1-yl]phenoxy)methyl]-6,7-dihydro-
5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Reddish yellow solid
Melting point: 206.5-207.5°C

Example 388

Preparation of (R)-2-nitro-7-{4-[4-(4-
trifluoromethylphenyl)piperidin-1-yl]phenoxy)methyl]-6,7-dihydro-
5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Yellow solid
Melting point: 229-230°C

Example 389

Preparation of (R)-2-nitro-7-{4-[4-(5-
trifluoromethyl)pyridin-2-yl]oxy)piperidin-1-yl]phenoxy)methyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 86 using suitable starting materials.
White powder
Example 390

Preparation of (S)-2-nitro-7-{4-[4-[3-(4-
trifluoromethoxy)phenyl]propyl]piperidin-1-yl}phenoxy)methyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.

Pale yellow powder

Melting point: 171-173°C

Example 391

Preparation of 7-methyl-2-nitro-7-{4-[4-[4-
trifluoromethoxybenzyl]piperidin-1-yl]phenoxy)methyl]-6,7-dihydro-
5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

Yellow powder

Melting point: 170.4-171.6°C

Example 392

Preparation of (R)-2-nitro-7-{4-[1-(4-
trifluoromethoxyphenyl)piperidin-4-yloxy]phenoxy)methyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

Pale yellow solid

Melting point: 155-157°C

Example 393

Preparation of (R)-2-nitro-7-{4-[1-(4-
trifluoromethylphenyl)piperidin-4-yloxy]phenoxy)methyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Pale yellow solid
Melting point: 162.5-164°C

Example 394

Preparation of (R)-2-nitro-7-{4-[4-{4-trifluoromethoxybenzyloxy}piperidin-1-yl]phenoxy}methyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.

Yellow powder
Melting point: 180.0-180.3°C

Example 395

Preparation of (R)-2-nitro-7-{4-[4-[3-(3-
 trifluoromethylphenoxy)propyl]piperidin-1-yl]phenoxy}methyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.

Orange solid
Melting point: 165.5-166.5°C

Example 396

Preparation of (R)-2-nitro-7-{4-[4-(3-
trifluoromethylphenoxy)methyl]piperidin-1-yl]phenoxy}methyl)-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.

Pink powder
Melting point: 160.9-161.4°C

Example 397

Preparation of (R)-2-nitro-7-{4-[4-(3-[4-trifluoromethylphenoxy)propyl]piperidin-1-yl]phenoxy}methyl)-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 86 using suitable starting materials.
Pale yellow powder  
Melting point: 185-186°C

5 Example 398

Preparation of (R)-2-nitro-7-(4-{4-{2-(4-trifluoromethylbenzyloxy)ethyl}piperidin-1-yl}phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as

in Example 86 using suitable starting materials.
Yellow solid  
Melting point: 154.5-155.2°C

Example 399

15 Preparation of (R)-2-nitro-7-(4-{4-{2-(4-trifluoromethoxybenzyloxy)ethyl}piperidin-1-yl}phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as

in Example 86 using suitable starting materials.
Orange solid  
Melting point: 147.5-148°C

Example 400

Preparation of (R)-2-nitro-7-(4-{4-{3-(4-trifluoromethylphenyl)propyl}piperidin-1-yl}phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as

in Example 1 using suitable starting materials.
Pale yellow solid  
Melting point: 178-179°C

Example 401

Preparation of (R)-7-{4-[3-chloro-5-trifluoromethylpyridin-2-yloxy)piperidin-1-yl]phenoxy)methyl}-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
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The title compound was prepared in the same manner as in Example 86 using suitable starting materials.
Pale yellow powder
Melting point: 161-162°C

Example 402

Preparation of 7-methyl-2-nitro-7-(4-[4-[(4-
trifluoromethoxybenzyl)piperazin-1-yl]phenoxy)methyl]-6,7-dihydro-
5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Yellow powder
Melting point: 178.8-178.9°C

Example 403

Preparation of 7-methyl-2-nitro-7-(4-[4-[(4-
trifluoromethylbenzyl)piperazin-1-yl]phenoxy)methyl]-6,7-dihydro-
5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Yellow powder
Melting point: 155.7-156.4°C

Example 404

Preparation of 7-methyl-2-nitro-7-(4-[{R}-3-(4-
trifluoromethylphenyl)allyl)piperazin-1-yl]phenoxy)methyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Yellow powder
Melting point: 186.2-186.9°C

Example 405

Preparation of (R)-2-nitro-7-(4-[3-5-
trifluoromethylpyridin-2-yl]oxy)propyl)piperidin-1-yl)
phenoxymethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.

Yellow powder

Melting point: 175.0-175.8°C

Example 406

Preparation of (R)-2-nitro-7-\{6-[4-(4-trifluoromethoxyphenyl)ethyl]piperidin-1-yl\}pyridin-3-yloxymethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.

Pale yellow flocculent crystal

Melting point: 194°C

Example 407

Preparation of (R)-2-nitro-7-\{4-\{4-(5-trifluoromethyl)pyridin-2-yloxymethyl\}piperidin-1-yl\}phenoxythenyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

White powder

Melting point: 199.5-199.9°C

Example 408

Preparation of (R)-2-nitro-7-\{4-[1′-(4-trifluoromethoxybenzyl)-4′-bipiperidin-1-yl]phenoxythenyl\}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 363 using suitable starting materials.

White powder

Melting point: 209.8-215.1°C
trifluoromethoxyphenyl)propyl]piperidin-1-yl)phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

Yellow powder
Melting point: 154.2-156.2°C

Example 410
Preparation of (R)-2-nitro-7-{6-[4-[(4-
trifluoromethoxybenzyl)piperidin-1-yl]pyridin-3-yloxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.
White powder
Melting point: 180.7°C

Example 411
Preparation of 7-methyl-2-nitro-7-(4-[(4-[E]-3-(4-
trifluoromethoxyphenyl)allylpiperazin-1-yl)phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.
Yellow powder
Melting point: 158.3-159.2°C

Example 412
Preparation of (R)-2-nitro-7-{6-[4-[(4-
trifluoromethylphenyl)propyl]piperidin-1-yl]pyridin-3-yloxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.
Pale yellow powder
Melting point: 171.7°C

Example 413
Preparation of (R)-2-nitro-7-[4-[4-(4-trifluoromethyl)cyclohexylmethyl]piperazin-1-yl]phenoxy[methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Example 414
Preparation of (R)-2-nitro-7-[4-[4-(4-trifluoromethyl)cyclohexylmethyl]piperazin-1-yl]phenoxy[methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 3 using suitable starting materials.

Example 415
Preparation of (R)-2-nitro-7-[4-[1′-(4-trifluoromethylbenzyl)-4,4′-bipiperidin-1-yl]phenoxy[methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 363 using suitable starting materials.

Example 416
Preparation of (R)-2-nitro-7-[4-[4-(2-(4-trifluoromethylphenyl)ethyl]piperidin-1-yl]phenoxy[methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.

Pale yellow solid
Melting point: 211.3°C
Example 417

Preparation of \((R)-2\text{-}\text{nitro}-7-(6\text{-}(4\text{-}(2\text{-}\text{trifluoromethylphenyl})\text{ethyl})\text{piperidin-1-yl})\text{pyridin-3-yloxymethyl})-6,7\text{-}\text{dihydro-5H-imidazo}[2,1-b][1,3]\text{oxazine}\)

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.
Pale yellow solid
Melting point: 211.2°C

Example 418

Preparation of \(N\text{-}\text{ethyl-N-[4-}(\text{4}-(\text{R})\text{-2-nitro-6,7-dihydro-5H-imidazo}[2,1-b][1,3]\text{oxazin-7-ylmethoxy})\text{phenyl}]-N-[1-(4\text{-}\text{trifluoromethoxyphenyl})\text{piperidin-4-yl}]\text{amine}\)

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Pale yellow powder
Melting point: 166.4-168.1°C

Example 419

Preparation of \(N\text{-}\text{methyl-N-[4-}(\text{4}-(\text{R})\text{-2-nitro-6,7-dihydro-5H-imidazo}[2,1-b][1,3]\text{oxazin-7-ylmethoxy})\text{phenyl}]-N-[1-(4\text{-}\text{trifluoromethoxyphenyl})\text{piperidin-4-yl}]\text{amine}\)

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Orange powder
Melting point: 182.1-184.2°C

Example 420

Preparation of \(4\text{-}[4-(\text{R})\text{-2-nitro-6,7-dihydro-5H-imidazo}[2,1-b][1,3]\text{oxazin-7-ylmethoxy})\text{phenyl}]\text{piperazine-1-carboxylic acid ethyl ester}\)

Triethylamine (0.31 ml) was added to a methylene chloride suspension (6 ml) of \((\text{R})\text{-2-nitro-7-}(4\text{-piperazin-1-ylphenoxymethyl})-6,7\text{-}\text{dihydro-5H-imidazo}[2,1-b][1,3]\text{oxazine}\) (0.40 g). Subsequently, chloroethyl formate (0.11 ml) was added thereto
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dropwise under ice cooling, and the mixture was stirred for 14
hours while it gradually returned to room temperature. A 0.5 N
hydrochloric acid aqueous solution was then added to the reaction
mixture, followed by extraction with methylene chloride. After
washing the organic layer with water and a saturated sodium
chloride aqueous solution, the organic layer was dried over
anhydrous sodium sulfate and the solvent was distilled off under
reduced pressure. The residue thus obtained was purified by
silica gel column chromatography (methylene chloride:methanol =
90:10) and recrystallized from acetone-water to afford the title
compound as a pale yellow powder (0.36 g).
Melting point: 218°C

Example 421
Preparation of (2-hydroxy-4-trifluoromethylphenyl)-(4-
(4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-
ylmethoxy)phenyl)piperazin-1-yl)methanone
1-Hydroxybenzotriazole (0.19 g) and 1-ethyl-3-(3-
dimethylaminopropyl)carbodiimide hydrochloride (0.24 g) were
added to a DMF solution (5 ml) of (R)-2-nitro-7-(4-piperazin-1-
ylphenoxymethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine (0.40
g) and 4-(trifluoromethyl)salicylic acid (0.25 g), and the
mixture was stirred at room temperature for 11 hours. Water was
added to the reaction mixture. After stirring the mixture for a
while, the precipitate was collected by filtration. The resulting
 crude product was purified by silica gel column chromatography
(methylene chloride:methanol = 90:10) and recrystallized from
ethanol-acetone to afford the title compound as a white powder
(0.42 g).
Melting point: 217-220°C

Example 422
Preparation of (R)-2-nitro-7-(6-(4-[3-(4-
trifluoromethoxyphenyl)propyl]piperidin-1-yl)pyridin-3-
yloxymethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

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The title compound was prepared in the same manner as in Example 86 using suitable starting materials.
Yellow solid
Melting point: 159.0-159.5°C

Example 423
Preparation of (R)-2-nitro-7-{4-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]phenoxymethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Yellow powder
Melting point: 186.5-187.2°C

Example 424
Preparation of (R)-2-nitro-7-{4-[4-(4-trifluoromethoxyphenyl)-3,6-dihydro-2H-pyridin-1-yl]phenoxymethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as in Example 86 using suitable starting materials.
Yellow powder
Melting point: 200.5-201.5°C

Example 425
Preparation of (R)-2-nitro-7-{4-[4-(4-trifluoromethoxybenzyl)-3,6-dihydro-2H-pyridin-1-yl]phenoxymethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as in Example 86 using suitable starting materials.
Yellow solid
Melting point: 164.8-165.2°C

Example 426
Preparation of (R)-7-{4-(4-methanesulfonylpiperazin-1-yl)phenoxymethyl}-2-nitro-6,7-dihydro-5H-imidazo[2,1-
Triethylamine (0.31 ml) was added to a methylene chloride suspension (6 ml) of (R)-2-nitro-7-(4-piperazin-1-ylphenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine (0.40 g). Subsequently, methanesulfonyl chloride (0.09 ml) was added thereto dropwise under ice cooling, and the mixture was stirred for 14 hours while it gradually returned to room temperature. A 0.5 N hydrochloric acid aqueous solution was added to the reaction mixture, followed by extraction with methylene chloride.

The organic layer was washed with water and a saturated sodium chloride aqueous solution, dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (methylene chloride: methanol = 90:10) and recrystallized from methylene chloride-methanol to afford the title compound as a beige powder (0.15 g).

Melting point: 149-151°C

Example 427

Preparation of (R)-2-nitro-7-{6-{4-[2-({4-
trifluoromethoxyphenoxy}ethyl)piperidin-1-yl]pyridin-3-
yl}oxy)methyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.

Pale yellow powder
Melting point: 137.6-140.9°C

Example 429

Preparation of (R)-2-nitro-7-{4-[4-({5-
trifluoromethylpyridin-2-yl}oxy)benzyl]piperazin-1-
yl)phenoxy)methyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
(R)-2-Nitro-7-(4-piperazin-1-ylphenoxy)methyl)-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine (0.50 g), 4-({5-
trifluoromethylpyridin-2-yl}oxy)benzaldehyde (0.41 g), N-
methylpyrrolidone (10 ml), and sodium triacetoxyborohydride (0.44
g) were mixed and stirred at room temperature for 16 hours. The reaction mixture was added to a 1 N sodium hydroxide aqueous solution. The precipitated crystal was collected by filtration. The crude crystal was purified by silica gel column chromatography (methylene chloride:ethyl acetate = 8:2-methylene chloride:ethyl acetate = 2:8) and recrystallized from acetone-ether to afford the title compound as a pale yellow powder (0.55 g).

