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THE PATENT OFFICE, INDIA
CONTENTS NOT VERIFIED
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22 FEB 2013
Bouddhik Sampada Bhawan
CP-2, Sector-V, Salt Lake City, Kol-91

February 21st, 2013

The Controller of Patents,
The Patent office,
Intellectual Property Office Building,
CP-2, Sector V, Salt Lake City,
Kolkata-700091.

Re: Representation u/s 25(1) of the Patents Act -
in Indian Patent Application **3865/KOLNP/2007** filed on 20/07/2009
National Phase of PCT Application No.PCT/US0616604 (Published as WO2006116764).
Applicant: Shionogi and Company Ltd.
Representation filed by: **Delhi Network of Positive People (DNP+)**
Our Ref: **OPP0043/CA**

Dear Sir,

We submit herewith a Representation u/s 25(1) of the Patents Act, 2005, along with evidence available with us.

We crave leave of the Controller to submit additional documents or evidence or if necessary to support any of the averments in the representation as may be necessitated in the proceeding.

The Controller is requested to take the documents on record and proceed further in the matter and keep the petitioner advised of each and every step taken in the matter.

Lastly, we request the Controller to grant us an opportunity of being heard before the above representation is finally decided.

Thanking you,

Rajeshwari

Rajeshwari H.
For Rajeshwari & Associates
AGENT FOR THE PETITIONER/OPPONENT

Encl: Representation with 5 volumes of documents.

BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, KOLKATA

IN THE MATTER OF THE PATENTS ACT, 1970 and THE PATENTS RULES 2003.

IN THE MATTER OF a pre-grant opposition under Section 25(1)

AND

IN THE MATTER OF:

Indian Patent Application **3865/KOLNP/2007** filed on 20/07/2009 claiming priority of Japanese Patent Application No.2005-131161 dated 28 April, 2005 and Japanese Patent Application No. 2005-312076 dated 27th October 2005 by Shionogi and Company Ltd. National Phase of PCT Application No.PCT/US0616604 (Published as WO2006116764).

AND

IN THE MATTER OF:

Delhi Network of Positive People (DNP+),

...PETITIONER/OPPONENT

VS.

SMITHKLINE BEECHAM CORPORATION

AND

SHIONOGI & CO. LTD.,

...RESPONDENTS/APPLICANTS

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8.	Duly executed Power of Attorney (Form-26)	**1127-1128**

Dated this 21st day of February, 2012.

Rajeshwari

[Rajeshwari H.]
AGENT FOR THE PETITIONER/OPPONENT

The Controller of Patents
The Patent Office, Kolkata.

BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, KOLKATA

IN THE MATTER OF THE PATENTS ACT, 1970 and THE PATENTS RULES 2003.

IN THE MATTER OF a pre-grant opposition under Section 25(1)

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Indian Patent Application **3865/KOLNP/2007** filed on 20/07/2009 claiming priority of Japanese Patent Application No.2005-131161 dated 28 April, 2005 and Japanese Patent Application No. 2005-312076 dated 27th October 2005 by Shionogi and Company Ltd. National Phase of PCT Application No.PCT/US0616604 (Published as WO2006116764).

AND

IN THE MATTER OF:

Delhi Network of Positive People (DNP+),
House No:64, Gali No: 3,
Near IGNOU, NEB Sarai,
New Delhi-110068

...PETITIONER/OPPONENT

VS.

SMITHKLINE BEECHAM CORPORATION
A UNITED STATES CORPORATION
ONE FRANKLIN PLAZA, P.O. BOX 7929
PHILADELPHIA, PA 19101,
UNITED STATES OF AMERICA.

AND

SHIONOGI & CO. LTD.,
A JAPANESE COMPANY
1-8 DOSHOMACHI 3-CHOME, CHUO-KU
OSAKA-SHI, OSAKA 541-0045
JAPAN.

...RESPONDENTS/APPLICANTS

STATEMENT OF CASE OF OPPONENT

1. The Opponent herein is a community based, non-profit organization representing the needs of people living with HIV/AIDS ("PLHAs"). The Delhi

STATEMENT OF CASE OF OPPONENT

1. The Opponent herein is a community based, non-profit organization representing the needs of people living with HIV/AIDS ("PLHAs"). The Delhi Network of Positive People ("DNP+") is registered as Society No.S-52850 under the Societies Registration Act XXI 1860, having its registered address at House No.64, Gali No.3, Near IGNOU, Neb Sarai, New Delhi-110068'. The present Pre-Grant Representation is being filed through Mr.Vikas Ahuja, President of the Delhi Network of Positive People. The Opponents represent and provide support to PLHAs in order to facilitate access to treatment and addressing issues of discrimination facing PLHAs in Indian society. DNP+ also advocates for policies and laws that aim to expand access to affordable HIV treatment to save lives and prevent the spread of the virus.

The HIV/AIDS epidemic poses one of the greatest challenges to global public health today, but even more so for developing countries, including India. 34 million people globally are living with HIV, with over 2 million estimated to be in India alone. Fresh scientific evidence shows that treatment with antiretroviral medicines (ARVs) not only saves lives, but is also a form of prevention, as it reduces the risk of transmission of HIV from one person to another by 96%. In the developing world, including those living with HIV in India, access to antiretroviral medicines and, therefore life itself, is only possible if affordable generic versions of these medicines are not blocked by low quality patents.

The opponents are particularly interested that the patent offices in India strictly apply patentability standards while examining patent applications related to integrase inhibitors. Integrase inhibitors is a class of HIV medicines that are now used to treat patients who have developed resistant to first and second line ARV treatment and have very limited treatment options. The first integrase inhibitor, raltegravir, was approved by the European Drug Regulatory Authority in 2007. This has triggered a race among multinational companies to patent different integrase inhibitors. Companies are in-fact

making a wide use of the so-called 'Markush claims' that is, claims that include a general formulae with multiple options that allow for the protection, under a single patent, of up to several millions of molecules. The admission of patents with such claims leads to a rather complex situation when it comes to pharmaceuticals, because a single patent may potentially limit or block research and development on and in this case the commercialization of an extremely large number of integrase inhibitors. The issue of 'Markush' claims is also an important aspect that must be analyzed in detail, so that the granting of patents with such claims does not become a constraint for research or an undue restriction to competition.

2. The Petitioner/Opponent has learnt that the Applicant has a Indian National Phase Application No. 3865/KOLNP/2007, which is currently pending before the Patent Office. The said application has been filed in respect of an invention for several thousands of compounds claimed by the Applicant to possess HIV integrase inhibitory activity. The said Application, purportedly includes, a chemical compound, known as Dolutegravir. The present invention is titled "POLYCYCLIC CARBAMOYLPYRIDONE DERIVATIVE HAVING HIV INTEGRASE, INHIBITORY ACTIVITY".

3. By way of back ground, it is submitted that the Indian Application is published with 56 claims. The Specification as mentioned in impugned Indian National Phase Application 3865/KOLNP/2007 is annexed herewith at **Annexure-A**. Initially the impugned application has been filed with 56 claims. A First Examination Report has been issued by this office on February, 27, 2012. It appears that the Applicant may have filed a response to the First Examination Report on 30th August, 2012, through their representatives. Along with the response, a set of amended claims also appear to have been filed. Since the Applicants by themselves have amended the claims, the said opposition is drawn to the Amended set of claims. The amended claims may be summarized as below:

- Claim 1 is drawn to a Markush Structure which Markush structure involves several possible thousands of compounds. The various options of the Markush structure is enumerated in claim 1. Claim 1 also provides for the various phosphonate esters of the Markush of claim 1.

- Claim 2 claims pharmaceutically acceptable salts or solvates of compounds of claim 1, when there are specific substituents in the Markush.

- Claim 3 claims pharmaceutically acceptable salts or solvates of the compound of claim 1, when the broken line represents the absence of a bond.

- Claims 4 and 5 claim the pharmaceutically acceptable salts and solvates thereof, when the Markush as claim 1 has certain specific substituents.

- Claim 6 is again another independent claim, drawn to the compound whose Markush is named as (I-1-1) and provides for further substituents.

- Claims 7 to 10 are drawn to the pharmaceutically acceptable salts or solvates when the markush as disclosed in claim 6,has certain specific substituents. Claim 11 discloses further substitutions of A ring to the compounds as claimed in claims 1 to 6 Markush (I-1) by 3 heterocycles, being a five membered, six membered and seven membered ring, each containing two substituents of N and Z. Z is further defined as either an oxygen atom or NR, wherein several possible substituents are again defined for R.

- Claims 12 to 21 define the compound of claim 11 with further substituents and their pharmaceutically acceptable salts and solvates thereof.

- Claims 22 and 23 define the compound of claim 6, the compound being the compound of Markush (I-1-1) with further substituents.

- Claim 24 describes Markush (I-11) with the five membered ring of nitrogen and provides for the various substitutions of the Markush structure

- Claims 25 and 26 lists various compounds by their IUPAC names along with their pharmaceutically acceptable salts, enatiomers and diastereoisomers

- Claim 27 claims the pharmaceutically acceptable salts of claims 25 and 26.

- Claim 28 claims the compounds of claims 1 to 27 as their pharmaceutical compositions and Claim 39 claims that the pharmaceutical composition is comprises an anti-HIV agent.

- Claim 30 claims a process of preparation of a Markush (I-20a) and Claim 31 claims a process for (I-20b).

- Claim 32, 33 and 34 respectively claim the process for preparation of the Markush (I-21a), (I-21b) and (I-22a). Claims 35 to 41 respectively claim the synthesis of Markush of (I-22b), (I-23a), (I-23b), (I-24a), (I-24b), (I-25), (I-26), (I-27).

- Claim 43 pertains to a method of treating HIV infection in a human comprising administering to a human any anti-viral compound of claims 1 to 27.

- Claim 44 claims the compounds of the present invention for in treatment or prophylaxis of HIV.

- Claim 45 claims the formulas of (I-21a), (I-21b) and (I-22a),(I-22b), (I-23a), (I-23b), (I-24a), (I-24b), (I-25), (I-26), (I-27) and claim 46 claims these compounds when P^1 is H along with its pharmaceutically acceptable salts and solvates thereof

- Claim 47 pertains to a composition of claim 28 with one additional therapeutic agent which may be a reverse transcriptase inhibitor or protease inhibitor.

- Claims 48 and 49 is specifically drawn to a compound of examples Y-3 also known as dolutegravir, provides for its structure and also claims its pharmaceutically acceptable salts and solvates thereof.

- Claim 50 is also drawn to one specific compound

- Claim 51 claims the product obtained by the process of claims 30 to 42.

The Opponent is not aware as to whether the claims stated hereinabove are the only amended claims or whether further amendments have been made but not taken on record. The Opponent craves leave to add new documents or evidence as may be required in support of such amended claims.