Melting point: 229-230°C

Example 429
Preparation of (R)-2-nitro-7-(6-[4-(4-
trifluoromethoxyphenoxymethyl)pyridin-1-yl]pyridin-3-
ylexymethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.
Pale yellow powder
Melting point: 182.9-183.3°C

Example 430
Preparation of (R)-2-nitro-7-(4-[4-(4-
trifluoromethoxyphenyl)piperidin-1-ylmethyl]phenoxymethyl)-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 428 using suitable starting materials.
Pale brown solid
Melting point: 165-167°C

Example 431
Preparation of (R)-2-nitro-7-[4-[4-(4-
trifluoromethoxybenzyl)piperidin-1-ylmethyl]phenoxymethyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 428 using suitable starting materials.
Pale brown solid
Melting point: 159.5-160.5°C

Example 432

Preparation of (R)-2-nitro-7-(4-(1-(4-
trifluoromethylbenzyl)-1,2,3,6-tetrahydropyridin-4-
yl)phenoxymethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
hydrochloride

Sodium triacetoxyborohydride (0.631 g) was added to a
mixture of (R)-2-nitro-7-(4-(1,2,3,6-tetrahydropyridin-4-
yl)phenoxymethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
trifluoroacetate (1.0 g), 4-(trifluoromethyl)benzaldehyde (0.41
ml) and N-methylpyrrolidone (10 ml), and the mixture was stirred
at room temperature for 9 hours. A sodium hydrogen carbonate
aqueous solution was added to the reaction mixture and stirred
for 10 minutes. The precipitate was then collected by filtration.
The residue thus obtained was purified by basic silica gel column
chromatography (methylene chloride). The resulting product was
dissolved in methylene chloride (30 ml), a 1 N hydrochloric acid
ethanol solution (1.32 ml) was added thereto and then stirred.

Thereafter, the solvent was distilled off under reduced pressure,
ethyl acetate was added to the residue, and the mixture was
stirred at room temperature. The precipitate was collected by
filtration, and the solid thus obtained was recrystallized using
ethanol-water to afford the title compound as a slightly yellow
powder (0.52 g).

Melting point: 210-213°C

Example 433

Preparation of (R)-7-(4-{4-[3-fluoro-4-{4-
trifluoromethoxybenzyloxy}benzyl]piperazin-1-yl)phenoxymethyl}-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 363 using suitable starting materials.

Pale brown solid

Melting point: 150-151°C
Example 434

Preparation of (R)-7-(4-{4-12-fluoro-4-(4-
trifluoromethoxybenzoyl)benzyl}piperazin-1-yl)phenoxy)methyl)-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 363 using suitable starting materials.
Pale brown solid
Melting point: 157-158°C

Example 435

Preparation of (R)-7-(4-{4-(3-methoxy-4-(4-
trifluoromethoxybenzoyl)benzyl}piperazin-1-yl)phenoxy)methyl)-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 363 using suitable starting materials.
Colorless solid
Melting point: 149.5-150°C

Example 436

Preparation of (R)-7-(4-{4-((E)-3,7-dimethyl-octa-2,6-
diynyl)piperazin-1-yl)phenoxy)methyl)-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 363 using suitable starting materials.
Pale brown solid
Melting point: 142.5-144°C

Example 437

Preparation of (R)-7-(4-{4-5-{4-chlorophenyl}furan-2-
ylmethyl)piperazin-1-yl)phenoxy)methyl)-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 363 using suitable starting materials.

Yellow solid
Melting point: 222-223.5°C

Example 438
Preparation of (R)-7-[4-(4-adamantan-2-yl)piperazin-1-yl]phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 363 using suitable starting materials.

Colorless solid

Melting point: 245.5-246.5°C

Example 439
Preparation of 2-[4-[4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperazin-1-ylmethyl]-5-(4-trifluoromethylbenzyloxy)phenol hydrochloride

The title compound was prepared in the same manner as in Example 432 using suitable starting materials.

Pale yellow powder

Melting point: 192-194°C

Example 440
Preparation of (R)-7-(4-[4-(2-methoxy-4-(4-trifluoromethylbenzyloxy)benzyl)piperazin-1-yl]phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine hydrochloride

The title compound was prepared in the same manner as in Example 432 using suitable starting materials.

Pale yellow powder

Melting point: 214-217°C

Example 441
Preparation of (R)-2-nitro-7-[(4-[4-[5-(4-trifluoromethylphenyl)thiophen-2-yl)methyl)piperazin-1-yl]phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 363 using suitable starting materials.
Pale brown solid
Melting point: 225-226°C

Example 442
Preparation of (R)-2-nitro-7-[(4-{5-[5-(4-
trifluoromethoxyphenyl)thiophen-2-ylmethyl]piperazin-1-
yl)phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 363 using suitable starting materials.

Pale brown solid
Melting point: 222-224°C

Example 443
Preparation of (R)-2-nitro-7-[(4-{5-[4-(4-
trifluoromethyl)phenyl]furan-2-ylmethyl]piperazin-1-
yl)phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 363 using suitable starting materials.
Pale yellow solid
Melting point: 235-237°C

Example 444
Preparation of (R)-2-nitro-7-[(4-{5-[4-(4-
trifluoromethoxyphenyl)furan-2-ylmethyl]piperazin-1-
yl)phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 363 using suitable starting materials.
Pale yellow solid
Melting point: 148.5-149.5°C

Example 445
Preparation of (R)-2-nitro-7-[(4-{5-
trifluoromethylbenzofuran-2-ylmethyl)piperidin-1-yl}
phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as
in Example 86 using suitable starting materials.
Pale yellow powder
Melting point: 159-161°C

5 Example 446

Preparation of \( \{R\}-2\text{-nitro-7-}\{4-\{4-\text{trifluoromethylsulfanylphenoxy}piperidin-1-yl\}phenoxy}methyl\}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine 

The title compound was prepared in the same manner as

in Example 86 using suitable starting materials.
Yellow powder
Melting point: 162.6-163.9°C

Example 447

Preparation of \( \{R\}-2\text{-nitro-7-}\{4-\{1-\{4-\text{trifluoromethylbenzoxoxy}benzyl\}-1,2,3,6\text{-tetracydro}pyridin-4-yl\}phenoxy}methyl\}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine 

Sodium triacetoxyborohydride (0.63 g) was added to a
mixture of \( \{R\}-2\text{-nitro-7-}\{4-\{1,2,3,6\text{-tetracydro}pyridin-4-yl\}phenoxy}methyl\}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine 
trifluorooacetate (1.0 g), 4-\{4-\text{trifluoromethylbenzoxoxy}benzaldehyde (0.72 g) and N-methylpyrrolidone (10 ml), and the mixture was stirred at room temperature for 11 hours. A sodium hydrogen carbonate aqueous solution was added to the reaction mixture and stirred for 10 minutes. The precipitate was collected by filtration. The residue thus obtained was purified by basic silica gel column chromatography (methylene chloride). The resulting product was
dissolved in methylene chloride (30 ml), a 4 N hydrochloric acid ethyl acetate solution (0.49 ml) was added thereto, and the mixture was stirred for a while. The solvent was distilled off under reduced pressure, and ethyl acetate was added to the residue. The mixture was stirred for 20 minutes and then crystal
was collected by filtration. The solid obtained was
recrystallized from ethanol-water to afford the title compound as a yellow powder (0.58 g).
Melting point: 212-214°C

Example 448
Preparation of \(|R\)-2-nitro-7-(4-[4-[4-(4-
trifluoromethylbenzyl)sulfanyl]benzyl]piperazin-1-
yl]phenoxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazino
hydrochloride

The title compound was prepared in the same manner as in Example 447 using suitable starting materials. Slightly yellow powder
Melting point: 181-184°C

Example 449
Preparation of \(N\text{-methyl-}N\text{-[1-}[4-\{(\text{R})-2\text{-nitro-6,7-
dihydro-5H-imidazo}[2,1-b][1,3]oxazin-7-
ylmethoxy]phenyl]piperidin-4-yl]-N\text{-[4-
trifluoromethoxybenzyl]}amine

The title compound was prepared in the same manner as in Example 180 using suitable starting materials. Colorless solid
Melting point: 173-174°C

Example 450
Preparation of \(N\text{-methyl-}N\text{-[2-}[1-\{(\text{R})-2\text{-nitro-6,7-
dihydro-5H-imidazo}[2,1-b][1,3]oxazin-7-
ylmethoxy]phenyl]piperidin-4-yl]-ethyl]-N\text{-[4-
trifluoromethoxyphenyl]}amine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials. Yellow solid
Melting point: 166.5-167°C

Example 451
Preparation of \( N\)-methyl-\( N\)-(1-[4-\((R)\)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethyl]phenyl)piperidin-4-ylmethyl\)-\( N\)-(4-trifluoromethoxybenzyl)amine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

Yellow solid

Melting point: 181.5-182.5°C

Example 452

Preparation of \((R)\)-2-nitro-7-[4-\([4-\{4-(4-trifluoromethyl)sulfanylbenzyl\}piperidin-1-yl\}phenoxymethyl\]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

Yellow powder

Melting point: 191.4-192.6°C

Example 453

Preparation of \((R)\)-2-nitro-7-[4-\([4-\{4-\{4-\{4-(4-trifluoromethyl)phenylmethanesulfonyl\}benzyl\}piperazin-1-yl\}phenoxymethyl\}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine hydrochloride

The title compound was prepared in the same manner as in Example 447 using suitable starting materials.

Slightly yellow powder

Melting point: 222-225°C

Example 454

Preparation of \((R)\)-2-nitro-7-[4-\([4-\{4-(4-(4-trifluoromethyl)phenylmethanesulfinyl)benzyl\}piperazin-1-yl\}phenoxymethyl\}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine hydrochloride

The title compound was prepared in the same manner as in Example 447 using suitable starting materials.
Beige powder  
Melting point: 205-208°C

Example 455

Preparation of (R)-2-nitro-7-{4-[4-{5-trifluoromethylbenzofuran-2-ylmethoxy}piperidin-1-yl]phenoxymethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 445 using suitable starting materials.

Pale yellow powder  
Melting point: 156-158°C

Example 456

Preparation of (R)-2-nitro-7-{4-[4-{4-trifluoromethoxyphenylsulfanyl}piperidin-1-yl]phenoxymethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 445 using suitable starting materials.

White powder  
Melting point: 161-162°C

Example 457

Preparation of (R)-2-nitro-7-{4-[4-{2-(4-trifluoromethoxyphenylsulfanyl)ethyl}piperidin-1-yl]phenoxymethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 445 using suitable starting materials.

White powder  
Melting point: 166.7-167.3°C

Example 458

Preparation of (R)-2-nitro-7-{4-{4-[4-(trifluoromethylbenzyloxy)benzyl]-3,6-dihydro-2H-pyridin-1-yl}phenoxymethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 445 using suitable starting materials.

Yellow powder

Melting point: 183-184°C

Example 459

Preparation of 1'-[4-{{(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy}phenyl}-[1,4']pipеридинyl-4-ol

4-{(tert-Bуtyldimethylsilanyloxy)-1'-[4-{{(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy}phenyl}][1,4']bipiperидинyl (190 mg) was dissolved in tetrahydrofuran (5 mL). While being stirred at room temperature, 1 M тетра бутил ammonium fluoride (1.11 mL) was added thereto, followed by stirring at 50°C for 5 hours. The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (methylenе chloride:methanol = 100:0-methylene chloride:methanol = 80:20) and recrystallized from methanol-isopropyl ether to afford the title compound as a yellow solid (40 mg).

Melting point: 234.5-235°C

Example 460

Preparation of 2-methoxy-4-{{(E)-3-(4-[4-{{(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy}phenyl}piperазin-1-yl)propенyl}phenol

The title compound was prepared in the same manner as in Example 428 using suitable starting materials.

Pale brown solid

Melting point: 109-111°C

Example 461

Preparation of 1-{{1-[4-{{(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy}phenyl}pipеридин-4-ylmethyl}pipеридин-4-ol

The title compound was prepared in the same manner as
-304-

in Example 459 using suitable starting materials.
Colorless solid
Melting point: 189-190.5°C

Example 462
Preparation of 1-(4-chlorophenoxy)-3-{4-[4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]piperazin-1-yl}propan-2-ol

(R)-2-Nitro-7-(4-piperazin-1-ylphenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine (250 mg), 2-(4-chlorophenoxy)methyl)oxirane (154 mg) and N-methylpyrrolidone (7 ml) were mixed and stirred at 100°C for 21 hours. The mixture was cooled to room temperature and water (23 ml) was added thereto, followed by stirring for 5 minutes. The precipitated crystal was collected by filtration and dried at 60°C. The residue thus obtained was purified by silica gel column chromatography (methylene chloride:methanol = 100:0-methylene chloride:methanol = 97:3) and recrystallized from 1,2-dichloroethane-methanol-ethyl acetate to afford the title compound as a colorless solid (204 mg).
Melting point: 203-205°C

Example 463
Preparation of 1-{4-[4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]piperazin-1-yl}-3-(4-trifluoromethoxyphenoxy)propan-2-ol

The title compound was prepared in the same manner as in Example 462 using suitable starting materials. Yellow solid
Melting point: 184.5-185°C

Example 464
Preparation of (R)-7-{4-[4-(3,4-dichlorobenzyl)piperidin-1-ylphenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as in Example 445 using suitable starting materials.
Pale yellow powder
Melting point: 190-192°C

Example 465
Preparation of (R)-7-(4-(4-(4-(E)-3,7-dimethylocta-2,6-dianyloxy)benzyl)piperazin-1-yl)phenoxy)methyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 428 using suitable starting materials.
Yellow solid
Melting point: 145-146.5°C

Example 466
Preparation of (R)-7-[4-(4-(4-(4-(E)-3-[4-((E)-3,7-dimethylocta-2,6-dianyloxy)phenyl]allyl)piperazin-1-yl)phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 428 using suitable starting materials.
Yellow solid
Melting point: 154-155°C

Example 467
Preparation of 1′-[4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)benzyl]-[1,4′]bipiperidiny1-4-ol

The title compound was prepared in the same manner as in Example 428 using suitable starting materials.
Colorless solid
Melting point: 164-165°C

Example 468
Preparation of 1-1-(4-(4(R)-2-nitro-6,7-dihydro-5H-
The title compound was prepared in the same manner as in Example 428 using suitable starting materials.

Example 469

Preparation of (R)-7-{4-[4-(3,4-
10 dichlorophenoxy)piperidin-1-yl]phenoxy)methyl}-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 445 using suitable starting materials.

Pale yellow powder

Example 470

Preparation of 1-[4-((R)-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]-4-(4-
20 trifluoromethylphenyl)piperidin-4-ol

A mixture of toluene-4-sulfonic acid (R)-4-(2-chloro-4-
nitroimidazol-1-yl)-2-hydroxybutyl ester (1.16 g), 1-(4-
hydroxyphenyl)-4-(4-trifluoromethylphenyl)piperidin-4-ol (1.0 g), tripotassium phosphate (2.52 g) in ethanol (10 ml) was stirred at 60°C for 15 hours under an argon atmosphere. The reaction mixture was added to an ammonium chloride aqueous solution, and the mixture was stirred for a while. The precipitated crude crystal was collected by filtration and dried at 60°C. The crude product thus obtained was purified by silica gel column chromatography (methylene chloride:ethyl acetate = 1:1) and recrystallized from acetone-water to afford the title compound as a beige powder (0.63 g).

Melting point: 201-202°C

Example 471
Preparation of \((R)-7-(4-[4-\text{methoxy-4-(4-trifluoromethylphenyl)piperidin-1-yl} \text{phenoxymethyl})-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine\)

The title compound was prepared in the same manner as in Example 470 using suitable starting materials. Slightly yellow powder
Melting point: 168-169°C

Example 472

Preparation of \((R)-7-(4-[4-\text{methoxy-4-(4-trifluoromethoxyphenyl)piperidin-1-yl} \text{phenoxymethyl})-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine\)

The title compound was prepared in the same manner as in Example 470 using suitable starting materials. Pale yellow powder
Melting point: 160-161°C

Example 473

Preparation of \(1-[4-\{(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-\text{-ylmethoxy} \text{phenyl})-4-(4-trifluoromethoxyphenyl)piperidin-4-ol\)

The title compound was prepared in the same manner as in Example 470 using suitable starting materials. Beige powder
Melting point: 204-206°C

Example 474

Preparation of \((R)-2-nitro-7-(4-[4-[4-(4-trifluoromethoxyphenoxy)phenoxypiperidin-1-yl} \text{phenoxymethyl})-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine\)

The title compound was prepared in the same manner as in Example 470 using suitable starting materials. Pale brown powder
Melting point: 140-142°C
Example 475

Preparation of (S)-2-nitro-7-{4-[4-((4-
trifluoromethoxybenzyl)piperidin-1-yl]phenoxy)methyl]-6,7-dihydro-
5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 470 using suitable starting materials.
Pale yellow powder
Melting point: 171-172°C

Example 476

Preparation of (R)-2-nitro-7-{4-[1-((4-
trifluoromethoxybenzyl)piperidin-4-ylmethoxy]phenoxy)methyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 428 using suitable starting materials.
Pale brown solid
Melting point: 149.5-150°C

Example 477

Preparation of (R)-2-nitro-7-{4-((2-[1-(4-
trifluoromethoxybenzyl)piperidin-4-yl]-ethoxy]phenoxy)methyl]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 428 using suitable starting materials.
Pale brown solid
Melting point: 132-133°C

Example 478

Preparation of (R)-2-nitro-7-{4-((E)-3-[4-(4-
30 trifluoromethoxybenzyl)piperazin-1-yl]propenyl]phenoxy)methyl]-
6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as
in Example 428 using suitable starting materials.
Pale brown solid
Melting point: 163-164°C
Example 479

Preparation of (R)-7-[(4-{4-[(4-furan-2-y1methoxy)benzyl]piperazin-1-yl}phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 428 using suitable starting materials.

Colorless solid

Melting point: 190-192°C

Example 480

Preparation of (R)-2-nitro-7-[(4-{4-[(4-pyridin-2-y1methoxy)benzyl]piperazin-1-yl}phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 428 using suitable starting materials.

Colorless solid

Melting point: 213-214°C

Example 481

Preparation of (R)-2-nitro-7-[(4-{4-[(4-thiophen-2-y1methoxy)benzyl]piperazin-1-yl}phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 428 using suitable starting materials.

Colorless solid

Melting point: 208-209.5°C

Example 482

Preparation of (R)-2-nitro-7-[(4-{4-{1-[4-{4-[4-trifluoromethyl]benzyl]oxyl phenyl]-ethyl}piperazin-1-yl}phenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

(R)-2-Nitro-7-(4-piperazin-1-ylphenoxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine (0.56 g) was added to an N-methylpyrrolidone solution (5 mL) of 1-(1-chloroethyl)-4-{4-
trifluoromethylbenzyloxy)benzene (0.54 g). Subsequently, diisopropylethylamine (0.54 ml) was added thereto, and the mixture was stirred at room temperature for 12 hours. Thereafter, the mixture was heated to 60°C and stirred for 7 hours. Water was added to the reaction mixture and the precipitated solid was collected by filtration. The solid thus obtained was purified by basic silica gel column chromatography (methylene chloride) and recrystallized from acetone-water to afford the title compound as a slightly yellow powder (0.15 g).

Example 483
Preparation of (R)-2-nitro-7-(4-{4-[4-(pyridin-4-ylmethoxy)benzyl]piperazin-1-yl}phenoxyethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 428 using suitable starting materials.
Colorless solid
Melting point: 190-191°C

Example 484
Preparation of (R)-7-(4-{4-[4-(3,5-dimethyl-isoxazol-4-ylmethoxy)benzyl]piperazin-1-yl}phenoxyethyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 428 using suitable starting materials.
Colorless solid
Melting point: 186-187°C

Example 485
Preparation of (R)-2-nitro-7-(4-{4-[6-trifluoromethylpyridin-3-ylmethoxy]benzyl}piperazin-1-yl)phenoxyethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 428 using suitable starting materials.
Colorless solid
Melting point: 191-192°C

Example 486

Preparation of (R)-2-nitro-7-{4-[4-[(pyrazin-2-
ylmethoxy)benzyl]piperazin-1-yl]phenoxy)methyl}-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 428 using suitable starting materials.

Yellow solid
Melting point: 233-233.5°C

Example 487

Preparation of (R)-7-[(4-[4-(3-methyl-
1,2,4]oxadiazol-5-ylmethoxy)benzyl]piperazin-1-
yl]phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-
b][1,3]oxazine

The title compound was prepared in the same manner as in Example 428 using suitable starting materials.

Colorless solid
Melting point: 194-195°C

Example 488

Preparation of (R)-7-[(4-[4-(2-methyl-thiazol-4-
yl)methoxy)benzyl]piperazin-1-yl]phenoxy)methyl]-2-nitro-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 428 using suitable starting materials.

Colorless solid
Melting point: 186.5-187°C

Example 489

Preparation of (R)-2-nitro-7-{4-[4-[(pyridin-3-
yl)methoxy]benzyl]piperazin-1-yl]phenoxy)methyl]-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazine
The title compound was prepared in the same manner as in Example 428 using suitable starting materials.

Colorless solid

Melting point: 212.5-213°C

Example 490

Preparation of (R)-7-[4-(4-((1-methyl-1-[4-((4-
trifluoromethylbenzyl)oxy)phenyl]ethyl)piperazin-1-
yl)phenoxymethyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-
b][1,3]oxazine

The title compound was prepared in the same manner as in Example 470 using suitable starting materials.

Slightly yellow powder

Melting point: 186-187°C

Example 491

Preparation of (S)-2-nitro-7-[4-{4-[4-(4-
trifluoromethyl)phenoxyl]benzyl]piperazin-1-y1)phenoxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

4-[4-((S)-2-Nitro-6,7-dihydro-5H-imidazo[2,1-
b][1,3]oxazin-7-ylmethoxy)phenyl]piperazine-1-carboxylic acid tert-butyl ester (300 mg) was suspended in methylene chloride (2 ml). Trifluoroacetic acid (2 ml) was added to the suspension, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure.

Methylene chloride (2 ml) and triethylamine (0.83 ml) were added to the residue and stirred at room temperature for 10 minutes. The reaction mixture was concentrated under reduced pressure and then dissolved in DMF (2 ml). Potassium carbonate (123 mg) was added thereto and 1-(bromomethyl)-4-(4-
trifluoromethyl)phenoxyl)benzene (197 mg) was further added under ice cooling, and the mixture was stirred at room temperature for 4 hours. Water was added to the reaction mixture, and the precipitated solid was collected by filtration. The crude product thus obtained was purified by silica gel column chromatography.
(methylene chloride:ethyl acetate = 1:0-methylene chloride:ethyl acetate = 2:3-methylene chloride:methanol=10:1) and recrystallized from acetone-water to afford the title compound as a pale yellow solid (197 mg).

Melting point: 182.2-185.4°C

Example 492

Preparation of (S)-2-nitro-7-(4-((4-(4-(trifluoromethyl)phenoxy)benzyl)piperidin-1-yl)phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 470 using suitable starting materials.

Yellow solid

Melting point: 198.0-199.3°C

Example 493

Preparation of 4-((4-(2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)benzyl)piperidine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

White powder

1H NMR (CDCl3) δ 1.06-1.17 (m, 2H), 1.46 (s, 9H), 1.55-1.66 (m, 3H), 2.32-2.42 (m, 1H), 2.46-2.52 (m, 3H), 2.54-2.71 (m, 2H), 3.97-4.24 (m, 5H), 4.28-4.33 (m, 1H), 4.72-4.78 (m, 1H), 6.83 (d, J = 8.5 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 7.46 (s, 1H).

Example 494

Preparation of 4-((2-(4-(2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperidine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

White powder

1H NMR (CDCl3) δ 1.05-1.34 (m, 4H), 1.47 (s, 9H), 1.52-1.60 (m,
3H), 2.29-2.37 (m, 1H), 2.44-2.55 (m, 3H), 2.42-2.65 (m, 2H),
3.95-4.20 (m, 5H), 4.25-4.30 (m, 1H), 4.72-4.79 (m, 1H), 5.81 (d,
J = 8.7 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 7.45 (s, 1H).

5 Example 495

Preparation of 4-[6-{(R)-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1.3]oxazin-7-ylmethoxy}quinolin-2-yl]piperazine-1-
carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as
in Example 132 using suitable starting materials.

Orange powder
1H NMR (CDCl3) δ 2.02 (s, 9H), 2.37-2.40 (m, 1H), 2.47-2.50 (m,
1H), 3.66 (br, 4H), 3.68 (br, 4H), 4.12-4.15 (m, 1H), 4.18-4.21
(m, 1H), 4.24-4.27 (m, 1H), 4.34-4.37 (m, 1H), 4.79 (br, 1H),
6.95-6.98 (m, 2H), 7.18-7.20 (m, 1H), 7.43 (s, 1H), 7.64 (d, J =
9.1 Hz, 1H), 7.82 (d, J = 9.1 Hz, 1H).

Example 496

Preparation of 4-[6-{(R)-2-nitro-6,7-dihydro-5H-
imidazo[2,1-b][1.3]oxazin-7-ylmethoxy}benzothiazol-2-
yl]piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as
in Example 132 using suitable starting materials.

White powder
1H NMR (CDCl3) δ 1.49 (s, 9H), 2.38-2.40 (m, 1H), 2.48-2.51 (m,
1H), 3.58 (br, 8H), 4.11-4.17 (m, 1H), 4.20-4.24 (m, 2H), 4.32-
4.35 (m, 1H), 4.75-4.77 (m, 1H), 6.90-6.92 (m, 1H), 7.18 (d, J =
2.5 Hz, 1H), 7.45-7.48 (m, 2H).