4. Accordingly, the Opponent submits their opposition by way of representation under Section 25(1) in respect of the said Indian Application No.3865/KOLNP/2007(Priority date: 28.04.2005) corresponding international WO publication number WO 2006/116764 on the following amongst other grounds listed below, which are without prejudice and in the alternative to each other.

Before traversing various grounds of the opposition, the Opponent has certain preliminary remarks in respect of the application. The impugned patent application at page 1 discloses the technical field and the background art. The

impugned application discloses that there are several HIV integrase inhibitors and carbamoyl substituted hydroxypyrimidinone derivatives that are already well established HIV integrase inhibitors. The specification does not proceed to describe the structures of the prior art compounds, however, the specification lists certain prior art publications and states that the problem to be solved by the invention is "the development of **a** novel integrase inhibitor has been desired" [sic]; though however, the impugned application lists and attempts to cover several possible thousands of compounds. The background does not describe, at any instance, any specific surprising effect or advantage of the compound(s) of the present invention. Meaning thereby that the compounds provided are a mere alternative to those in the prior art.

The impugned specification discloses a set of compounds denoted by the Markush structure of formula I. This Markush structure contains only one six membered ring with nitrogen, and an option of another ring is provided, this ring being indefinite and may be converted into a five membered, six membered or a seven membered ring. The Principal structure also contains a side chain attached with the first ring. The second ring is confirmed as a six membered ring containing two nitrogen atoms, with an option that a further heterocycle, may be attached to a second ring containing two nitrogen atoms. This Markush structure is termed as (I-1). A Markush structure (I-11) in which the second structure is a five membered ring comprising two nitrogens which may be attached to another heterocycle D. is disclosed.

Then the impugned specification defines certain common scientific terms and provides a general disclosure for substitution of phosphoric acid or a phosphonate. Further compounds with various substitutions covered under Markush (I-1) are disclosed including possible options of the heterocycle ring A that may be five membered, six or seven membered ring comprising nitrogen as one of the hetero atoms and there may be another hetero atom, which may be oxygen, sulphur, nitrogen. Further examples of the said A ring is provided. The specification also clearly states that the impugned application includes compounds with various stereochemistries. The specification further discloses that compound (I), comprises of compound (I-1) and (I-1-1) and (I-

8). (I-1) provides for a saturated ring system, (I-1-1) provides for an unsaturated ring system and (I-8) provides a hydroxyl group at a position ortho to the nitrogen of the first ring.

The specification also lists compound (I-3) in which the third ring is a five membered ring and also recites a structure in which the second ring is a five membered ring. All structures represented here below at Figure 1 for ready reference.

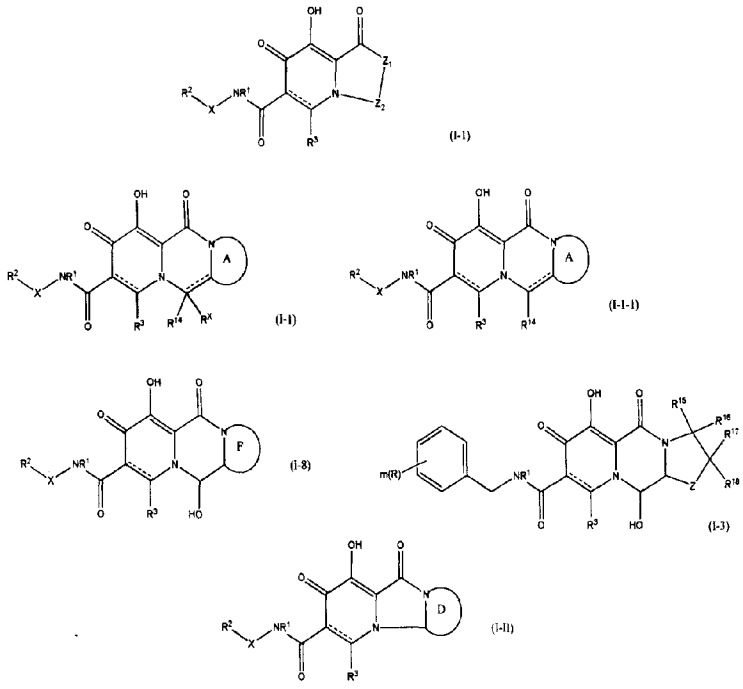


Fig. 1.: Markush structures of the impugned application.

The methods of preparing the compound of the impugned specification are disclosed, which comprises of 51 steps and 10 processes. Intermediates of the process (I-P) are shown on page 72 onwards and lists (I-20a), (I-20b), (I-21a), (I-21b), (I-22a) (I-22b), (I-23a), (I-23b), (I-24a) (I-24b), (I-25), (I-26), (I-27). The process for producing the above mentioned intermediates is also listed.

Various examples are listed for the synthesis of certain compounds covered by of the Markush, namely A-1, C-1 to C-21, F-1 to F-64; H-1 and H-2; I-1 is

listed and I-2; L-1; M-1; X-1 to X-4; Y-1 to Y-18 and it is stated that these compounds are synthesized as per examples C-21.

It is also stated that the corresponding amino alcohol derivatives of Y-1 to Y-18 are synthesized in optically pure version in certain prior art. The application also proceeds to lists certain compounds in table ZZ and states that these compounds are mixtures of diastereomers at the depicted stereocenter in the ratio of 1:1 to >10:1. Further it is disclosed in the specification that the compounds of all examples have >95% ee and >6:1 diastereomeric purity unless indicated otherwise.

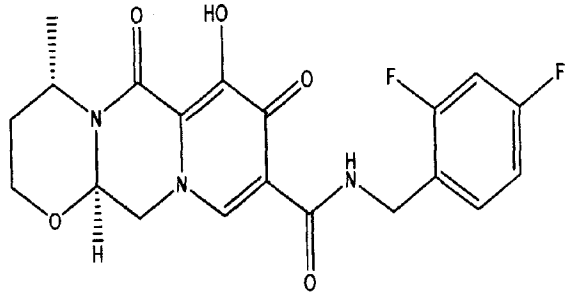
Then application provides certain synthetic methods for synthesis of the compounds of formula 68 to 83 with a general listing of compounds at examples Z-1 to ZZ-24. The structures of ZZ-1 to ZZ-24 are listed at pages 238 to 241 in a table.

The specification also discloses compounds covered by a Markush structure of (I-7) with possible substituents, which substituents are listed at table B. The specification also provides certain experimental example testing the HIV integrase inhibitory activity in an *in vitro* assay, namely Example No. C-2, F-2 and H-2. Another experimental example is provides which tests the example Z-1 to Z-60. The specification also provides in Example 1, Example 1 and 2 a formulation comprising the compounds of the impugned application. Then the application ends with certain claims.

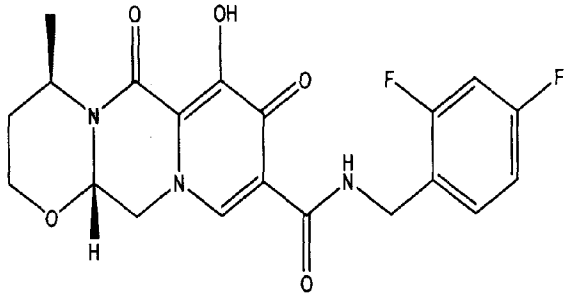
By way of background, it is submitted that HIV/AIDS epidemic is one of the greatest challenges to global public health. Roughly 34 million people worldwide are living with HIV, majority of them in developing countries (UNAIDS). As more and more patients develop drug resistance to already available first or second line HIV medications, the interest of public health are best served in a framework where rigorous standards of patentability are used to examine applications relating to integrase inhibitors especially as regards non-obviousness, novelty and disclosure, so that - India a key supplier of medicines in the developing world - avoids a proliferation of 'evergreening'

pharmaceutical patents that can block generic competition and thereby limit access to these class of medicines. This impugned patent application too claims HIV integrase inhibitors, which inhibitors includes Dolutegravir, which is one such drug.

Dolutegravir, also known as S/GSK1349572 or simply '572 is an integrase inhibitor that is said to have HIV inhibitory activity and is said to block the strand transfer step of integration of the viral genome into the host cell's DNA currently the application for approval is being submitted an processed by the drug regulatory authorities. The structure of Dolutegravir is disclosed in example Y-3 and its isomer is disclosed in Example Y-2. These compounds are specifically claimed and presented here below at Figure-2.



(4s,9ar)-5-hydroxy-4-methyl-6,10-dioxo,3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene7-carboxylic acid 2,4,-difluoro-benzylamide



(4R,9as)-5-hydroxy-4-methyl-6,10-dioxo,3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene7-carboxylic acid 2,4,-difluoro-benzylamide

Figure 2: Structure of compounds at example Y-2 and Y-3 of the impugned application.

It is submitted that all compounds including Dolutegravir are well known and well established by that of disclosure in prior art and ought to be rejected. The impugned application ought to be rejected on any of the following grounds as below:

GROUND I

I) Section 25(1)(b)/(c): Lack of novelty

The invention as claimed in Claims 1-51 lacks novelty and are not patentable under Section **25(1)**(b)-(c) of the Patents Act, 1970 (as amended in 2005; hereinafter referred to as "the Act"). It is submitted that none of the claims of 3865/KOLNP/2007are novel and they are all liable to be rejected on this ground alone.

It is submitted that US 2005/0054645 published on March 10, 2005 by Miyazaki et. al., anticipates all compounds of the impugned application. This application is annexed herewith as **Annexure – B** and referred to as US'645.

The compounds No.180, 196, 213 and 214, 234, 273, 372, 377 and 378, 380, 428, anticipate the compounds covered by Markush structure of the impugned application. All these compounds are represented at Table 1.

Table 1: Representative compounds of US 2005/0054645

M^+	Compound	Page
180		105
196		108
213		111
214		111
234		114
273		116
372		125
377		126
378		126
380		127
428		135

US'645, as described herein above clearly discloses compounds that are claimed within the Markush structure of the impugned application. The disclosed compounds may be considered as the species compounds. It is well understood that a species will anticipate a claim to a genus and that a generic claim will be considered as anticipated if the prior art discloses a species falling within the claimed genus. The species in that case will anticipate the genus. Further, it is submitted that when the species is clearly named, the species claim is anticipated no matter how many other species compounds are additionally named/claimed.

It is submitted that the prior art for this impugned application i.e., US'645, as disclosed herein, teaches a generic formula embracing a certain number of compounds closely related to each other in structure and the properties possessed by the compounds and the structural semblance of the compound are the same as that of the impugned application.

Hence, the compounds disclosed in US'645 anticipate the compounds claimed by the impugned application.

Thus, all claims stand anticipated by disclosure in prior art and hence this application, ought to be rejected.