Example 497

Preparation of (R)-7-{4-[4,4-dimethoxypiperidin-1-
yl]phenoxymethyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-
b][1.3]oxazine

The title compound was prepared in the same manner as
in Example 1 using suitable starting materials.
Yellow solid
1H NMR (CDCl3) δ 1.90 (t, 4H), 2.17-2.48 (m, 2H), 3.12 (t, J = 5.9 Hz, 4H), 3.23 (s, 6H), 4.05-4.18 (m, 3H), 4.18-4.32 (dd, J = 10 Hz, 4.2 Hz, 1H), 4.70-4.76 (m, 1H), 6.80-6.95 (m, 4H), 7.45 (s, 1H).

Example 498
Preparation of 1-[(4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperidin-4-one (R)-7-[4-(4,4-Dimethoxypiperidin-1-yl)phenoxymethyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine (5.16 g), acetone (100 ml) and water (17 ml) were mixed. A 6 N hydrochloric acid aqueous solution (41 ml) was added thereto, followed by stirring at room temperature overnight. The reaction mixture was concentrated under reduced pressure. The remaining water layer was ice-cooled and neutralized by adding a 20% sodium carbonate aqueous solution. After being stirred at the same temperature for 10 minutes, the precipitated crystal was collected by filtration. The crystal thus obtained was dried at 60°C to afford the title compound as a yellow solid (4.57 g).
1H NMR (CDCl3) δ 2.30 (m, 6H), 3.48 (t, J = 5.9 Hz, 4H), 4.05-4.32 (m, 4H), 4.70-4.80 (m, 1H), 6.87 (d, J = 9.2 Hz, 2H), 6.96 (d, J = 9.1 Hz, 2H), 7.45 (s, 1H).

25 Example 499
Preparation of (4-4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperazin-1-yl)carbamic acid tert-butyl ester
The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

Yellow powder
1H NMR (CDCl3) δ 1.47 (s, 9H), 2.33-2.47 (m, 2H), 2.93-2.97 (m, 4H), 3.18-3.22 (m, 4H), 4.10-4.25 (m, 3H), 4.25-4.35 (dd, J = 10 Hz, 4.3 Hz, 1H), 4.65-4.80 (m, 1H), 5.46 (br s, 1H), 6.78-6.92 (m, 4H), 7.45 (s, 1H).
Example 500

Preparation of 4-[4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenoxy]piperidine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

White powder

$^1$H NMR (CDCl$_3$) $\delta$ 1.46 (s, 9H), 1.65-1.77 (m, 2H), 1.86-1.93 (m, 2H), 2.35-2.54 (m, 2H), 3.29-3.41 (m, 2H), 3.68-3.80 (m, 2H), 4.10-4.38 (m, 5H), 4.74-4.80 (m, 1H), 6.81-6.90 (m, 4H), 7.46 (s, 1H).

Example 501

Preparation of 4-[4-((S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenoxy]piperidine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

White powder

$^1$H NMR (CDCl$_3$) $\delta$ 1.47 (s, 9H), 1.64-1.77 (m, 2H), 1.83-1.95 (m, 2H), 2.32-2.52 (m, 2H), 3.25-3.37 (m, 2H), 3.68-3.80 (m, 2H), 4.12-4.38 (m, 5H), 4.71-4.78 (m, 1H), 6.80-6.86 (m, 4H), 7.45 (s, 1H).

Example 502

Preparation of 4-[5-((S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)benzo[1,2-c:4,5-c']oxazol-2-yl]piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.

Yellow powder

$^1$H NMR (CDCl$_3$) $\delta$ 1.49 (s, 9H), 2.38-2.41 (m, 1H), 2.48-2.52 (m, 1H), 3.55-3.57 (m, 4H), 3.65-3.66 (m, 4H), 4.10-4.16 (m, 1H), 4.19-4.22 (m, 2H), 4.30-4.33 (m, 1H), 4.75-4.77 (m, 1H), 6.59-
Example 503

Preparation of 4-[5-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)benzoxazol-2-yl]piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.

Yellow powder
1H NMR (CDCl3) δ 1.49 (s, 9H), 2.38-2.41 (m, 1H), 2.48-2.49 (m, 1H), 3.55-3.57 (m, 4H), 3.65-3.67 (m, 4H), 4.10-4.16 (m, 1H), 4.20-4.23 (m, 2H), 4.30-4.33 (m, 1H), 4.75-4.77 (m, 1H), 6.59-6.61 (m, 1H), 6.91-6.92 (d, J = 2.5 Hz, 1H), 7.15 (d, J = 8.7 Hz, 1H), 7.46 (s, 1H).

Example 504

Preparation of (S)-7-[4-(4,4-dimethoxypiperidin-1-yl)phenoxyethyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.

Pale yellow powder
1H NMR (CDCl3) δ 1.89-1.91 (m, 4H), 2.34-2.38 (m, 1H), 2.46-2.49 (m, 1H), 3.10-3.13 (m, 4H), 3.23 (s, 6H), 4.10-4.22 (m, 3H), 4.26-4.29 (m, 1H), 4.71-4.74 (m, 1H), 6.82-6.84 (m, 2H), 6.89-6.92 (m, 2H), 7.45 (s, 1H).

Example 505

Preparation of 1-[4-((S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]piperidin-4-one

The title compound was prepared in the same manner as in Example 498 using suitable starting materials.

Pale yellow powder
1H NMR (DMSO-d6) δ 2.42 (m, 1H), 2.43 (m, 1H), 2.50-2.51 (m, 4H),
Example 506

Preparation of 5-((S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-1,3-dihydroisoindole-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.

1H NMR (CDCl₃) δ 1.52 (s, 9H), 2.37-2.41 (m, 1H), 2.48-2.50 (m, 1H), 4.11-4.17 (m, 1H), 4.20-4.24 (m, 2H), 4.30-4.33 (m, 1H), 4.59-4.66 (m, 4H), 4.75-4.77 (m, 1H), 6.77-6.84 (m, 2H), 7.13-7.19 (m, 1H), 7.46 (s, 1H).

Example 507

Preparation of 5-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-1,3-dihydroisoindole-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.

Yellow powder

1H NMR (CDCl₃) δ 1.52 (s, 9H), 2.37-2.42 (m, 1H), 2.48-2.50 (m, 1H), 4.11-4.17 (m, 1H), 4.19-4.24 (m, 2H), 4.30-4.34 (m, 1H), 4.59-4.66 (m, 4H), 4.74-4.78 (m, 1H), 6.77-6.84 (m, 2H), 7.13-7.19 (m, 1H), 7.46 (s, 1H).

Example 508

Preparation of 7-((S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-3,4-dihydro-1H-isquinoline-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.

Pale yellow powder

1H NMR (CDCl₃) δ 1.49 (s, 9H), 2.36-2.39 (m, 1H), 2.46-2.49 (m,
1H), 2.77 (br, 2H), 3.63 (br, 2H), 4.10-4.23 (m, 3H), 4.28-4.31 (m, 1H), 4.54 (s, 2H), 4.74-4.75 (m, 1H), 6.65 (m, 1H), 6.73-6.75 (m, 1H), 7.05-7.07 (m, 1H), 7.46 (s, 1H).

Example 509

Preparation of 7-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.

Yellow powder

1H NMR (CDCl3) δ 1.49 (s, 9H), 2.36-2.39 (m, 1H), 2.46-2.49 (m, 1H), 2.77 (br, 2H), 3.62 (br, 2H), 4.10-4.23 (m, 3H), 4.28-4.31 (m, 1H), 4.53 (s, 2H), 4.73-4.76 (m, 1H), 6.65 (d, J = 2.3 Hz, 1H), 6.73-6.75 (m, 1H), 7.05-7.07 (m, 1H), 7.46 (s, 1H).

Example 510

Preparation of 7-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-1,3,4,5-tetrahydrobenzo[c]azepine-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 132 using suitable starting materials.

White powder

1H NMR (CDCl3) δ 1.39 (s, 9H), 1.76-1.77 (m, 2H), 2.37 (m, 1H), 2.47 (m, 1H), 2.89 (m, 2H), 3.64-3.68 (m, 2H), 4.11-4.22 (m, 3H), 4.30-4.37 (m, 3H), 4.74 (m, 1H), 6.54-6.71 (m, 2H), 7.10-7.11 (m, 1H), 7.45 (s, 1H).

Example 511

Preparation of 6-((S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 132 using suitable starting materials.

White powder
1H NMR (CDCl3) δ 1.49 (s, 9H), 2.36-2.39 (m, 1H), 2.46-2.49 (m, 1H), 2.79-2.81 (m, 2H), 3.62 (m, 2H), 4.10-4.22 (m, 3H), 4.29-4.32 (m, 1H), 4.51 (s, 2H), 4.73-4.75 (m, 1H), 6.68 (d, J = 2.4 Hz, 1H), 6.74-6.76 (m, 1H), 7.02-7.05 (m, 1H), 7.45 (s, 1H).

Example 512

Preparation of 6-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 69 using suitable starting materials.

Pale yellow powder
1H NMR (CDCl3) δ 1.49 (s, 9H), 2.36-2.39 (m, 1H), 2.46-2.49 (m, 1H), 2.79-2.81 (m, 2H), 3.62 (m, 2H), 4.10-4.22 (m, 3H), 4.29-4.32 (m, 1H), 4.51 (s, 2H), 4.73-4.75 (m, 1H), 6.58 (d, J = 2.4 Hz, 1H), 6.74-6.76 (m, 1H), 7.02-7.05 (m, 1H), 7.45 (s, 1H).

Example 513

Preparation of 7-((S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-1,3,4,5-tetrahydrobenzo[c]azepine-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 132 using suitable starting materials.

Yellow powder
1H NMR (CDCl3) δ 1.39 (s, 9H), 1.76-1.77 (m, 2H), 2.37 (m, 1H), 2.47 (m, 1H), 2.89 (m, 2H), 3.64-3.68 (m, 2H), 4.11-4.22 (m, 3H), 4.30-4.37 (m, 3H), 4.74 (m, 1H), 6.54-6.71 (m, 2H), 7.10-7.11 (m, 1H), 7.45 (s, 1H).

Example 514

Preparation of (2R,5S)-2,5-dimethyl-4-[(4-((S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 132 using suitable starting materials.
Yellow powder

1H NMR (CDCl3) δ 0.96 (d, J = 6.5 Hz, 3H), 1.26 (d, J = 6.8 Hz, 3H), 1.48 (s, 9H), 2.34-2.42 (m, 1H), 2.42-2.53 (m, 1H), 2.94 (m, 1H), 3.22-3.25 (m, 1H), 3.41-3.45 (m, 1H), 3.77-3.85 (m, 2H), 4.11-4.25 (m, 3H), 4.26-4.29 (m, 1H), 4.43 (br, 1H), 4.73 (m, 1H), 6.79-6.84 (m, 4H), 7.44 (s, 1H).

Example 515

Preparation of (2R,5S)-2,5-dimethyl-4-[4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 132 using suitable starting materials.

Yellow powder

1H NMR (CDCl3) δ 0.96 (d, J = 6.5 Hz, 3H), 1.26 (d, J = 6.8 Hz, 3H), 1.48 (s, 9H), 2.34-2.42 (m, 1H), 2.42-2.53 (m, 1H), 2.94 (m, 1H), 3.22-3.25 (m, 1H), 3.41-3.45 (m, 1H), 3.77-3.85 (m, 2H), 4.11-4.25 (m, 3H), 4.26-4.29 (m, 1H), 4.43 (br, 1H), 4.73 (m, 1H), 6.79-6.84 (m, 4H), 7.44 (s, 1H).

Example 516

Preparation of 4-[5-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)pyridin-2-yl]piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

Pale brown solid

1H NMR (CDCl3) δ 1.48 (s, 9H), 2.42-2.44 (m, 2H), 3.39-3.43 (m, 4H), 3.51-3.57 (m, 4H), 4.12-4.27 (m, 4H), 4.65-4.78 (m, 1H), 6.64 (d, J = 9.0 Hz, 1H), 7.19 (dd, J = 10.0 Hz, 3.3 Hz, 1H), 7.45 (s, 1H), 7.94 (d, J = 3.0 Hz, 1H).

Example 517

Preparation of 4-[5-((S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)pyridin-2-yl]piperazine-1-
carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 1 using suitable starting materials. Pale brown solid

1H NMR (CDCl3) δ 1.48 (s, 9H), 2.28-2.50 (m, 2H), 3.36-3.47 (m, 4H), 3.47-3.58 (m, 4H), 4.12-4.27 (m, 4H), 4.65-4.78 (m, 1H), 6.64 (d, J = 9.0 Hz, 1H), 7.19 (dd, J = 10.0 Hz, 3.3 Hz, 1H), 7.45 (s, 1H), 7.94 (d, J = 3.0 Hz, 1H).