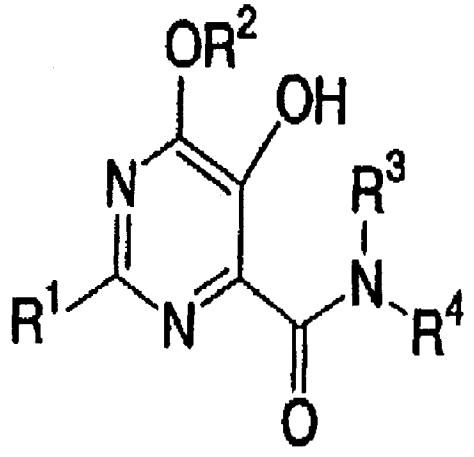
GROUND II

II) Section 25(1)(e): Lack of inventive step

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 as mentioned in clause (b) or having regard to what was used in India before the priority date of the claim.

It is submitted that the claims of the impugned application are not inventive and obvious in view of WO03/35076, WO03/35077, WO2004/58758 and WO2004/58757.

WO 03/035076 (hereinafter referred to as W0'076 and annexed herewith as **Annexure-C**), published on 1st May 2003 by ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA discloses Dihydroxypyrimidine carboxamide inhibitors of HIV integrase. It is to be noted that the basic structure of this compound is the same as that of the impugned specification. The Markush structure of WO'076 as present in the abstract is reproduced here below at figure 3.



(I)

Fig.3 Markush structure of WO'076

WO'076 discloses several compounds represented by a common Markush structure as in figure 3. The compounds with various substitutions are disclosed from page 2 to 51. More importantly, WO'076 discloses certain specific compounds that are embraced by the said Markush structure and envisaged within the Markush and some of these compounds (species) are set out presented in various tables in the specification (Table 1-24, 15B, 17B, 21B, 22B, 23B). It may be noted that the compounds exemplified comprises

the basic moiety *N* – benzyl-5,6-dihydroxypyrimidine-4-carboxamide (see **figure 4**).

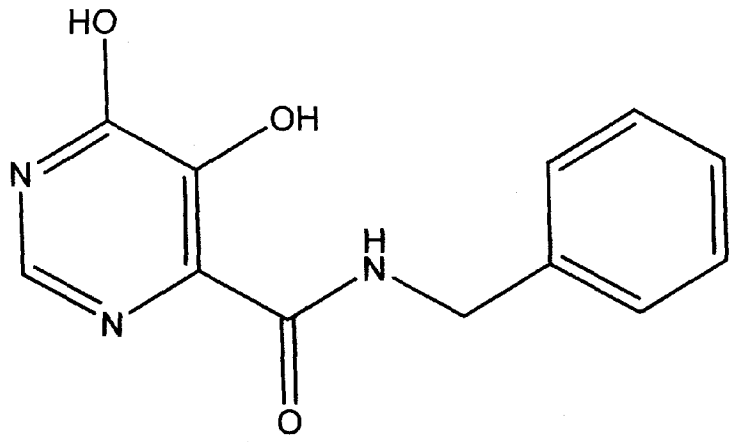
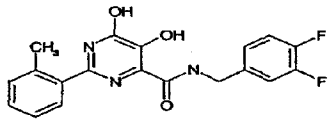
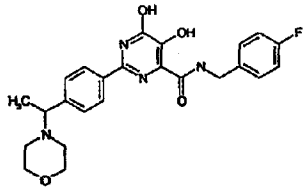
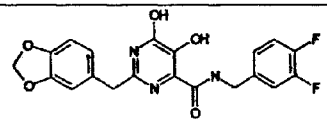
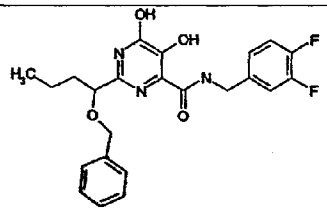
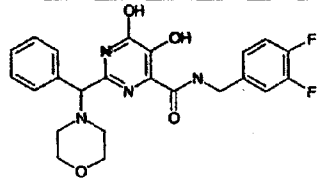
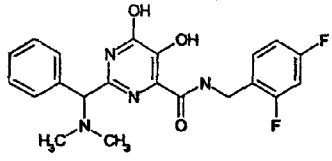
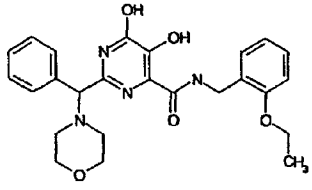
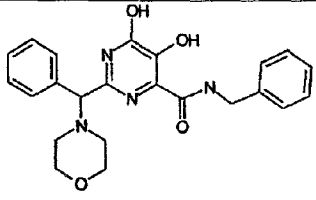


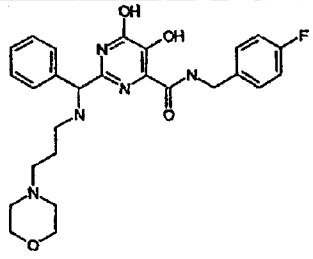
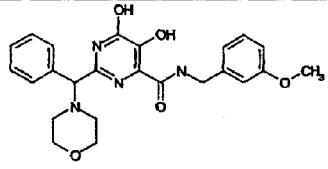
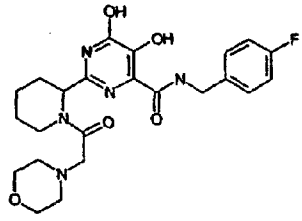
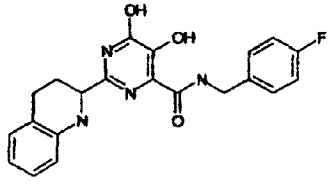
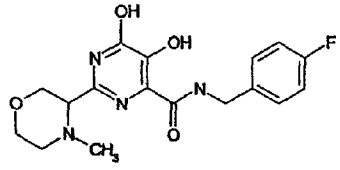
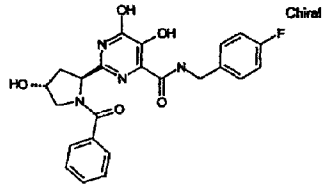
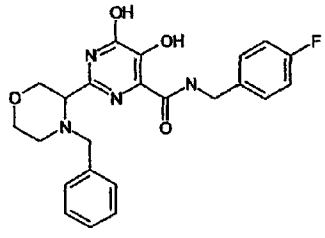
Fig 4. Structure of N-benzyl-5,6-dihydroxypyrimidine-4-carboxamide

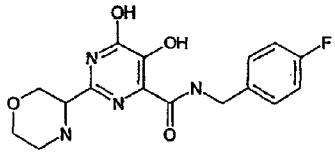
It may be noted that this moiety may be considered as equivalent to one part of the molecule of that of the impugned patent, including the molecules disclosed at examples Y-2 and Y-3 also known as Dolutegravir.

On examining a few representative structure of WO'076, (see Table 2), it may be seen that the basic moiety of Fig. 4 is present in all structures. In addition, it may be noted that WO'076, also discloses several compounds that comprise a difluro substitution at the Benzyl ring and six membered heterocyclic rings comprising both heteroatoms of oxygen and nitrogen. It is to be noted that all these compounds are HIV integrate inhibitors and hence very important and relevant.

Table 2: Representative compounds of WO'076

M^+	Compound	Page
372		167
453		178
416		184
444		195
457		203
415		205
465		207
421		207

496		207
451		210
474		218
395		225
363		231
453		231
439		231

349		231

From the above **Table 2**, it is clear that there are several species of compounds that fall within the scope of the Markush of the impugned application are disclosed by WO'076. In addition it may be seen that the critical elements of the structure of example Y-2 and Y-3 are also disclosed by WO'076. WO'076 also discloses that the compound of the present invention may be used for HIV integrase inhibition and that these compounds may also be administered as a pharmaceutical composition. (see pages 65 and 66).

WO 03/035077 herein after referred to as WO'077 and annexed herewith as **Annexure-D**. WO'077 has been published on 1st May 2003, again by ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA. This application has been published on the same date as that of WO'076 and relates to hydroxy pyrimidine compounds. All these compounds are HIV integrase inhibitors. The basic Markush of WO'077 is represented herebelow. (see figure 5).

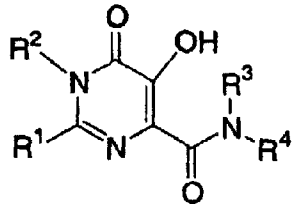


Fig 5. Markush of WO'077

The compounds with various substitutions and embraced by the Markush structure of WO'077 are disclosed and the specific embodiments are presented

both as examples and tables in the specification. On examining all the examples, it may be seen that all the structures contain the following feature which are depicted in Figure 6. The structure may be chemically called as N–benzyl-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxamide. (see figure 6).

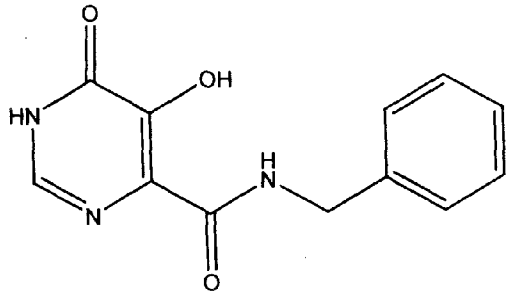
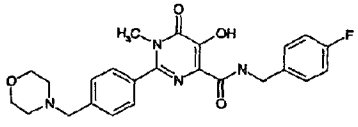


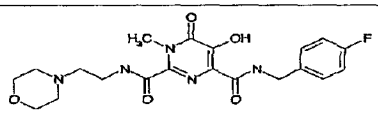
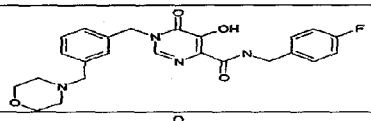
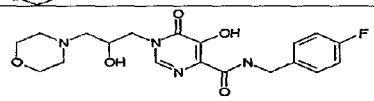
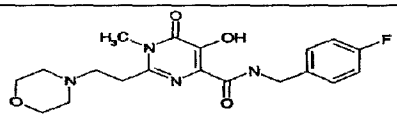
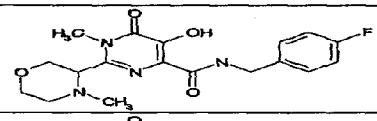
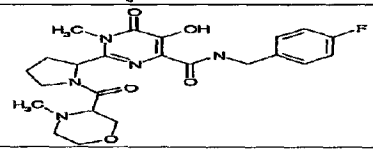
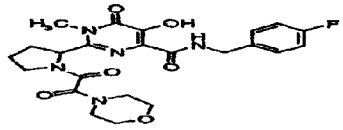
Fig.6. Structure of N–benzyl-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxamide

From Fig 6. it can be clearly seen that the basic moiety as represented falls within the scope of the Markush structure of the impugned patent.

Also, on comparing a few representative examples of WO'077, it can be clearly seen that all aspects of the impugned application and that of example Y-2 and Y-3 are disclosed by WO'077(See **Table 3.**)

Table 3: Representative examples of WO'077

M^+	Compound	Page
453		145

434		149
453		149
407		150
390.9		150
377		152
474		155
488		164

From **Table 3,** above, it can be clearly seen that the basic ring and several compounds, fall within the scope and of the Markush structure of claim 1 of the impugned application are already known and well established in prior art. The use of these compounds as an HIV integrase inhibitor has already been established in prior art.

WO 2004/058756 hereinafter referred to as WO'756 and annexed herewith as **Annexure-E,** published on July 15, 2004 filed also by ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA discloses of hydroxy pyrimidine containing compounds for HIV integrase inhibition. The Markush structure of WO'756 is depicted at **Figure 7.**

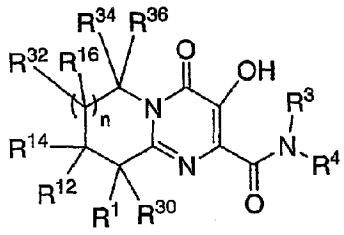
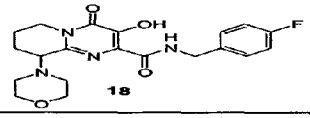
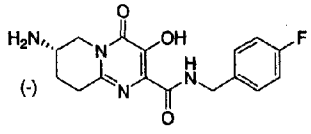
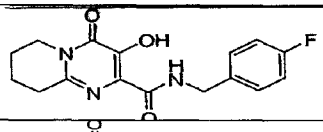
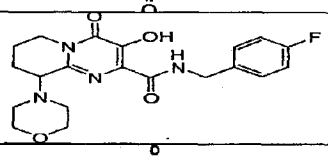
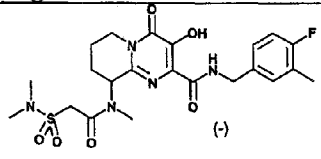


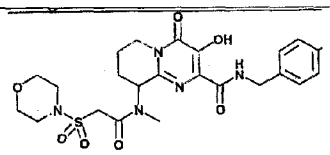
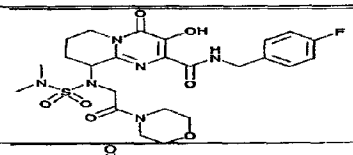
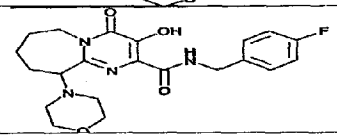
Fig.7. Markush of WO'756

As may be seen from the Figure 7, WO'756 discloses hydroxy pyrimidinones with an addition of another ring attached to the pyrimidine ring. In another words WO'756 is drawn to TETRAHYDRO-4H-PYRIDO[1,2-A]PYRIMIDINES. Again the application provides several possible compounds with various substitutions represented by a common Markush structure and also exemplifies certain compounds. These compounds are set out as examples and as specific compounds.

A few representative example compounds disclosed by WO'756 are depicted in table 4.

Table 4: A few representative compounds of WO 2004/058756

M_+	Compounds	Page
Example 2		42
Example 14		70
M+318		73
M+403		74
M+510		79

M+538		82
M+567		83
M+417		84

From the above mentioned table 4, it can be clearly seen that WO'756 read with WO'076 and WO'077 disclose as to how tetra hydro pyrimidines can act as effective HIV integrase inhibitors.

WO 2004/058757 is hereinafter referred to as "WO'757" and annexed herewith as **Annexure-F**. WO'757 is also drawn to TETRAHYDRO-4H-PYRIDO[1,2-A]PYRIMIDINES and is also filed by ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI SPA. This application also discloses HIV integrase inhibitors. The general Markush structure of WO'757 is presented at **Figure 8.**

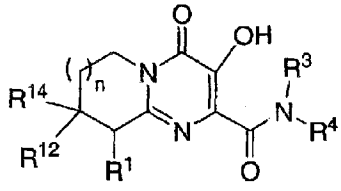
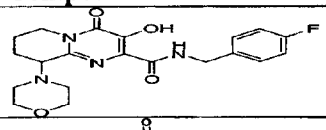
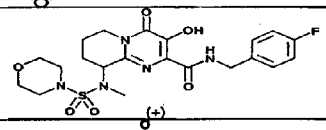
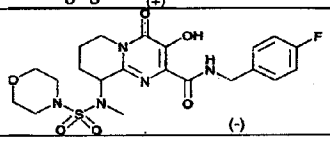


Figure 8: Markush structure of WO'757

WO '757 also provides several examples of compounds that fall within the scope and sweep of the impugned specification. Certain representative compounds of WO'757 are presented here below at Table 5.

Table 5. Representative compounds of WO'757

M^+	Compounds	Page
M+403		41
M+496 (+)		43
M+496 (-)		43

From the above discussion it is clear that the prior art when read together leads to the compounds claimed by the impugned patent application, examples Y-2 and Y-3 in particular. A person skilled in the art after reading the prior art would easily arrive at the compound claimed rendering them obvious.

Hence, all aspects of this invention are obvious by disclosure in prior art and hence on this ground alone this application ought to be rejected.

GROUND III

III) Section 25(1)(a): the Applicant has wrongfully obtained the patent.

It is submitted that the basic research leading to the compounds of the impugned application has been conducted by certain research institutes. The Applicant has neither taken the requisite permissions, nor acknowledged the prior art in this regard.

The Opponent craves leave to submit further evidence in this regard.

GROUND IV

IV) Section 25(1)(f) : that the subject of any claim is not an invention within the meaning of this act.

IVA) Section 3(d): Subject of Claims 1-51 of the complete specification is not patentable under this Act

Claims 1-51 are drawn to compounds represented by Markush structure comprising millions of chemical compounds. It is submitted all these compounds are derivatives of known compounds. These compounds are purported to be novel HIV integrase inhibitors. However, the impugned specification has not at any instance demonstrated the biological activity of all the said compounds.

The few experimental examples provided in the impugned specification demonstrate a certain value of HIV integrase inhibition which value is not compared with any of the prior art compounds or standard compounds. Hence it is unclear as to whether these compounds posses any notable activity at all. Moreover, the activity as presented is a mere *in vitro* test, which may not be equated to therapeutic efficacy.

Assuming, but not admitting, that these compounds do actually posses HIV inhibitory activity, it is submitted that such activity is not enhanced activity as compared to already known prior art compounds. Thereby, all compounds of this impugned specification ought to be rejected.

It is to be noted that a mere handful of compounds are tested in the specification. These examples in no manner serve as sufficient examples.
Notwithstanding, it is clear that the compounds should possess enhanced efficacy if they have to overcome section 3(d) of this Act. Enhanced therapeutic efficacy has to be proved by comparing the compounds of the present invention to that of closest compounds in prior art. There are several compounds in prior art that fall within the scope of the Markush of the impugned application as claimed in claim 1 and extremely close in structure to that of the compounds exemplified in the impugned application, however the specification does not at any instance demonstrate any enhanced efficacy as compared to that of prior art compounds.

It is submitted that the compound Y-2 and Y-3, have not even been tested and there is no indication in the specification that these compounds are active. Hence these compounds and all other compounds that have not been tested at all have to be rejected out rightly. Hence, Claim 1 and all claims dependent on Claim 1, ought to be rejected on this ground only.

IVB) Section 3(e): Subject of claims 28, 29 and 47 of the complete specification is not patentable under this Act

Claims 28 and 29 are drawn to a pharmaceutical composition that comprises of an admixture of the compounds of Claim 1 and its dependent Claims along with pharmaceutical acceptable excipients. The pharmaceutical composition as claimed is a mere admixture and not a synergistic mixture and hence these pharmaceutical compositions are not patentable under Section 3(e) of this Act. Hence these claims pertain to a mere admixture of trial components which perform their functions and hence on this ground alone it ought to be rejected.

IVC) Section 3(i): Subject of claims 29, 43 and 44 of the complete specification are not patentable under this Act

Claim29 is drawn to a method of use of the compounds of the present invention for use in inhibition of HIV integrase and for a method of treatment to render a subject free from HIV in the garb of a composition. Claims 43 and 44 blatantly, claim the use of the compounds of the impugned application for treatment and/or prophylaxis. Such claims fall squarely within the scope and sweep of Section 3(i) of the Patents Act and ought to be rejected on this ground only.

GROUND V

V) Section 25(1) (f): Subject of claims 1 to 51 is not an invention within the meaning of this Act or is not patentable under this Act

It is submitted that since claims 1-51 are not novel, are not inventive and lack industrial application, they do not constitute an 'invention' under the Act. In

this regard, the Opponent craves leave to refer and rely on submission made in Grounds I-IV above which are not being repeated for the sake of brevity.

i) **Subject of claims are not patentable under section 2(1)(ja) of this act:**
The claimed invention falls under the mischief of Section 2(1)(ja) being devoid of inventive step as according to definition of inventive step, the invention should have a technical advancement over the prior art and should not be obvious to a person skilled in the art. The alleged invention as claimed is not a technical advancement and hence ought to be rejected on this ground only.

GROUND VI

VI) **Section 25(1)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed**

It is submitted that the complete specification of 3865/KOLNP/2007 does not describe the invention claimed or the method by which it is be performed.

Claims indeterminate

All claims of the impugned application are indeterminate and on this ground alone ought to be rejected. Further it is submitted that there are several independent claims in the application, which practice is not allowed in India. Further it is submitted, that claims do not have antecedent basis and on this ground alone, ought to be rejected.

Claims inadequate

Claims 1-51 of the application at hand bitterly suffer from lack of adequate description and are liable to be rejected.

(i) The claims of the impugned patent application are drawn to several millions of compounds, obtainable by using the various possible substitutions of (I-1), (I-1-1) and (I-11). However, the bulk of the claims are more broadly directed toward the use of classes of compounds that include dolutegravir and its analogues compounds for HIV integrase inhibition. All of these are mere potential compounds

and only few examples have been tested and certain classes have not been tested at all. Further, the patent application does not particularly identify or disclose the specific compound that works and could be used as a drug.

(ii) The experimental examples 1 and 2 only demonstrate the activity of ZZ series and one compound in C, F and H series, the other series such as the F series and the Y series do not even have one representative sample that is tested and or demonstrated in the specifications. In absence of such data it is submitted that the whole series of compounds ought to be rejected as their utility has not been demonstrated at all.

(iii) There are millions of compounds that are encompassed by the structure of the claim Markush. Claim, however, a mere hand-full of compounds have been synthesized and represented in the application. The claims have not been enabled across its breath and the best mode of performing the invention has not been disclosed. These compounds are not sufficient to cover all possible substitutions of the Markush structure and thereby the Markush of the principal claim is not exemplified. Hence, it is not possible for a person skilled in the art to synthesize the compounds of the impugned patent and ought to be rejected on this ground.

(iv) The intermediates and the processes as disclosed in the specification, does not cover all possible compounds of the impugned specification. Hence it is not possible to synthesize the compounds of the impugned invention, based on the disclosure in prior art.

GROUND VI

VII) **Section 25(1)(h): The patentee has failed to disclose to the Controller the information required under Section 8:**

It is submitted that the Applicant-Respondent has failed to disclose the details of corresponding foreign applications filed and on this ground alone the patent application should be rejected.