Example 518

Preparation of (R)-7-[4-((2S,5R)-2,5-dimethylpiperazin-1-yl)phenoxy methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine trifluoroacetate

Trifluoroacetic acid (4 ml) was added to a dichloromethane solution (4 ml) of (2R,5S)-2,5-dimethyl-4-[4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-yldimethoxy)phenyl]piperazine-1-carboxylic acid tert-butyl ester (1.31 g), and the mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure to afford the title compound as a brown amorphous compound (1.35 g).

1H NMR (DMSO-d6) δ 0.84 (d, J = 10.2 Hz, 3H), 1.21 (d, J = 10.6 Hz, 3H), 2.15-2.40 (m, 2H), 2.71-2.85 (m, 2H), 3.08-3.26 (m, 2H), 3.36-3.40 (m, 2H), 4.11-4.33 (m, 4H), 4.88-4.91 (m, 1H), 6.96-6.99 (d, J = 14.8 Hz, 2H), 7.08-7.11 (d, J = 14.8 Hz, 2H), 8.10 (s, 1H), 8.89 (br, 1H), 9.21 (br, 1H).

Example 519

Preparation of 5-[(S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-yldimethoxy)phenyl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 69 using suitable starting materials. Powder

1H NMR (CDCl3) δ 1.40-1.44 (br, 9H), 1.83-2.08 (m, 2H), 2.32-2.48 (m, 2H), 3.01-3.22 (m, 1H), 3.32-3.65 (m, 3H), 4.07-4.36 (m, 5H),
4.31-4.46 (m, 1H), 4.60 (br, 1H), 6.47-6.50 (m, 2H), 6.82-6.85 (m, 2H), 7.44 (s, 1H).

Example 520

Preparation of 4-[4′-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)biphenyl-4-yl]piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

Pale yellow solid

1H NMR (DMSO-d6) δ 1.43 (s, 9H), 2.13-2.42 (m, 2H), 3.1-3.15 (t, J = 4.9 Hz, 4H), 3.40-3.55 (t, J = 5.4 Hz, 4H), 4.04-4.40 (m, 4H), 4.88-4.96 (m, 1H), 7.01 (d, J = 8.4 Hz, 2H), 7.04 (J = 8.5 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 8.11 (s, 1H).

Example 521

Preparation of 4-[4′-((S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)biphenyl-4-yl]piperazine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

Pale yellow solid

1H NMR (DMSO-d6) δ 1.43 (s, 9H), 2.13-2.42 (m, 2H), 3.1-3.15 (t, J = 4.9 Hz, 4H), 3.40-3.55 (t, J = 5.4 Hz, 4H), 4.04-4.40 (m, 4H), 4.88-4.96 (m, 1H), 7.01 (d, J = 8.4 Hz, 2H), 7.04 (J = 8.5 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 8.11 (s, 1H).

Example 522

Preparation of (S)-7-[4-(2,5-diazabicyclo[2.2.1]hept-2-yl)phenoxyethyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine trifluoroacetate

The title compound was prepared in the same manner as in Example 518 using suitable starting materials.
Brown amorphous

1H NMR (DMSO-d6) δ 1.87-1.90 (m, 1H), 2.11-2.29 (m, 3H), 3.13-3.18 (m, 3H), 3.57-3.60 (m, 1H), 4.09-4.21 (m, 4H), 4.41-4.53 (m, 2H), 4.80-4.91 (m, 1H), 6.61-6.64 (d, J = 15.0 Hz, 2H), 6.90-6.93 (d, J = 15.0 Hz, 2H), 8.10 (s, 1H), 8.52 (br, 1H), 8.96 (br, 1H).

Example 523

Preparation of 5-[(4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 132 using suitable starting materials.

Pale yellow powder

1H NMR (CDCl3) δ 1.40-1.44 (br, 9H), 1.83-2.06 (m, 2H), 2.33-2.48 (m, 2H), 3.02-3.22 (m, 1H), 3.32-3.52 (m, 2H), 3.54-3.60 (m, 1H), 4.08-4.31 (m, 5H), 4.46-4.61 (m, 1H), 4.70-4.73 (m, 1H), 6.48-6.50 (m, 2H), 6.62-6.85 (m, 2H), 7.44 (s, 1H).

Example 524

Preparation of (R)-7-[(4-(2,5-diazabicyclo[2.2.1]hept-2-yl)phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 518 using suitable starting materials.

Brown amorphous

1H NMR (DMSO-d6) δ 1.64-2.40 (m, 4H), 2.83-4.40 (m, 11H), 4.84 (m, 1H), 6.51-6.53 (d, J = 14.8 Hz, 2H), 6.84-6.87 (d, J = 14.9 Hz, 2H), 8.09 (s, 1H).

Example 525

Preparation of 4-[(4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl)piperidine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.
Reddish brown solid

1H NMR (CDCl3) δ 1.48 (s, 9H), 1.51-1.64 (m, 3H), 1.78 (d, J = 12.6 Hz, 2H), 2.32-2.42 (m, 1H), 2.44-2.52 (m, 1H), 2.55-2.63 (m, 1H), 2.79 (br s, 2H), 4.10-4.35 (m, 5H), 4.70-4.79 (m, 1H), 6.86 (d, J = 8.7 Hz, 2H), 7.13 (d, J = 8.6 Hz, 2H), 7.45 (s, 1H).

Example 526
Preparation of (R)-7-{4-(4,4-diethoxypiperidin-1-yl)phenoxy methyl}-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.

Yellow powder

1H NMR (CDCl3) δ 1.20 (t, J = 7.1 Hz, 6H), 1.89-1.95 (m, 4H), 2.31-2.41 (m, 1H), 2.45-2.52 (m, 1H), 3.06-3.17 (m, 4H), 3.51 (q, J = 7.1 Hz, 4H), 4.07-4.24 (m, 3H), 4.28 (dd, J = 10.1 Hz, 4.2 Hz, 1H), 4.71-4.76 (m, 1H), 6.81-6.85 (m, 2H), 6.88-6.93 (m, 2H), 7.44 (s, 1H).

Example 527
Preparation of (R)-2-nitro-7-(4-piperazin-1-ylphenoxy methyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

A 4 N hydrochloric acid 1,4-dioxane solution (22 ml) was gradually added to a methylene chloride (22 ml) suspension of 4-{4-[(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy]phenyl}piperazine-1-carboxylic acid tert-butyl ester (4.51 g), and the mixture was stirred at room temperature for 2 hours. The mixture was diluted with ethyl acetate and the precipitate was collected by filtration. The solid thus obtained was subjected to triturate with ethanol, collected by filtration and then dried. Hydrochloride of the title product was dissolved in water and neutralized using a 5 N sodium hydroxide aqueous solution under ice cooling, followed by stirring. The precipitate was collected by filtration and dried at 60°C to afford the title compound as a yellow powder (3.0 g).
Example 528

Preparation of (R)-2-nitro-7-(4-piperazin-1-ylphenoxymethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine trifluoroacetate

The title compound was prepared in the same manner as in Example 518 using suitable starting materials.

Pale brown powder

1H NMR (CDCl3) δ 2.31-2.42 (m, 1H), 2.44-2.53 (m, 1H), 3.01-3.08 (m, 9H), 4.08-4.23 (m, 3H), 4.29 (dd, J = 10.2 Hz, 4.2 Hz, 1H), 4.69-4.75 (m, 1H), 6.83-6.87 (m, 2H), 6.87-6.91 (m, 2H), 7.45 (s, 1H).

Example 529

Preparation of 1'-[4-([(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy]phenyl)-[4,4']bipiperidinyl-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 86 using suitable starting materials.

Pale yellow powder

1H NMR (CDCl3) δ 1.10-1.33 (m, 4H), 1.35-1.45 (m, 2H), 1.46 (s, 9H), 1.65-1.75 (m, 2H), 1.77-1.85 (m, 2H), 2.25-2.48 (m, 2H), 2.49-2.77 (m, 4H), 3.51-3.59 (m, 2H), 4.05-4.23 (m, 5H), 4.24-4.29 (m, 1H), 4.71-4.77 (m, 1H), 6.81-6.85 (m, 2H), 6.88-6.92 (m, 2H), 7.44 (s, 1H).

Example 530

Preparation of 4-{4-([(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy]phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as
in Example 86 using suitable starting materials.

White powder

1H NMR (CDCl3) δ 1.49 (s, 9H), 2.34-2.44 (m, 1H), 2.44-2.53 (m, 3H), 3.61-3.67 (m, 2H), 4.03-4.09 (m, 2H), 4.09-4.18 (m, 1H), 4.18-4.26 (m, 2H), 4.33 (dd, J = 10.2 Hz, 4.2 Hz, 1H), 4.72-4.80 (m, 1H), 5.91-6.02 (m, 1H), 6.85-6.92 (m, 2H), 7.32 (s, J = 8.8 Hz, 2H), 7.46 (s, 1H).

Example 531

Preparation of (R)-2-nitro-7-[4-(1,2,3,6-tetrahydroacridin-4-yl)phenoxyethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine trifluoroacetate

The title compound was prepared in the same manner as in Example 518 using suitable starting materials.

Pale green powder

1H NMR (DMSO-d6) δ 2.14-2.25 (m, 1H), 2.28-2.38 (m, 1H), 2.61-2.69 (m, 2H), 3.27-3.39 (m, 2H), 3.71-3.78 (m, 2H), 4.10 (dt, J = 5.2 Hz, 12.4 Hz, 1H), 4.15-4.22 (m, 1H), 4.28 (dd, J = 11.1 Hz, 5.8 Hz, 1H), 4.34 (dd, J = 11.1 Hz, 3.2 Hz, 1H), 4.88-4.95 (m, 1H), 6.09-6.13 (m, 1H), 7.01 (d, J = 8.9 Hz, 2H), 7.45 (d, J = 8.9 Hz, 2H), 8.11 (s, 1H), 8.80 (brs, 2H).

Example 532

Preparation of 4-(tert-butyldimethylsilyl-anorgyloxy)-1′-[4-(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]-[1,4′]piperidinyl

The title compound was prepared in the same manner as in Example 1 using suitable starting materials.

Yellow powder

1H NMR (CDCl3) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.53-1.96 (m, 7H), 2.31-2.53 (m, 6H), 2.64 (t, J = 10.6 Hz, 2H), 2.82 (br s, 2H), 3.59 (d, J = 12.1 Hz, 2H), 3.72 (br s, 1H), 4.05-4.22 (m, 3H), 4.22-4.30 (dd, J = 10.0 Hz, 4.3 Hz, 1H), 4.68-4.77 (m, 1H), 6.82 (d, J = 9.1 Hz, 2H), 6.89 (d, J = 9.1 Hz, 2H), 7.45 (s, 1H).
Example 533

Preparation of (R)-7-(4-{4-[4-(tert-butyldimethylsilyl)oxy]piperidin-1-ylmethyl}piperidin-1-yl)phenoxy methyl)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 470 using suitable starting materials.

Reddish yellow powder

1H NMR (CDCl3) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.25-1.38 (m, 2H), 1.50-1.65 (m, 3H), 1.73 (br s, 2H), 1.85 (d, J = 12.4 Hz, 2H), 2.05-2.25 (m, 4H), 2.28-2.40 (m, 1H), 2.40-2.50 (m, 1H), 2.50-2.70 (m, 4H), 3.52 (d, J = 12.0 Hz, 2H), 3.63-3.72 (m, 1H), 4.04-4.21 (m, 3H), 4.21-4.30 (dd, J = 10.3 Hz, 4.3 Hz, 1H), 4.65-4.75 (m, 1H), 6.76-6.85 (m, 2H), 6.85-6.94 (m, 2H), 7.44 (s, 1H).

Example 534

Preparation of 4-{4-{[(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy]phenoxy}methyl}piperidine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 470 using suitable starting materials.

Yellow solid

1H NMR (CDCl3) δ 1.18-1.30 (m, 2H), 1.46 (s, 9H), 1.81 (d, J = 13.1 Hz, 2H), 1.93 (br s, 1H), 2.33-2.44 (m, 1H), 2.44-2.53 (m, 1H), 2.74 (br s, 2H), 3.75 (d, J = 6.4 Hz, 2H), 4.06-4.30 (m, 5H), 4.66-4.76 (m, 1H), 6.78-6.87 (m, 4H), 7.45 (s, 1H).

Example 535

Preparation of 4-{2-[4-{[(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy]phenoxy}ethyl}piperidine-1-carboxylic acid tert-butyl ester

The title compound was prepared in the same manner as in Example 470 using suitable starting materials.

Yellow solid

1H NMR (CDCl3) δ 1.10-1.21 (m, 2H), 1.46 (s, 9H), 1.64-1.75 (m, 6H), 2.30-2.41 (m, 1H), 2.41-2.53 (m, 1H), 2.70 (br s, 2H), 3.96
(t, J = 5.9 Hz, 2H), 4.01-4.24 (m, 4H), 4.24-4.31 (dd, J = 10.2 Hz, 4.2 Hz, 1H), 4.68-4.76 (m, 1H), 6.76-6.85 (m, 4H), 7.45 (s, 1H).

Example 536

Preparation of (R)-2-nitro-7-{4-{piperidin-4-ylmethoxy}phenoxy(methyl)}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 518 using suitable starting materials.