The applicant is required to provide all the information regarding the prosecution of the equivalent applications till the grant of the Indian application to the Controller in writing from time to time and also within the prescribed time. Therefore the applicant has failed to comply with the requirements of the section 8 of the act and the opponent demands rejection on this ground also.

PRAYER

In the fact and circumstances of the case the Opponent prays as follows:

i. that Indian Patent Application No. 3865/KOLNP/2007made by **SMITHKLINE BEECHAM CORPORATION,** A United States Corporation , One Franklin Plaza, p.o. box 7929, philadelphia, pa 19101, united states of america. **AND SHIONOGI & CO. LTD.,** a Japanese company, 1-8 doshomachi 3-chome, chuo-ku, osaka-shi, osaka 541-0045. japan., rejected under Section 25(1) of the Patents (Amendment) Act, 2005;

ii. the Opponent may be allowed to file further grounds and documents as evidence if necessary to support their averments;

iii. The Opponent may be granted an opportunity of being heard in the matter before any final orders are passed.

iv. the Opponent may be allowed to make further submissions in case the applicant makes any amendments in claims;

v. any other reliefs considering the facts and circumstances may be granted in favour of the Opponent in the interest of justice.

Dated this 21st day of February, 2013

Rajeshwari H.
[For RAJESHWARI & ASSOCIATES]
AGENT FOR THE OPPONENT

The Controller of Patents
The Patent Office, Kolkata

.quaforest TIFF Junction Evaluation

Annexure-A 29

FORM 2

THE PATENTS ACT, 1970
(39 OF 1970)
&
THE PATENTS RULES, 2003

COMPLETE SPECIFICATION
(See Section 10; Rule 13)

TITLE

POLYCYCLIC CARBAMOYLPYRIDONE DERIVATIVE HAVING HIV INTEGRASE INHIBITORY ACTIVITY

APPLICANT'S

SHIONOGI & CO. LTD.
A JAPANESE COMPANY
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JAPAN

&

SMITHKLINE BEECHAM CORPORATION
A UNITED STATES CORPORATION
of ONE FRANKLIN PLAZA, P.O. BOX 7929,
PHILADELPHIA, PA 19101,
UNITED STATES OF AMERICA

The following specification particularly describes the nature of the invention and the manner in which it is to be performed.

30

SPECIFICATION

Polycyclic Carbamoylpyridone Derivative Having HIV Integrase Inhibitory Activity

[Technical Field]

[0001]

The present invention relates to novel compounds possessing an antiviral activity, in detail polycyclic carbamoylpyridone derivatives possessing an inhibitory activity against HIV integrase and a pharmaceutical composition containing the same, especially an anti-HIV agent.

[Background Art]

[0002]

Among viruses, human immunodeficiency virus (HIV), a kind of retrovirus, is known to cause acquired immunodeficiency syndrome (AIDS). The therapeutic agent for AIDS is mainly selected from a group of reverse transcriptase inhibitors (e g , AZT, 3TC) and protease inhibitors (e.g., Indinavir), but they are proved to be accompanied by side effects such as nephropathy and the emergence of resistant viruses. Thus, the development of anti-HIV agents having the other mechanism of action has been desired.

On the other hand, a combination therapy is reported to be efficient in treatment for AIDS because of the frequent emergence of the resistant mutant. Reverse transcriptase inhibitors and protease inhibitors are clinically used as an anti-HIV agent, however agents having the same mechanism of action often exhibit cross-resistance or only an additional activity. Therefore, anti-HIV agents having the other mechanism of action are desired

Under the circumstances above, an HIV integrase inhibitor has been focused on as an anti-HIV agent having a novel mechanism of action (Ref. Patent Documents 1 and 2) . As an anti-HIV agent having such a mechanism of action, known are carbamoyl-substituted hydroxypyrimidinone derivative (Ref Patent Documents 3 and 4) and carbamoyl-substituted hydroxypyrrolidione derivative (Ref Patent Document 5) Further, a patent application concerning carbamoyl-substituted hydroxypyridone derivative has been filed (Ref. Patent Document 6, Example 8)

Other known carbamoylpyridone derivatives include 5-alkoxypyridine-3-carboxamide derivatives and γ-pyrone-3 carboxamide derivatives, which are a plant growth inhibitor or herbicide (Ref. Patent Documents 7-9).

Other HIV integrase inhibitors include N-containing condensed cyclic compounds

(Ref: Patent Document 10).

[Patent Document 1]WO03/0166275

[Patent Document 2]WO2004/024693

[Patent Document 3]WO03/035076

[Patent Document 4]WO03/035076

[Patent Document 5]WO2004/004657

[Patent Document 6]JP Patent Application 2003-32772

[Patent Document 7]JP Patent Publication 1990-108668

[Patent Document 8]JP Patent Publication 1990-108683

[Patent Document 9]JP Patent Publication 1990-96506

[Patent Document 10]WO2005/016927

[Disclosure of Invention]

[Problem to be Solved by the Invention]

[0003]

The development of a novel integrase inhibitor has been desired.

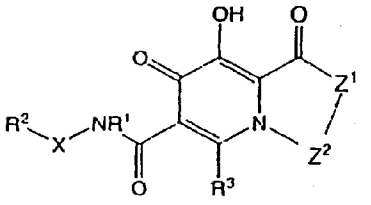
[Means to Solve the Problem]

[0004]

The present inventors have intensively studied to find that a novel polycyclic carbamoylpyridone derivative possesses a potent HIV integrase inhibitory activity

Moreover, the present inventors have discovered that a compound of the present invention and a pharmaceutical composition containing the same are useful as an antiviral agent, an antiretroviral agent, an anti-HIV agent, an anti-HTLV-1 (Human T cell leukemia virus type 1) agent, an anti-FIV (Feline immunodeficiency virus) agent or an anti-SIV (Simian immunodeficiency virus) agent, especially an anti-HIV agent or anti-AIDS agent, to accomplish the present invention shown below.

(1)A compound of the formula:



(1)

(wherein,

Z^1 is NR^4;

R^1 is hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy, optionally substituted amino, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from CO, O, S, SO, SO_2, NR^4 (R^4 is hydrogen or lower alkyl), ·N= and =N·)), O or CH_2;

Z^2 is optionally substituted lower alkylene or optionally substituted lower alkenylene, each may be intervened by a heteroatom group selected from O, S, SO, SO_2, NR^5 (R^5 is hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy or optionally substituted amino, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from CO, O, S, SO, SO_2 NR^5 (R^5 is selected independently from the same substituent group as R^4), ·N= and =N·)), ·N= or =N·

R^1 is hydrogen or lower alkyl;

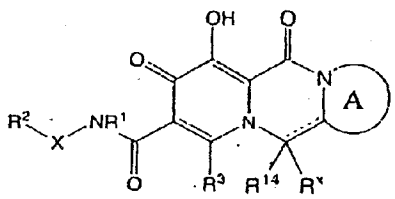
X is a single bond, a heteroatom group selected from O, S, SO, SO_2 and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom;

R^2 is optionally substituted aryl;

R^3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted

lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino;

R^4 and Z^2 part taken together forms a ring, where the compound (I) is represented by the following formula (I-1), or (I-11):



(I-1)

(wherein,

A ring is optionally substituted heterocycle;

R^{14} and R^X are independently hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from O, S, SO, SO_2 NR^6 (R^5 is selected independently from the same substituent group as R^4), -N= and =N-), hydroxy, optionally substituted amino, optionally substituted lower alkyl carbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkyl carbonyl, optionally substituted lower alkoxy carbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted aryloxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkyl carbonyl, optionally substituted heterocycleoxy carbonyl or optionally substituted aminocarbonyl;

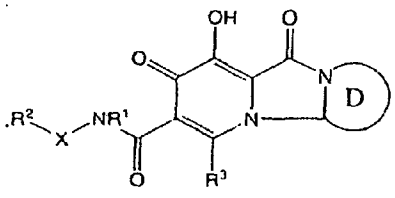
a broken line represents the presence or absence of a bond, provided that when the broken line represents the presence of a bond, R^X is not present;

R^1 is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO_2 and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;

R^2 is optionally substituted aryl;

R^3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino)



(I-11)

(wherein,

D ring is optionally substituted heterocycle;

R^1 is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO_2 and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group,

R^2 is optionally substituted aryl,

R^3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino)), its pharmaceutically acceptable salt, or solvate thereof.

(2) A compound according to the above (1), pharmaceutically acceptable salt, or solvate thereof, wherein R^1 is hydrogen.

(3) A compound according to the above (1), pharmaceutically acceptable salt, or

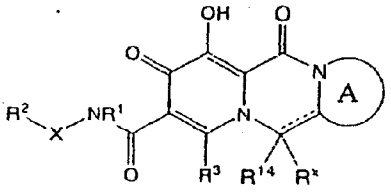
solvate thereof, wherein X is lower alkylene; R^2 is phenyl or phenyl substituted with at least halogen

(4) A compound according to the above (1), pharmaceutically acceptable salt, or solvate thereof, wherein R^4 is hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino

(5) A compound according to the above (1), pharmaceutically acceptable salt, or solvate thereof, wherein R^3 is hydrogen.

(6) A compound according to the above (1), pharmaceutically acceptable salt, or solvate thereof, wherein R^1 is hydrogen or lower alkyl, X is lower alkylene; R^2 is phenyl or phenyl substituted with at least halogen; R^4 is hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino

(7) A compound of the formula



(I-1)

(wherein,

A ring is optionally substituted heterocycle.

R^{14} and R^x are independently hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or

lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from O, S, SO, SO_2 NR^5 (R^5 is selected independently from the same substituent group as R^4), -N= and =N-), hydroxy, optionally substituted amino, optionally substituted lower alkyl carbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkyl carbonyl, optionally substituted lower alkoxy carbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted aryloxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkyl carbonyl, optionally substituted heterocycleoxy carbonyl or optionally substituted aminocarbonyl;

a broken line represents the presence or absence of a bond, provided that when the broken line represents the presence of a bond, R^8 is not present;

R^1 is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO_2 and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;

R^2 is optionally substituted aryl;

R^3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino), its pharmaceutically acceptable salt, or solvate thereof

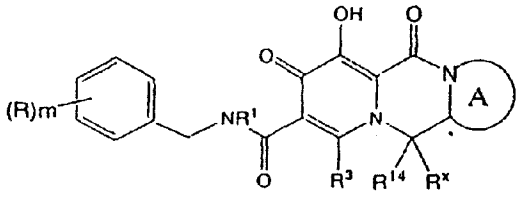
(8) A compound according to the above (7), pharmaceutically acceptable salt, or solvate thereof, wherein R^1 is hydrogen or lower alkyl; X is lower alkylene; R^2 is phenyl or phenyl substituted with at least halogen; R^3 is hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino.

(9) A compound according to the above (7), pharmaceutically acceptable salt, or solvate thereof, wherein a broken line represents the absence of a bond.

(10) A compound according to the above (7), pharmaceutically acceptable salt, or solvate thereof, wherein R^8 is hydrogen; R^{14} is hydrogen or optionally substituted lower alkyl.

(11) A compound according to the above (7), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is an optionally substituted and optionally condensed 5- to 7- membered heterocycle containing 1 to 2 hetero atom(s).

(12) A compound of the formula



(I-1-1)

(wherein,

A ring is an optionally substituted and optionally condensed 5- to 7- membered heterocycle containing 1 to 2 hetero atom(s);

the stereochemistry of an asymmetric carbon represented by * shows R- or S-configuration, or a mixture thereof,

R^{14} and R^X are independently hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened by a heteroatom group selected from O, S, SO, SO_2, NR^5 (R^5 is selected independently from the same substituent group as R^4), -N= and =N-), hydroxy, optionally substituted amino, optionally substituted lower alkyl carbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkyl carbonyl, optionally substituted lower alkoxy carbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkyl carbonyl, optionally substituted

aryloxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkyl carbonyl, optionally substituted heterocycleoxy carbonyl or optionally substituted aminocarbonyl.

R^J is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino), its pharmaceutically acceptable salt, or

R^1 is hydrogen or lower alkyl;

R is independently selected from halogen and Substituent group S1;

Substituent group S1(· optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, or lower alkyl substituted with optionally substituted phosphoric acid residue (wherein the lower alkyl may be intervened with a heteroatom group(s) selected from CO, O, O, S, SO, SO_2, NR^a (R^a is hydrogen or lower alkyl), -N= and =N-), lower alkoxy lower alkyl, amino lower alkyl optionally substituted with mono- or di- lower alkyl, halogenated lower alkyl, lower alkoxy, carbamoyl optionally substituted with mono- or di- lower alkyl, optionally substituted lower alkyl sulfonyl amino, halogenated lower alkoxy, hydroxy lower alkyl)

m is an integer of 0 to 3, its pharmaceutically acceptable salt, or solvate thereof.

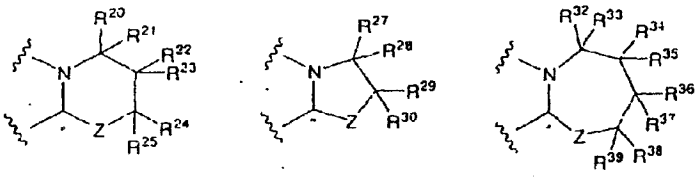
(13) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein R^X and R^{14} are independently hydrogen or optionally substituted lower

(14) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein R^X and R^{14} are hydrogens

(15) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein R^J is hydrogen

(16) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein m is 0, or 1 to 3 and at least one of R is halogen.

(17) A compound according to the above (7) or (12), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is any one of the following:



Z = O or NR^{26} (A-1)

Z = O or NR^{31} (A-2)

Z = O or NR^{40} (A-3)

(wherein, R^{20} to R^{40} are each independently a group selected from Substituent group S2, or any two groups of R^{20} to R^{40}, which bonds to the same carbon atom, taken together with the carbon atom, may form an optionally substituted carbocyle or optionally substituted heterocycle, or each combination of (R^{20} and R^{22}), (R^{24} and R^{24}), (R^{25} and R^{26}), (R^{27} and R^{29}), (R^{30} and R^{31}), (R^{32} and R^{34}), (R^{35} and R^{36}), (R^{37} and R^{38}), and (R^{39}andR^{40}), taken together with the neighboring atom, may form an optionally substituted carbocyle or optionally substituted heterocycle

Substituent group S2: hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocycle, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy, optionally substituted amino, optionally substituted lower alkylcarbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkylcarbonyl, optionally substituted lower alkoxycarbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkylcarbonyl, optionally substituted aryl oxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkylcarbonyl, optionally substituted heterocycleoxycarbonyl,

optionally substituted aminocarbonyl, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened with a heteroatom group(s) selected from CO, O, S, SO, SO_2, NR^5 (R^5 is independently selected from the same Substituent group as R^4), -N= and =N-)

the stereochemistry of an asymmetric carbon represented by * shows R- or S- configuration, or a mixture thereof)

(18) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein R^{20} to R^{40} are each independently hydrogen or substituted lower alkyl, or any two groups of R^{20} to R^{40}, which bonds to the same carbon atom, taken together with the carbon atom, may form an optionally substituted 3- to 7-membered carbocyle or optionally substituted 3- to 7- membered heterocycle, or each combination of (R^{20} and R^{22}), (R^{23} and R^{24}), (R^{25} and R^{26}), (R^{27} and R^{29}), (R^{30} and R^{31}), (R^{32} and R^{34}), (R^{35} and R^{36}), (R^{37} and R^{38}), and (R^{39}andR^{40}), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocyle or optionally substituted 5- to 7- membered heterocycle

(19) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-1); one of R^{20} to R^{26} is optionally substituted lower alkyl and the others are hydrogens.

(20) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-1); one of (R^{20} and R^{22}), (R^{23} and R^{24}), and (R^{25} and R^{26}), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocyle or optionally substituted 5- to 7-membered heterocycle.

(21) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-1), Z=NR^{26}, and R^{25} and R^{26} taken together with the neighboring atom may form an optionally substituted 5- to 7-

membered heterocycle

(22) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-2); one of R^{27} to R^{30} is optionally substituted lower alkyl and the others are hydrogens.

(23) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-2); one of (R^{27} and R^{29}) and (R^{30} and R^{31}), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocyle or optionally substituted 5- to 7- membered heterocycle

(24) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-2); Z=NR^{31}, and R^{30} and R^{31} taken together with the neighboring atom may form an optionally substituted 5- to 7- membered heterocycle

(25) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-3), one of R^{32} to R^{39} is optionally substituted lower alkyl and the others are hydrogens

(26) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-3); one of (R^{32} and R^{34}), (R^{35} and R^{36}), (R^{37} and R^{38}), and (R^{39} and R^{40}), taken together with the neighboring atom, may form an optionally substituted 5- to 7- membered carbocyle or optionally substituted 5- to 7- membered heterocycle.

(27) A compound according to the above (17), pharmaceutically acceptable salt, or solvate thereof, wherein A ring is a ring represented by (A-3); Z=NR^{40}, and R^{39} and R^{40} taken together with the neighboring atom may form an optionally substituted 5- to 7- membered heterocycle

(28) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein R^{A} is hydrogen; R^{14} is hydrogen or optionally substituted lower; R^{3} is hydrogen; m is 1 to 3 and at least one of Rs is halogen; A ring is a ring

described in Claim 17

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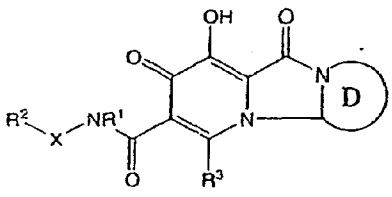
(29) A compound according to the above (12), pharmaceutically acceptable salt, or solvate thereof, wherein R^X is hydrogen; R^{11} is hydrogen; R^3 is hydrogen; m is 0, or 1 to 3 and at least one of Rs is halogen; A ring is a ring described in Claim 17, R^{20} to R^{40} are each independently hydrogen or substituted lower alkyl, or any two groups of R^{20} to R^{40}, which bonds to the same carbon atom, taken together with the carbon atom, may form an optionally substituted 3- to 7- membered carbocyle or optionally substituted 3- to 7- membered heterocycle, or each combination of (R^{20} and R^{22}), (R^{23} and R^{24}), (R^{25} and R^{26}), (R^{27} and R^{29}), (R^{30} and R^{31}), (R^{32} and R^{34}), (R^{35} and R^{36}), (R^{37} and R^{38}), and (R^{39}andR^{40}), taken together with the neighboring carbon atom, may form an optionally substituted 5- to 7- membered carbocyle or optionally substituted 5- to 7- membered heterocycle.

(30) A compound of the formula:



(I-11)

(wherein,

D ring is optionally substituted heterocycle;

R^1 is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO_2 and NH, or lower alkylene or lower alkenylene each may be intervened by the heteroatom group;

R^2 is optionally substituted aryl,

R^3 is hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy or optionally substituted amino), pharmaceutically acceptable salt, or solvate thereof

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(31) A compound selected from the group consisting of:

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(4a*R*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide;

(3a*S*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carboxamide;

(4a*S*,13a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide;

(4a*S*,13a*R*)-*N*-[(4-Fluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3a*S*,13a*S*)-*N*-[(4-Fluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(1*S*)-1-methylpropyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(4-Fluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-3-(1,1-dimethylethyl)-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-3-(1,1-Dimethylethyl)-*N*-[(4-fluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(hydroxymethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(2*S*,3*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(2-methylpropyl) 5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide,

(5a*R*,14a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-*a*]pyrido[1',2':3,4]imidazo[1,2-*d*]pyrazine-9-carboxamide;

(2*S*,3*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(methyloxy)methyl]-5,7-dioxo-2-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-3 (Cyclohexylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide,

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1 methylethyl)-5,7-dioxo 2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(5a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-5a,6a,7,11,13,14a-hexahydro-5*H*-indeno[1',2':4,5][1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-10-carboxamide;

(2*S*,3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(2*S*,3*R*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1-methylethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylthio)ethyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylsulfonyl)ethyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1*H*-indol-3-ylmethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(4*R*,12a*R*)-*N*-[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*R*,12a*R*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-1-(Cyclopropylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-1-(2-furanylmethyl)-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(1,3-thiazol-2-ylmethyl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4a*R*,6a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide;

(4a*R*,6a*R*,14a*S*)-*N*-[(4-Fluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide;

(3*S*,4a*R*,6a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-3-phenyl-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide;

(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-(2-methylpropyl)-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide,

(6aR,7aS,11aS)-N-[(2,4-Difluorophenyl)methyl]-1-hydroxy-2,13-dioxo-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide,

(6aS,7aS,11aS)-N-[(2,4-Difluorophenyl)methyl]-1 hydroxy-2,13-dioxo-2,6a,7,7a,8,9,10,11,11a,13-decahydro-6H-pyrido[1',2':4,5]pyrazino[1,2-a]benzimidazole-3-carboxamide;

(5aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-a]pyrido[1',2'-3,4]imidazo[1,2-d]pyrazine-9-carboxamide;

(4aR,14aR)-N-[(2,4-Difluorophenyl)methyl]-9-hydroxy-8,10-dioxo-2,3,4,4a,5,6,8,10,14,

14a-decahydro-1H-pyrido[1,2-c]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-11-carboxamide,

(4*R*,12a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(3-methylbutyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(3-methylbutyl)-6,8-dioxo-1,2,3,4,6,8,12,12a octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8 dioxo-1-(3-pyridinylmethyl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-1-Cyclopropyl-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8 dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-[2-(methyloxy)ethyl]-