Pale brown solid

1H NMR (CDCl3) δ 1.22-1.34 (m, 2H), 1.76-1.97 (m, 5H), 2.31-2.45 (m, 1H), 2.45-2.53 (m, 1H), 2.60-2.75 (m, 2H), 3.14 (d, J = 12.1 Hz, 2H), 3.74 (d, J = 6.3 Hz, 2H), 4.04-4.32 (m, 3H), 4.60-4.78 (m, 1H), 6.78-6.88 (m, 4H), 7.45 (s, 1H).

Example 537

Preparation of (R)-2-nitro-7-{4-{2-piperidin-4-ylmethoxy}phenoxy(methyl)}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine

The title compound was prepared in the same manner as in Example 518 using suitable starting materials.

Yellow solid

1H NMR (CDCl3) δ 1.14-1.30 (m, 2H), 1.61-1.83 (m, 5H), 2.05-2.53 (m, 3H), 2.60-2.70 (m, 2H), 3.10 (d, J = 12.1 Hz, 2H), 3.95 (t, J = 6.2 Hz, 2H), 4.02-4.31 (m, 4H), 4.70-4.78 (m, 1H), 6.83 (s, 4H), 7.45 (s, 1H).

Example 538

Preparation of 4-[(E)-3-{4-{{(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl}allyl}piperazine-1-carboxylic acid tert-buty1 ester

The title compound was prepared in the same manner as in Example 470 using suitable starting materials.

Yellow solid

1H NMR (CDCl3) δ 1.46 (s, 9H), 2.28-2.52 (m, 6H), 3.15 (d, J =
-330-

6.7 Hz, 2H), 3.46 (br s, 4H), 4.07-4.18 (m, 1H), 4.18-4.27 (m, 2H), 4.30-4.38 (dd, J = 10.2 Hz, 4.2 Hz, 1H), 4.70-4.82 (m, 1H), 6.10-6.20 (m, 1H), 6.46 (d, J = 15.8 Hz, 1H), 6.86 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 7.46 (s, 1H).

Example 539

Preparation of (R)-2-nitro-7-[4-((E)-3-piperazin-1-yl-propenyl)phenoxy methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine trifluoroacetate

The title compound was prepared in the same manner as in Example 518 using suitable starting materials.

Yellow powder

1H NMR (CDCl3) δ 2.33 (m, 2H), 2.60 (s, 1H), 3.28-3.56 (m, 4H), 3.56-3.78 (m, 4H), 4.06-4.42 (m, 4H), 4.78-4.88 (m, 2H), 6.05-6.18 (m, 1H), 6.66 (d, J = 15.6 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 7.62 (s, 1H).

Examples 540 to 772

The following products were prepared in the same manner as in Examples above using suitable starting materials.
Table 1

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Table 2

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|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| R       | H   | H   | H   | H   | H   | H   | H   | H   | H   | H   | H   | H   | H   | H   | H   | H   | H   | H   | H   | H   |
| X       |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Y       |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Z       |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| R       |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| R       |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| X       |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Y       |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Z       |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| R       |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| R       |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| X       |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Y       |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Z       |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

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Table 3

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Table 6

| Example 543 | -H -H -SCF₂ -H -H | 594 |
| Example 644 | -H -CF₃ -H -CF₂ -H | 630 |
| Example 645 | -H -H -H -OCF₃ -H | 578 |
| Example 646 | -H -H -H -H -OCF₃ | 578 |
| Example 647 | -F -F -F -F -F | 584 |
| Example 648 | -H -Cl -H -Cl -H | 562 |
| Example 649 | -H -H -C₃F₇ -H -H | 522 |
| Example 650 | -H -H -C₃F₇ -H -H | 570 |
| Example 652 | -H -H -H -H | 559 |

Example 653 | -N -N | -N -N | 559

![Diagram](image.png)
### Table 7

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<td>Example 737</td>
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<td>Example 738</td>
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<td>Example 739</td>
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<td>Example 740</td>
<td>530</td>
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## Table 17

<table>
<thead>
<tr>
<th>Example 741</th>
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<td>Example 742</td>
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<td>Example</td>
<td>Chemical Structure</td>
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<td>751</td>
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<td><img src="image8" alt="Chemical Structure" /></td>
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<td>759</td>
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<tr>
<td>760</td>
<td><img src="image10" alt="Chemical Structure" /></td>
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Table 19

<table>
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<tr>
<th>Example</th>
<th>Structure</th>
<th>Number</th>
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<td>Example 763</td>
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<td>Example 767</td>
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<td>Example 768</td>
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<td>Example 769</td>
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<tr>
<td>Example 770</td>
<td><img src="example_770.png" alt="Image" /></td>
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</table>
Table 20

<table>
<thead>
<tr>
<th>Example No.</th>
<th>R^i</th>
<th>MS(M+1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 771</td>
<td><img src="Image" alt="Chemical Structure" /></td>
<td>570</td>
</tr>
<tr>
<td>Example 772</td>
<td><img src="Image" alt="Chemical Structure" /></td>
<td>631</td>
</tr>
</tbody>
</table>
Test Example 1
Antimicrobial Assay (Agar Plate Dilution Method)

The minimum inhibitory concentration of the 2,3-dihydro-6-nitro-imidazo[2,1-b]oxazole compound obtained in Example 228 against Mycobacterium tuberculosis (M. tuberculosis H37Rv) was determined using a 7H11 medium (manufactured by BBL). The above strain had been cultured on a 7H9 medium (manufactured by BBL) and stored by freezing at -80°C. The number of viable cells had been counted. A bacterial suspension with a final viable cell count of approximately $10^6$ CFU/ml was prepared by using the bacterial stock mentioned above. Approximately 5 µl of the thus prepared bacterial suspension was inoculated onto the 7H11 agar medium containing the test compound and then cultured at 37°C for 14 days. Thereafter, the culture was subjected to a test to determine the minimum inhibitory concentration. The minimum inhibitory concentration of the compound against M. tuberculosis H37Rv was ≤ 0.0004 µg/ml.

Test Example 2
Antimicrobial Assay (Agar Plate Dilution Method)

The minimal inhibitory concentrations against Mycobacterium tuberculosis (M. tuberculosis kuroko) of the compounds listed in the table below were determined using a 7H11 medium (manufactured by BBL). M. tuberculosis kuroko strain had been cultured on a 7H9 medium (manufactured by BBL) and stored by freezing at -80°C. The number of viable cells had been counted. A bacterial suspension with a final viable cell count of approximately $10^6$ CFU/ml was prepared by using a bacterial stock mentioned above. Approximately 5 µl of the thus prepared bacterial suspension was inoculated onto the 7H11 agar medium containing the test compounds and then cultured at 37°C for 14 days. Thereafter, the culture was subjected to a test to determine the minimum inhibitory concentration. The results are shown in the table below.
<table>
<thead>
<tr>
<th>Compound Tested</th>
<th>Minimum Inhibitory Concentration (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound of Example 1</td>
<td>0.024</td>
</tr>
<tr>
<td>Compound of Example 3</td>
<td>0.05</td>
</tr>
<tr>
<td>Compound of Example 53</td>
<td>0.1</td>
</tr>
<tr>
<td>Compound of Example 56</td>
<td>0.012</td>
</tr>
<tr>
<td>Compound of Example 64</td>
<td>≤0.006</td>
</tr>
<tr>
<td>Compound of Example 79</td>
<td>0.012</td>
</tr>
<tr>
<td>Compound of Example 90</td>
<td>0.012</td>
</tr>
<tr>
<td>Compound of Example 143</td>
<td>0.1</td>
</tr>
<tr>
<td>Compound of Example 147</td>
<td>0.05</td>
</tr>
<tr>
<td>Compound of Example 153</td>
<td>0.024</td>
</tr>
<tr>
<td>Compound of Example 182</td>
<td>≤0.0015</td>
</tr>
<tr>
<td>Compound of Example 198</td>
<td>≤0.0015</td>
</tr>
<tr>
<td>Compound of Example 206</td>
<td>≤0.0015</td>
</tr>
<tr>
<td>Compound of Example 228</td>
<td>0.0008</td>
</tr>
<tr>
<td>Compound of Example 254</td>
<td>0.0008</td>
</tr>
<tr>
<td>Compound of Example 282</td>
<td>0.006</td>
</tr>
<tr>
<td>Compound of Example 290</td>
<td>0.0008</td>
</tr>
<tr>
<td>Compound of Example 299</td>
<td>0.0008</td>
</tr>
<tr>
<td>Compound of Example 304</td>
<td>0.012</td>
</tr>
<tr>
<td>Compound of Example 335</td>
<td>0.0015</td>
</tr>
<tr>
<td>Compound of Example 364</td>
<td>0.024</td>
</tr>
<tr>
<td>Compound of Example 372</td>
<td>0.006</td>
</tr>
<tr>
<td>Compound of Example 379</td>
<td>0.1</td>
</tr>
<tr>
<td>Compound of Example 380</td>
<td>0.012</td>
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<tr>
<td>Compound of Example 382</td>
<td>0.012</td>
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<tr>
<td>Compound of Example 383</td>
<td>0.003</td>
</tr>
<tr>
<td>Compound of Example 395</td>
<td>0.003</td>
</tr>
<tr>
<td>Compound of Example 400</td>
<td>≤0.0004</td>
</tr>
<tr>
<td>Compound of Example 411</td>
<td>0.006</td>
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<tr>
<td>Compound of Example 414</td>
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<tr>
<td>Compound of Example 415</td>
<td>0.0015</td>
</tr>
<tr>
<td>Compound of Example 446</td>
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<tr>
<td>Compound of Example 471</td>
<td>0.012</td>
</tr>
<tr>
<td>Compound of Example 490</td>
<td>0.0008</td>
</tr>
</tbody>
</table>
[Claim 1]

A compound represented by Formula (1):

\[
\text{O}_2\text{N} \quad \text{N} \quad \text{O} \quad \text{R}^2 \quad \text{O} \quad \text{R}^1
\]  

or a salt thereof,

wherein \( R^1 \) represents tetrahydroisoquinolyl, tetrahydroquinolyl, tetrahydrobenzoxepinyl, benzoxazolyl, benzothiazolyl, indolyl, isoindolyl, naphthyl, quinolyl, phenyl, biphenyl, or pyridyl, these groups being optionally substituted.

the phenyl and pyridyl represented by \( R^1 \) each being

substituted directly or via a linker with at least one group selected from the group consisting of tetrahydropyridyl, diazepanyl, diazabicycloheptanyl, tetrahydrotriazolopyrazinyl, tetrahydroimidazopyrazinyl, azabicyclooctanyl, oxazolyl, piperazinyl, piperidyl, and thiazolyl, each of these groups being optionally substituted;

the biphenyl represented by \( R^1 \) being substituted directly or via a linker with at least one group selected from the group consisting of tetrahydropyridyl, diazepanyl, diazabicycloheptanyl, tetrahydrotriazolopyrazinyl, tetrahydroimidazopyrazinyl, azabicyclooctanyl, oxazolyl, piperazinyl, piperidyl, thiazolyl, and phenyl, each of these groups being optionally substituted;

and \( R^1 \) represents hydrogen or lower alkyl.

[Claim 2]

The compound according to claim 1, or a salt thereof,

wherein \( R^1 \) is a group represented by Formula (2):

\[-A-L_1-B-L_2-C-D\]  

wherein \( A \) represents a divalent group selected from (A1) to (A12):

(A1) tetrahydroisoquinolinediyl,
(A2) tetrahydroquinolinediyl,  
(A3) tetrahydrobenzosazepinediyl,  
(A4) benzoxazolidiyl,  
(A5) benzothiazolidiyl,  
5  (A6) indoladiyl,  
(A7) isoindolenediyl,  
(A8) naphthalenediyl,  
(A9) quinolinediyl,  
(A10) phenylene,  
10  (A11) biphenyldiyl, and  
(A12) pyridinediyl,  
these groups (A1) to (A12) being optionally substituted  
on the ring(s) with at least one group selected from the group  
consisting of halogen and lower alkyl;  
15  L1 represents a single bond, lower alkylene, -N(lower  
alkyl)-, -O-, -O-lower alkylene, -O-lower alkylene-O-, lower  
alkylene-O-, lower alkylene-O-lower alkylene, or lower  
alkylene;  
B represents a divalent group selected from (B1) to  
20  (B11):  
(B1) tetrahydropyridinediyl,  
(B2) diazepinediyl,  
(B3) diazabicycloheptanediyl,  
(B4) tetrahydrotriazolopyrazinediyl,  
25  (B5) tetrahydroimidazopyrazinediyl,  
(B6) azabicyclooctanediyl,  
(B7) oxazolidiyl,  
(B8) piperazinediyl,  
(B9) piperidinediyl,  
30  (B10) thiazolidiyl, and  
(B11) phenylene,  
these groups (B1) to (B11) being optionally substituted  
on the ring(s) with at least one group selected from the group  
consisting of lower alkyl, halo-lower alkyl, alkenyl, lower  
35  alkoxy, halo-lower alkoxy, lower alkoxy carbonyl, lower
alkenyloxy carbonyl, hydroxy, lower alkylsulfonfyl, and halo-lower alkylsulfonfyl;