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6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(3aS,5aS,13aS)-N-[(2,4-Difluorophenyl)methyl]-11-hydroxy-5-(2-methylpropyl)-10,12-dioxo-2,3,3a,4,5,5a,6,10,12,13a-decahydro-1H-cyclopenta[e]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide;

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-3-ethyl-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-[2-(4-morpholinyl)ethyl]-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(3aR,5aR,13aS)-N-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,3a,4,5a,6,10,12,13a-decahydrocyclopenta[d]pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazine-9-carboxamide;

(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-methyl-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-[2-(methyloxy)ethyl]-11,

13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2'-4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(4aS,6aS,14aS)-6-[2-(Acetylamino)ethyl]-N-[(2,4-difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2'-4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-3-ethyl-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-3-Butyl-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(4-hydroxyphenyl)methyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(4S,12aS)-1-Cyclobutyl-N-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2'-4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2'-4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

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(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-1,4-bis(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-6-(2-hydroxyethyl)-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(4aS,6aS,14aS)-6-Cyclopropyl-N-[(2,4-difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(4aS,6aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-6-[2-(1-pyrrolidinyl)ethyl]-1,2,3,4,4a,5,6,6a,7,11,13,14a-dodecahydropyrido[1',2':4,5]pyrazino[1,2-a]quinazoline-10-carboxamide;

(4aS,14aS)-N-[(2,4-Difluorophenyl)methyl]-9-hydroxy-8,10-dioxo-2,3,4,4a,5,6,8,10,14,14a-decahydro-1H-pyrido[1,2-c]pyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-11-carboxamide;

(4S,12aS)-N-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-[2-(methyloxy)ethyl]-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide,

(4S,12aS)-1-Cyclobutyl-N-[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2'-4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide;

(4S,12aS)-N-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2'-4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide;

(4S,12aS)-N-[(4-Fluorophenyl)methyl]-7-hydroxy-1,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2'-4,5]pyrazino[1,2-a]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1-(tetrahydro-2*H*-thiopyran-4-yl)-1,2,3,4,6,8,12,12a-octahydropyrido[1',2'-4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-1,4-dimethyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2'-4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2'-4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4*S*,12a*S*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-1,4-bis(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2'-4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

enantiomers thereof; diastereomers thereof; mixtures of enantiomers thereof; mixtures of diastereomers thereof; mixtures of enantiomers and diastereomers thereof; and pharmaceutically acceptable salts thereof.

(32) A compound selected from the group consisting of:

(4a*S*,13a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide;

(4a*S*,13a*R*)-*N*-[(4-Fluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(1*S*)-1-methylpropyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(3*S*,11a*R*)-*N*-[(4-Fluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide;

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxa

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mide;

(4*S*,12a*S*)-1-(Cyclopropylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide;

(4a*R*,6a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide;

(4a*R*,6a*R*,14a*S*)-*N*-[(4-Fluorophenyl)methyl]-12-hydroxy-11,13-dioxo-1,3,4,4a,5,6a,7,11,13,14a-decahydro-2*H* pyrido[1',2' 4,5]pyrazino[1,2-*a*][3,1]benzoxazine-10-carboxamide;

4S,9aR)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4,-difluoro-benylamide;

4R,9aS)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4,-difluoro-benylamide;

2R,9aS)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benylamide;

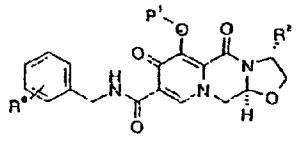
enantiomers thereof; diastereomers thereof, mixtures of enantiomers thereof; mixtures of diastereomers thereof, mixtures of enantiomers and diastereomers thereof; and pharmaceutically acceptable salts thereof

(33) A compound according to the above (31) or (32) wherein the pharmaceutically acceptable salt is a sodium salt

(34) A pharmaceutical composition comprising a compound according to any one of the above (1) to (33), or a pharmaceutically acceptable salt, or solvate thereof.

(35) A pharmaceutical composition according to the above (34), which is an anti-HIV agent.

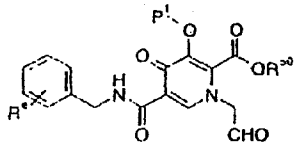
(36) A process for the preparation of a compound of formula (I-20a)



(I-20a)

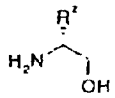
wherein R^e is one or two halogen; R^c is C_{1-8}alkyl, C_{6-14}arylC_{1-8}alkyl, C_{6-14}aryl, or alkoxy; and P^1 is C_{6-14}arylC_{1-8}alkyl;

comprising condensing a compound of the formula



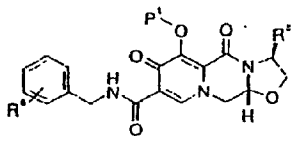
wherein R^e is one or two halogen; R^{60} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl;

with a compound of the formula



wherein R^z is C_{1-}alkyl, C_{6-14}arylC_{1-}alkyl, C_{6-14}aryl, or alkoxy;
to form a compound of formula (I-20a)

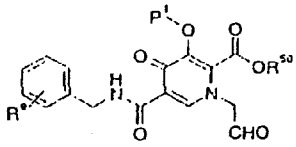
(37) A process for the preparation of a compound of formula (I-20b)



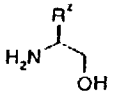
(I-20b)

wherein R^e is one or two halogen; R^z is C_{1-}alkyl, C_{6-14}arylC_{1-}alkyl, C_{6-14}aryl, or alkoxy; and P^1 is C_{6-14}arylC_{1-}alkyl;

comprising condensing a compound of the formula

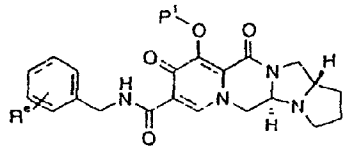


wherein R^e is one or two halogen; R^{50} is C_{1-}alkyl; and P^1 is C_{6-14}arylC_{1-}alkyl,
with a compound of the formula



wherein R^z is C_{1-}alkyl, C_{6-14}arylC_{1-}alkyl, C_{6-14}aryl, or alkoxy,
to form a compound of formula (I-20b).

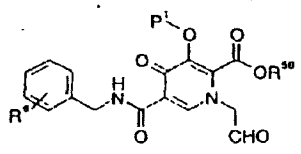
(38) A process for the preparation of a compound of formula (I-21a)



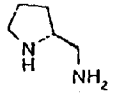
(I-21a)

wherein R^e is one or two halogen; and P^1 is C_{6-14}arylC_{1-4}alkyl;

comprising condensing a compound of the formula

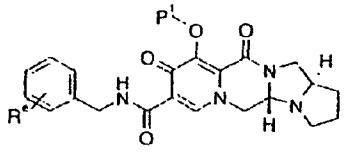


wherein R^e is one or two halogen; R^{50} is C_{1-4}alkyl; and P^1 is C_{6-14}arylC_{1-4}alkyl, with a compound of the formula



to form a compound of formula (I-21a).

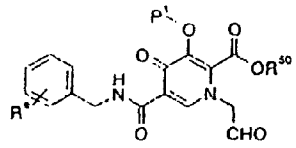
(39) A process for the preparation of a compound of formula (I-21b)



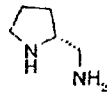
(I-21b)

wherein R^e is one or two halogen; and P^1 is C_{6-14}arylC_{1-4}alkyl;

comprising condensing a compound of the formula

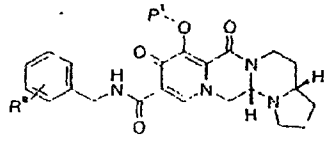


wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl; with a compound of the formula



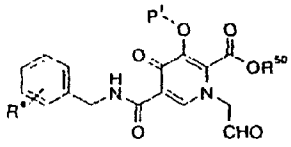
to form a compound of formula (I-21b).

(40) A process for the preparation of a compound of formula (I-22a)

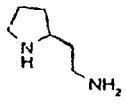


(I-22a)

wherein R^e is one or two halogen; and P^1 is C_{6-14}arylC_{1-8}alkyl; comprising condensing a compound of the formula

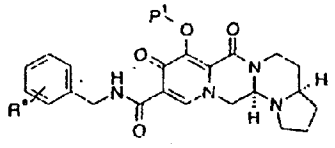


wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl; with a compound of the formula



to form a compound of formula (I-22a).

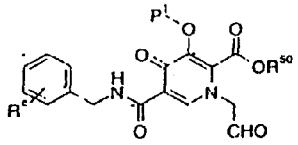
(41) A process for the preparation of a compound of formula (I-22b)



(I-22b)

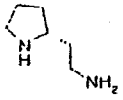
wherein R^e is one or two halogen; and P^1 is C_{6-14}arylC$_{1-8}$alkyl;

comprising condensing a compound of the formula



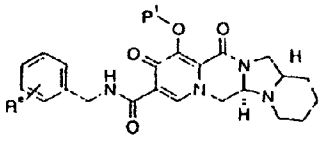
wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC$_{1-8}$alkyl,

with a compound of the formula



to form a compound of formula (I-22b).

(42) A process for the preparation of a compound of formula (I-23a)

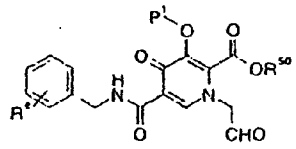


(I-23a)

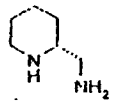
wherein R^e is one or two halogen; and P^1 is C_{6-14}arylC$_{1-8}$alkyl;

61

comprising condensing a compound of the formula

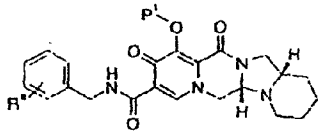


wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl, with a compound of the formula



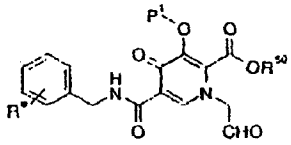
to form a compound of formula (I-23a).