L2 represents a single bond, -CO-, -C=O-, -COO- lower alkynylene, -COO- lower alkylene (this lower alkylene is optionally substituted with phenyl), -COO-lower alkynylene, -N(lower alkyl)-, -N(lower alkyl)-lower alkylene, -NH-, -NH-lower alkylene, -O-, -O-lower alkylene, -S-, lower alkylene (this lower alkylene is optionally substituted with optionally protected hydroxy), lower alkylene (this lower alkylene is optionally substituted with optionally protected hydroxy)-O-, lower alkylene-N-(lower alkyl)-, lower alkylene-N(lower alkyl)-lower alkylene, lower alkylene-O-lower alkylene, lower alkylene-S-, or lower alkylene (this lower alkylene is optionally substituted with lower alkyl or phenyl);

C represents a divalent group or a single bond selected from (C1) to (C28):
(C1) tetrahydroquinolinediyl,
(C2) dihydrobenzodioxindiyl,
(C3) dihydrobenzoazolediyl,
(C4) dihydrobenzofurandiyl,
(C5) dihydrobenzoazinediyl,
(C6) adamantane diyl,
(C7) benzothiophenediyl,
(C8) benzdioxolediyl,
(C9) benzimidazole diyl,
(C10) benzofurandiyl,
(C11) carbazolediyl,
(C12) chromandiyl,
(C13) cyclohexanediyl,
(C14) fluorane diyl,
(C15) furandiyl,
(C16) imidazopyridinediyl,
(C17) imidazolediyl,
(C18) indolediyl,
(C19) naphthalenediyl,
(C20) piperidinediyl,  
(C21) pyrazolediyl,  
(C22) pyridinediyl,  
(C23) pyrrolediyl,  
(C24) quinolinediyl,  
(C25) thiazolodiyl,  
(C26) thiophenediyl,  
(C27) phenylene, and  
(C28) single bond,  

these groups (C1) to (C27) being optionally substituted  
on the ring(s) with at least one group selected from the group  
consisting of alkoxy, halo-lower alkoxy, alkyl, haloalkyl,  
halogen, hydroxy, lower alkoxy carbonyl, oxo, lower alkanoylamino,  
lower alkanoyloxy, nitro, lower alkylthio, halo-lower alkylthio,  
cyclo-lower-alkyl, cyclo-lower alkoxy, cyano, lower  
alkoxy carbonylamino, nitro, amino, (mono- or di-lower alkyl)amino,  
lower alkylsulfonyl, lower alkylsulfonlamino, alkenyloxy, and  
(mono- or di-lower alkyl)amino lower alkoxy;  

D represents a group or an atom selected from (D1) to  

(D35):  
(D1) oxadiazolyl-lower alkoxy,  
(D2) triazolyl,  
(D3) isoxazolyl-lower alkoxy,  
(D4) imidazolyl,  
(D5) imidazolyl-lower alkyl,  
(D6) thiazolyl-lower alkoxy,  
(D7) thienyl,  
(D8) thieryl-lower alkoxy,  
(D9) furyl-lower alkoxy,  
(D10) tetrahydropyranyl,  
(D11) pyrazinyl-lower alkoxy,  
(D12) piperazinylphenyl,  
(D13) pyrazolyl,  
(D14) pyridyl,  
(D15) pyridyloxy,
(D16) pyridyl-lower alkoxy,
(D17) pyrrolidinyl,
(D18) pyrrolyl,
(D19) phenyl,
5  (D20) (mono- or di-phenyl)amino,
(D21) phenyl-lower alkyl,
(D22) phenyl-lower alkenyl,
(D23) (phenyl-lower alkyl)(lower alkyl)amino,
(D24) (phenyl-lower alkyl)amino,
10  (D25) phenyl-lower alkysulfonyl,
(D26) phenyl-lower alkylsulfanyl,
(D27) phenyl-lower alkylthio,
(D28) phenyl-lower alkenylxy,
(D29) phenyl-lower alkoxy,
15  (D30) phenyl-lower alkoxyphenyl,
(D31) phenoxy,
(D32) phenoxy-lower alkyl,
(D33) phenoxy-piperidyl,
(D34) morpholinyl-lower alkyl, and
20  (D35) hydrogen,

these groups (D1) to (D34) being optionally substituted on the ring(s) with at least one group selected from the group consisting of lower alkyl, halo-lower alkyl, lower alkylthio, lower alkoxy, halo-lower alkoxy, and halogen,
25  with the proviso that when A is group (A10) or (A12), and B is group (B11), C is selected from groups (C1) to (C27).

[Claim 3]

The compound according to claim 2, or a salt thereof,
30  wherein, in Formula (2), A is
(A1) tetrahydroisoquinolinediyl,
(A2) tetrahydroquinolinediyl,
(A9) quinolinediyl,
(A10) phenylene,
35  (A11) biphenyldiyl, or
(A12) pyridinediyl,
these groups (A1), (A2), and (A9) to (A12) being optionally substituted on the ring(s) with at least one group selected from the group consisting of halogen and lower alkyl.

[Claim 4]
The compound according to claim 2 or 3, or a salt thereof,
wherein, in Formula (2), A is
(A1) tetrahydroisoquinolinediyl,
(A2) tetrahydroquinolinediyl,
(A9) quinolinediyl,
(A10) phenylene,
(A11) biphenyldiyl, or
(A12) pyridinediyl,
these groups (A1), (A2), and (A9) to (A12) being optionally substituted on the ring(s) with one or two halogen atoms;
L1 is a single bond, lower alkylene, -O-, -O-lower alkylene, or lower alkylene-O-;
B is
(B7) oxazolinediyl,
(B8) piperazinediyl,
(B9) piperidinediyl,
(B10) thiazolinediyl, or
(B11) phenylene,
these groups (B7) to (B11) being optionally substituted on the ring with at least one or two groups selected from the group consisting of lower alkyl, halo-lower alkyl, halo-lower alkoxy, hydroxy, and halo-lower alkylsulfonyl;
L2 is a single bond, -N(lower alkyl)-, -O-, -O-lower alkylene, lower alkylene, lower alkylene-O-, or lower alkenylene;
C is
(C13) cyclohexanediyl,
(C20) piperidinediyl,
(C27) phenylene, or
(C28) single bond,
these groups (C13), (C20), and (C27) being optionally
substituted on the ring with one or two groups selected from the
group consisting of halo-lower alkoxyl, halo-lower alkyl, hydroxy,
and halo-lower alkylthio;

D is
(D21) phenyl-lower alkyl,
(D24) (phenyl-lower alkyl)amino,
(D29) phenyl-lower alkoxy,
(D31) phenoxy, or
(D35) hydrogen,
these groups (D21), (D24), (D29), and (D31) being
optionally substituted on the ring with one or two groups
selected from the group consisting of halo-lower alkyl and halo-
lower alkoxy,
with the proviso that when A is (A10) or (A12), and B
is (B11), C is (C13), (C20), or (C27).

[Claim 5]
The compound according to claim 2, 3, or 4, or a salt
thereof, which is represented by Formula (1-1):

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{R}^2 \\
\text{O} & \quad \text{R}^1 \\
\text{N} & \quad \text{L}1 \quad \text{B} \quad \text{L}2 \quad \text{C} \quad \text{D}
\end{align*}
\]  

wherein \( \text{R}^1 \) is halogen or lower alkyl, \( m \) is \( 0, 1, \) or \( 2 \), wherein
when \( m \) is \( 2 \), each \( \text{R}^1 \) is the same or different, and \( \text{R}^2, \text{L}1, \text{B}, \text{L}2, \text{C}, \) and \( \text{D} \) are the same as defined above;

Formula (1-2):
wherein R^1, m, R^2, L1, B, L2, C, and D are the same as defined above;

**Formula (1-3):**

\[
\text{O}_2\text{N} \quad \text{N} \quad \text{O} \quad \text{R}^2 \quad (\text{R}^1_m) \quad \text{L1--B--L2--C--D}
\]  

wherein R^1, m, R^2, L1, B, L2, C, and D are the same as defined above;

**Formula (1-4):**

\[
\text{O}_2\text{N} \quad \text{N} \quad \text{O} \quad \text{R}^2 \quad (\text{R}^1_m) \quad \text{L1--B--L2--C}^1--D
\]

wherein E is N or CH; C^1 is a divalent group selected from groups (C1) to (C27) above (the substituents on the ring(s) of these groups are the same as defined above); and R^1, m, R^2, L1, B, L2, and D are the same as defined above; or

**Formula (1-5):**

\[
\text{O}_2\text{N} \quad \text{N} \quad \text{O} \quad \text{R}^2 \quad (\text{R}^1_m) \quad \text{L1--B--L2--C}--D
\]

wherein R^1, m, E^1, L1, B, L2, C, and D are the same as defined above.

**[Claim 6]**

The compound of claim 1, which is selected from the
group consisting of the following compounds, or a salt thereof:
• 2-nitro-7-(4-{4-{4-trifluoromethoxyphenoxo}piperidin-1-yl}phenoxymethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine;
• 2-nitro-7-(4-{4-{3-trifluoromethoxybenzyl}piperazin-1-yl}phenoxymethyl)-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine;
• 2-nitro-7-{4-[(2-{4-(trifluoromethoxyphenoxy)methyl}oxazol-4-yl)phenoxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine;
• 2-nitro-7-[(2-{4-(trifluoromethoxyphenyl)thiazol-4-yl)phenoxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine;
• 2-nitro-7-{4-{3-[(4-(4-trifluoromethoxyphenoxy)phenyl)propyl]piperazin-1-yl}phenoxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine;
• 2-nitro-7-[(6-{4-[2-(4-trifluoromethoxyphenoxy)ethyl]piperidin-1-yl}pyridin-3-yloxy)methyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine;
• N-methyl-N-{1-[4-((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]piperidin-4-yl}-N-(4-trifluoromethoxyphenyl)amine;
• 6-{2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-1-[3-{4-trifluoromethoxyphenoxy}propyl]-1,2,3,4-tetrahydroquinoline;
• 7-{3-fluoro-4-{4-{4-trifluoromethoxyphenoxy}piperidin-1-yl}phenoxymethyl}-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine;
• 6-{((R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)-2-(4-trifluoromethoxybenzyl)oxyloxy)quinoline
• (R)-2-nitro-7-{4-{4-[4-(4-trifluoromethylbenzyl)oxyloxy)benzyl]piperazin-1-yl}phenoxymethyl}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine;
• (R)-2-nitro-7-{4-{4-(4-trifluoromethoxybenzyl)oxyloxy)phenyl}piperazin-1-yl)phenoxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine,
• (R)-2-nitro-7-{4-[(4-{4-(4-trifluoromethoxybenzyl)oxyloxy)benzyl]piperidin-4-yloxy)phenoxymethyl]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine;
-360-

* (R)-2-nitro-7-(4-{4-[4-(4-
trifluoromethoxyphenoxyl)benzyl]piperidin-1-yl}phenoxyethyl)-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine;

* (S)-2-nitro-7-(4-{4-[4-(4-
trifluoromethylbenzyloxy)benzyl]piperidin-1-yl}phenoxyethyl)-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine;

* 6-{(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)benzyl]piperazine-1-ylmethyl)phenyl}-N-
(4-trifluoromethylbenzyl)amine;

* 6-{(R)-2-nitro-7-{4-{4-trifluoromethoxyphenoxyl)piperidin-1-
ylmethyl}biphenyl-4-yloxyethyl}]-6,7-dihydro-5H-imidazo[2,1-
b][1,3]oxazine;

* N-[(S)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-ylmethoxy)phenyl]piperazin-1-ylmethyl)phenyl}-N-
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* (R)-7-{4-[4-{4-(4-
trifluoromethylbenzyloxy)benzyl]piperazin-1-yl}phenoxyethyl}-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine;

* 6-{(R)-2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazin-7-
ylmethoxy)-2-[4-(4-trifluoromethylbenzyloxy)benzyl]-1,2,3,4-
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* (R)-7-{4-{4-{4-
trifluoromethoxyphenoxyl)benzyl]piperazin-1-yl}phenoxyethyl}-2-
nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine;

* 2-nitro-7-{4-[1-(4-trifluoromethoxybenzyl)piperidin-4-
yl]phenoxyethyl}]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine;

* (R)-2-nitro-7-{4-{4-[4-
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* 1-{4-{4-[2-(4-
trifluoromethoxyphenoxyl)ethyl]piperidin-1-yl}phenoxyethyl}]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine;

* 7-methyl-2-nitro-7-{4-{4-[2-(4-
trifluoromethoxybenzyl)piperidin-1-yl]phenoxyethyl}]-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine;

* (R)-2-nitro-7-{4-{4-[4-(4-
trifluoromethoxybenzyl)piperidin-1-
yl]phenoxyethyl}]-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine;
-361-

* (R)-2-nitro-7-(4-{4-[3-(3-
trifluoromethylphenoxy)propyl]piperidin-1-yl}phenoxy)methyl)-6,7-
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* (R)-2-nitro-7-(4-{4-[3-(4-
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* 7-methyl-2-nitro-7-(4-{4-[(E)-3-(4-
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* (R)-2-nitro-7-(4-{4-[4-(trifluoromethyl-
cyclohexyl)methyl]piperazin-1-yl}phenoxy)methyl)-6,7-dihydro-5H-
imidazo[2,1-b][1,3]oxazine;
* (R)-2-nitro-7-(4-{4-[4-(trifluoromethylbenzyl)-4,4'-
bipiperidin-1-yl}phenoxy)methyl)-6,7-dihydro-5H-imidazo[2,1-
b][1,3]oxazine;
* (R)-2-nitro-7-(4-{4-{(4-
trifluoromethylsulfonylphenoxy)piperidin-1-yl}phenoxy)methyl)-6,7-
dihydro-5H-imidazo[2,1-b][1,3]oxazine;
* (R)-7-(4-[4-methoxy-4-(4-trifluoromethylphenyl)piperidin-1-
yl]phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-
b][1,3]oxazine; and
* (R)-7-[4-{4-(1-methyl-1-[4-(4-
trifluoromethylbenzyloxy)phenyl]ethyl)piperazin-1-
yl]phenoxy)methyl]-2-nitro-6,7-dihydro-5H-imidazo[2,1-
b][1,3]oxazine.

[Claim 7]
A pharmaceutical composition comprising a compound of claim 1 or 2, or a salt thereof, and a pharmaceutically acceptable carrier.

[Claim 8]
A prophylactic and/or therapeutic agent for tuberculosis, comprising a compound of claim 1 or 2, or a salt thereof, and a pharmaceutically acceptable carrier.
[Claim 9]
A compound of claim 1 or 2, or a salt thereof, for use in the prevention and/or treatment of tuberculosis.

[Claim 10]
Use of a compound of claim 1 or 2, or a salt thereof, for the preparation of a pharmaceutical composition.

[Claim 11]
Use of a compound of claim 1 or 2, or a salt thereof, as a pharmaceutical composition.

[Claim 12]
A method for preventing and/or treating tuberculosis, comprising administering an effective amount of a compound of claim 1 or 2, or a salt thereof, to a patient.
### INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D498/04 A61K31/5365 A61P31/04 A61P31/06

**ADD.**

According to International Patent Classification (IPC) or to both national classification and IPC.

**B. FIELD-OF-SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the sections searched

Electronic data banks searched during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Relevant to claim no.</th>
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<td>WO 2011/014776 A1 (GLOBAL ALLIANCE FOR TB DRUG DEV [US]; THOMPSON ANDREW M [NZ]; DENNY WI) 3 February 2011 (2011-02-03) cited in the application claims 1,6,7; figures 19-21</td>
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<td>WO 2009/120789 A1 (GLOBAL ALLIANCE FOR TB DRUG DEV [US]; DING CHARLES Z [US]; LU GENLIANG) 1 October 2009 (2009-10-01) paragraph [0008]; claims 1,10; examples 1,2</td>
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<td>WO 2011/014774 A1 (GLOBAL ALLIANCE FOR TB DRUG DEV [US]; DENNY WILLIAM ALEXANDER [NZ]; TH) 3 February 2011 (2011-02-03) claims 1,6,7</td>
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**D. Further documents are listed in the continuation of Box C.**

**X** See patent family annex.

- Special categories of cited documents:
  - "D" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier application or patent but published on or after the international filing date
  - "L" document which may throw doubts on priority claims or which is cited to establish the publication data of another citation or other special reason (as specified)
  - "O" document relating to an oral proceedings, use, exhibition or other means
  - "P" document published prior to the international filing date but later than the priority date claimed

**E. Date of the actual completion of the international search**

26 June 2012

**F. Name and mailing address of the ISA/ European Patent Office, P.B. 5814 Fontenay-Aux-Roses 2 92800 Puteaux, Tel: (33) 1-59-22-22-00, Fax: (33) 1-59-22-22-01**

**G. Date of mailing of the international search report**

03/07/2012

**H. Authorized officer**

Gettins, Marc
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THE PATENTS ACT 1970

(AMENDED BY THE PATENTS ACT 2005)

AND

THE PATENT RULES, 2003

(AMENDED BY THE PATENT RULES 2006)

In the matter of Patent application No.

314/MUM/2008 Application Date 13/02/2008

AND

In the matter of Section (14)

& (15) of the Patents Act

RAJEEV M. HUZURBAZAR………..The Applicant

Present: RAJEEV M. HUZURBAZAR.
DECISION

The instant Patent Application filed as ORDINARY APPLICATION filed on 13/02/2008 entitled ‘ORAL FOOD SUPPLEMENT POWDER FOR DIARRHOEA IN PAEDIATRICS’. The initially filed claims in its Complete Specification were examined in accordance with the Patents Act 1970 and consequently numbers of objections comprising of both formal and technical were conveyed by the Patent office, Mumbai to the applicant as per First Examination Report dated 28th April 2010 which is the part of file of the instant case. The main technical objections were u/s 10(4) & u/s 3(e) of the Patents Act.

The initially filed set of claims are stated as follows:

1. An Oral Food Supplement composition, for Diarrhea for paediatric patients, comprising,
   Mixed Fruit Powder 1 to 50%
   Potato Powder 15 to 30%
   Rice Powder 11 to 15%
   Soyabean Powder 1.5 to 10%
   Sago Powder .5 to 10%
   Lentil Powder 1 to 5%
   Tur Powder 1 to 5%
2. A process of making the food supplement composition as claimed in claim 1, where in the all the powder are spray Dried, Powder are weighed and added to mixer and process is continued for 30 min. mixing mass is then transferred to stainless steel vessel, powder is then transferred to filling machine and packed in containers.

The applicants had filed their reply to the First Examination Report (FER) 11\(^{th}\) January 2011 ie within the prescribed period enclosing therewith the desired Forms, revised retyped papers etc. They simultaneously made some rewording of the said claims. The said reply & the set of claims is also part of file of the instant case. Further Second Examination Report has been issued by the office maintaining the main requirements which has been replied by the applicant.

The last date to put the application in order for grant has been expired on 28/04/2011. As the Patent office was still not satisfied with the said compliance, the above objections were maintained & stated that the revised set of claims are not allowable under section 3(e) of the Act. For the sake of natural justice the applicant has been offered an hearing on 04/07/2011.

The main requirements of the First Examination Report (FER) the claims fall within the scope of section 3(e) of the Act.

Applicant Sri Rajeev Huzurbazar appeared for hearing before me on 04/07/2011.

The set of claims on record are stated as follows.
The applicant submitted that the present Invention relate to application of Oral Food Supplement Powder in case of diarrhea in pediatric patient. Diarrhea is too frequent passage of poorly formed stools i.e passage of excessive water in faces. Diarrheal diseases constitute a major cause of morbidity and mortality worldwide. More than five million children under age of five years die every year of diarrhea. Diarrhea has been shown to have significant impact on nutrition. Child with multiple episodes of diarrhea suffers most severely from protein energy malnutrition. A considerable quantity of nutrients is lost in diarrheal stool. Protein energy malnutrition develops. A vicious cycle of diarrhea-malnutrition-diarrhea sets in. Significant death occur as a result of malnutrition, unnecessary starvation, consequent series of diarrhea. Pediatric diarrheal patients by administering an effective daily amount of Food Supplement Powder of composition comprising mixture of Mixed Fruit Powder, Rice, Potato, Soyabean, Sago, when given in definite proportion and dose with other drugs controls the diarrhea, formation of normal stool very fast as compared to drugs given alone to
paediatric patients. Food Supplement powder not only reduces the fluidity and frequency of loose stool which is necessary to alter the picture of diarrhea, but also prevents malnutrition. The formulation may be available in biscuit form.

The applicant merely repeated the same thing which they have submitted during the reply to the FER that the claims has been revised & it meets the requirement of Section 3(e) & it is a synergistic composition & not a admixture. The Applicant stated that they submitted the clinical data while filing reply to first examination report & further data in view of their reply to hearing. They stated that it is not the individual effect of the ingredients but due to the combined effect of all the ingredients that they are using in the food supplement composition & that help to control the diarrhea. They stated that if using the hundred percent of one the ingredient in the composition it has an adverse effect on body & not effective to control diarrhea. Further, they stated that indifferent proportion of different ingredients will also not give result & will not be effective in controlling diarrhea.

So, they requested you to waive the objection.

The above submission to the hearing is also part of the instant case. Their submissions have been considered carefully but it does not fulfill the requirement of Section 3(e) of the Act.

I had gone through the specification & their submission. The instant application relates to an oral food supplement in the form of composition, for controlling diarrhea particularly for paediatric patients, infants & babies. It comprising mainly different fruit powder, potato powder, rice powder, soyabeen powder, sago powder, lentil powder, tur dal powder in a proportion mentioned in the specification & claimed in the claims.
Section 3(e) of the Act says "...a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance."

So, the question of synergism are matters of scientific facts which are required to be embodied in the specification so that the said characteristics are apparent from the specification.

Claims as stated above of the applicant claimed a composition comprising fruit powder, potato powder, rice powder, soyabeen powder, sago powder, lentil powder, tur dal powder in a different proportion. The composition claimed by the applicant is a mere admixture of above mentioned ingredients without showing any synergism. The combination does not result in any enhanced additive effect. There is not a single example in the entire specification which demonstrates that the said combination provides surprising results apart from being a mere collocation of the properties of the individual ingredients. What applicant claiming as a synergy has not been demonstrated at all in the complete specification. What applicant tries to show in the form of clinical data & other data at the time filing reply to the first examination report & reply to the hearing has not filed as a part of description in the specification.

So, it is pertinent to mention here that, at the time of filing of instant application for patent no where mentioned in the specification that how the components or ingredients of the composition act together and is responsible for controlling the diarrhea. No comparative results/data on the controlling in respect diarrhea of the claimed composition is disclosed. A mere statement at the time of hearing & filing reply on enhanced property
of the composition regarding controlling diarrhea in absence of experimental/technical evidences in the specification itself is not credible. The specification is silent on unexpected effect/synergism of the claimed composition. The question of efficacy and or synergism are matters of scientific facts which are required to be embodied in the specification so that the said characteristics are apparent from the specification. The applicant vaguely claimed that the composition is a synergistic composition but no support in this regard was provided in the specification. Actually applicant has to study the ingredients used in the composition individually and need to see whether these ingredients possess property towards controlling the diarrhea individually & how effective in controlling diarrhea when these have mixed together in particular proportion. So, the applicant failed to demonstrate the data of individual ingredients and when these have mixed together, need to be mentioned in the description of specification.

In the absence of such evidence, it is evident that the claims cannot be patented under Section 3(e) of the Act and ought to be rejected.

It is not uncommon for the effect of two or more chemicals/ingredients on an organism to be greater than the effect of each chemical/ingredient individually, or the sum of the individual effects. The presence of different ingredient together enhances the effects of the composition as a whole. This is called a synergistic effect or synergy. The applicant has to define the synergy i.e how different entities cooperate advantageously for a final outcome shall be defined in the specification which applicant failed to define.

In the absence of synergism between the defined components, which applicant failed, the claimed composition of the alleged application is considered mere admixture as defined under clause (e) of Section 3 of the Act.
So, considering the clause (e) of Section 3 of the Act & in the absence of synergistic data in the specification as stated above, the composition claimed herein in claims is a mere admixture.

Further the revised set of claims which applicant has filed after the hearing, claim 2 is not the same claim which applicant has filed at the time of filing of the application. What applicant claimed in the initially file set claims in claim 2 is process of making he composition. However, it has been converted to the product claim & now claiming composition with synergistic effect which they have not demonstrated in the specification and claimed in such a way that it lacks clarity. Further, applicant has added the the matter regarding the fruit powder. They are now claiming fruit powder used in the composition is made from fruits apple, banana & guava are not fully supported by the description of the initially filed specification. Applicant has carried out the voluntary amendments without following the prescribed procedure under the Act. Though applicant has explained in their submission of first examination report regarding the steps used for making the composition, they have not taken the care to explain these each of the steps in the complete specification filed initially. So, the complete specification does not meet the requirement of 10 (4) of the Patents Act, 1970.

As per Section 10 (4) of the Patents Act every complete specification shall –

a) fully & particularly describe the invention & its operation or use & the method by which it is to be performed;

b) disclose the best method of performing the the invention which is known to the applicant & for which he is entitled to claim the protection; and

c) end with a claim or claims defining the scope of the invention for which protection is claimed;

d) be accompanied by an abstract to provide the technical information on the invention.
The Complete Specification describing the invention is a techno-legal document. It should disclose the invention completely to meet the requirement of the Patents Act and should also enable a person possessing average skill in the art to work the invention without assistance of the patentee. This is possible when the complete specification describes the invention fully and particularly and describes its operation and/or method by which it is to be performed. It is also essential that the best method for performing the invention, which is known to the applicant is disclosed in the Complete Specification. The complete specification must describe an embodiment of the invention claimed in claims & that description must be sufficient to enable those in the industry concerned to carry it into effect without their making further invention. The ordinary skilled person in the art must be able to perform the invention which satisfies the requirement of disclosure. Further as stated above, applicant failed to demonstrate the synergy with required data in the specification.

Having considered all the circumstances, reply, submission made by the agent for the applicant, I hereby refuse the application on the grounds as stated above.


Dated: 05.10.2012. (A. T.PATRE)

Place: Mumbai Asstt. Controller of Patents & Designs