(43) A process for the preparation of a compound of formula (I-23b)

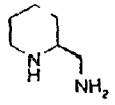


(I-23b)

wherein R^e is one or two halogen, and P^1 is C_{6-14}arylC_{1-8}alkyl; comprising condensing a compound of the formula

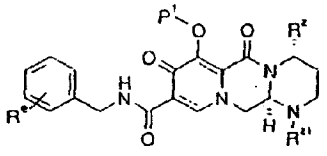


wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl, with a compound of the formula



to form a compound of formula (I-23b)

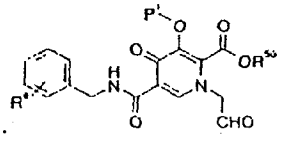
(44) A process for the preparation of a compound of formula (I-24a)



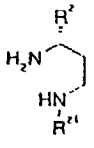
(I-24a)

wherein R^e is one or two halogen, R^z is C_{1-8}alkyl; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with –C(O)C_{1-8}alkyl or C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl.

comprising condensing a compound of the formula



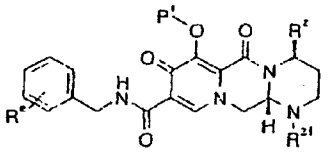
wherein R^e is one or two halogen; and R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl; with a compound of the formula



wherein R^z is C_{1-8}alkyl. R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with –C(O)C_{1-8}alkyl or C_{1-8}alkyl;

to form a compound of the formula (I·24a)

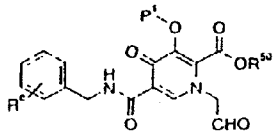
(45) A process for the preparation of a compound of formula (I·24b)



(I·24b)

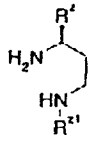
wherein R^e is one or two halogen; R^z is C_{1-8}alkyl; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl; or amino, wherein said amino may be optionally substituted with –C(O)C_{1-8}alkyl or C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl;

comprising condensing a compound of the formula



wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl;

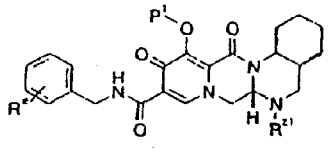
with a compound of the formula



wherein R^z is C_{1-8}alkyl; and R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with –C(O)C_{1-8}alkyl or C_{1-8}alkyl;

to form a compound of the formula (I·24b).

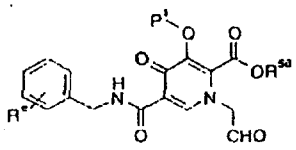
(46) A process for the preparation of a racemic compound of formula (I-25)



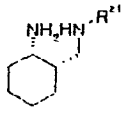
(I-25)

wherein R^e is one or two halogen, R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with –C(O)C_{1-8}alkyl or C_{1-8}alkyl; and P^1 is is C_{6-14}arylC_{1-8}alkyl;

comprising condensing a compound of the formula



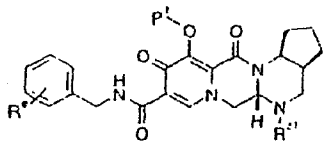
wherein R^e is one or two halogen; and R^{30} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl; with a racemic compound of the formula



wherein R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with –C(O)C_{1-8}alkyl or C_{1-8}alkyl,

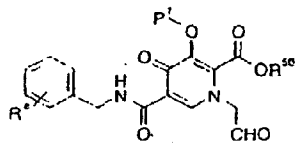
to form a racemic compound of the formula (I-25).

(47) A process for the preparation of a racemic compound of formula (I-26)

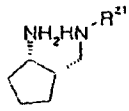


(I-26)

wherein R^e is one or two halogen; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with –C(O)C_{1-8}alkyl or C_{1-8}alkyl, and P^1 is C_{6-14}arylC_{1-8}alkyl;
comprising condensing a compound of the formula



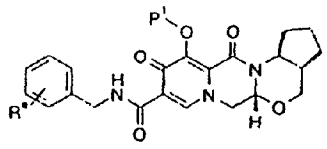
wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl;
with a racemic compound of the formula



wherein R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with –C(O)C_{1-8}alkyl or C_{1-8}alkyl;

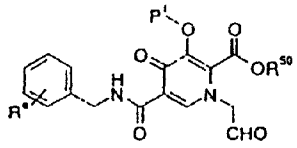
to form a racemic compound of formula (I-26)

(48) A process for the preparation of a racemic compound of formula (I-27)

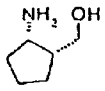


(I-27)

wherein R^e is halogen; and P^1 is C_{6-14}arylC_{1-8}alkyl; comprising condensing a compound of the formula



wherein R^e is one or two halogen; R^{50} is C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl; with a racemic compound of the formula



to form a racemic compound of formula (I-27).

(49). A compound of formula (I-20a) described in above (36) formula (I-20b) described in above (37), formula (I-21a) described in above (38), formula (I-21b) described in above (39), formula (I-22a) described in above (40), formula (I-22b) described in above (41), formula (I-23a) described in above (42), formula (I-23b) described in above (43), formula (I-24a) described in above (44), formula (I-24b) described in above (45), formula (I-25) described in above (46), formula (I-26) described in above (47), or formula (I-27) described in above (48), or a pharmaceutically acceptable salt thereof.

(50) A compound of formula (I-20a) described in above (36) formula (I-20b) described in above (37), formula (I-21a) described in above (38), formula (I-21b) described in above (39), formula (I-22a) described in above (40), formula (I-22b) described in above (41), formula (I-23a) described in above (42), formula (I-23b)

described in above (43), formula (I-24a) described in above (44), formula (I-24b) described in above (45), formula (I-25) described in above (46), formula (I-26) described in above (47), or formula (I-27) described in above (48), or a pharmaceutically acceptable salt thereof, wherein each P^1 is hydrogen.

The present invention further provides a pharmaceutical composition containing any of the compounds shown above, a pharmaceutically acceptable salt or a solvate thereof, especially an anti-HIV agent

[Effect of the Invention]

[0005]

The present invention compounds possess an integrase inhibitory activity and/or a cell-growth inhibitory activity against virus, especially HIV. Accordingly, they are useful for the prevention or treatment of various diseases mediated by integrase or virus infection diseases (e.g., AIDS) The present invention further provides a process for preparing a diastereomer, a mixture thereof, or racemate.

[Preferred Embodiment of the Invention]

[0006]

The terms used herein are explained below Each term, alone or in combination with another tem, means as follows

"Lower alkylene" means a straight or branched C1 to C6 alkylene such as methylene, ethylene, trimethylene, n-propylene, tetramethylene, ethylethylene, pentamethylene, or hexamethylene, preferably C1 to C4 straight alkylene such as methylene, ethylene, trimethylene, and tetramethylene, more preferably methylene or ethylene.

"Lower alkenylene" means a straight or branched C2 to C6 alkenylene, which consists of the above "Lower alkylene" having one or more double bonds, such as vinylene, propylene, or butenylene, preferably a straight C2 to C3 alkenylene such as vinylene or propylene.

"Lower alkyl" means a straight or branched C1 to C10 alkyl such as methyl, ethyl, n-propyl, i-propyl, t-butyl, isobutyl, sec-butyl, n-pentyl, and n-hexyl, and preferred is C1 to C3 alkyl, more preferred is methyl, ethyl or n-propyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, n-hexyl, isohexyl, n-heptyl, n-octyl, n-nonyl, and n-desyl, preferably C1 to C6 lower alkyl, more preferably C1 to C4 lower alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, n-hexyl, and isohexyl

When lower alkyl is intervened with "-N=" or "=N-", the lower alkyl may have a double bond to form $-CH_2-N=CH_2$, $CH=N-CH_3$ etc.

"Alkenyl" means a straight or branched C2 to C8 alkenyl, which consists of the above "alkyl" having one or more double bonds, such as vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1,3-butadienyl, and 3-methyl-2 butenyl, preferably C2 to C6 alkenyl, and more preferably C2 to C4 alkenyl.

"Lower alkenyloxy" means oxy attached to the above lower alkenyl, such as vinyloxy, 1-propenyloxy, 2-propenyloxy, 1-butenyloxy, 2-butenyloxy, 3-butenyloxy, 1,3-butadienyloxy, and 3-methyl-2-butenyloxy.

"Cycloalkyl" means C3 to C8 cyclic saturated hydrocarbon, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl, and cyclooctyl, preferably C3 to C6 cycloalkyl.

"Cycloalkyl lower alkyl" means lower alkyl substituted with the above cycloalkyl, such as cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, and cyclohexylethyl, and preferably C3 to C6 cycloalkyl lower alkyl.

"Aryl" means monocyclic aromatic hydrocarbon (e.g., phenyl) and polycyclic hydrocarbon (e.g., 1-naphthyl,2- naphthyl, 1-anthryl, 2-anthryl, 9-anthryl, 1-phenanthryl, 2-phenanthryl, 3-phenanthryl, 4-phenanthryl, 9-phenanthryl), preferably phenyl or naphthyl (e.g., 1-napthyl, 2-naphthyl).

"Aralkyl" or "aryl lower alkyl" means the above lower alkyl substituted with 1 to 3 of the above aryl, such as benzyl, diphenylmethyl, triphenylmethyl, phenethyl, 1-napthylmethyl, 2- napthylmethyl, preferably benzyl

"Aryloxy" means oxy attached to the above aryl, such as 1-naphthyloxy, 2-naphthyloxy, 1-anthryloxy, 2-anthryloxy, 9-anthryloxy, 1-phenanthryloxy, 2-phenanthryloxy, 3-phenanthryloxy, 4-phenanthryloxy, and 9-phenanthryloxy, preferably phenyloxy or naphthyloxy (e.g., 1- napthyloxy, 2-naphthyloxy)

"Heterocyclic group" means "heteroring" or "heteroaryl".

"Heteroring" means a non-aromatic ring which has at least one of N, O and/or S in the ring and may be bonded at any substitutable position, preferably 5- to 7-membered ring, such as 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1-imidazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, 1-pyrazolinyl, 3-pyrazolinyl, 4-pyrazolinyl, 1-pyrazolidinyl, 3-pyrazolidinyl, 4-pyrazolidinyl, piperidino, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-piperadinyl, 2-piperadinyl, 2-morpholinyl, 3-morpholinyl, morpholino, and tetrahydropyranyl. The non-aromatic ring is a

saturated or unsaturated ring

"Heteroaryl" means monocyclic aromatic hetero-type ring or condensed aromatic hetero-type ring.

"Monocyclic aromatic hetero-type ring" means a 5- to 8- membered aromatic ring, which contains 1 to 4 of O, S, P and/or N and may be bonded at any substitutable position.

"Condensed aromatic hetero type ring" means a group wherein an aromatic ring containing 1 to 4 of O, S, P and/or N is condensed with 1 to 4 of 5- to 8-membered aromatic ring(s) or the other 5- to 8-membered aromatic heteroring(s)

Examples of "heteroaryl" include furyl (e.g., 2-furyl, 3-furyl), thienyl (e.g., 2-thienyl, 3-thienyl), pyrrolyl (e.g., 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), imidazolyl (e.g., 1-imidazolyl, 2-imidazolyl, 4-imidazolyl), pyrazolyl (e.g., 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), triazolyl (e.g., 1,2,4-triazole-1-yl, 1,2,4-triazole-3-yl, 1,2,4-triazole-4-yl), tetrazolyl (e.g., 1-tetrazolyl, 2-tetrazolyl, 5-tetrazolyl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), thiadiazolyl, isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), pyridil(e.g., 2-pyridil, 3-pyridil, 4-pyridil), pyridazinyl (e.g., 3-pyridazinyl, 4-pyridazinyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), furazanyl (e.g., 3-furazanyl), pyrazinyl (e.g., 2-pyrazinyl), oxadiazolyl (e.g., 1,3,4-oxadiazole-2-yl), benzofuryl (e.g., 2-benzo[b]furyl, 3-benzo[b]furyl, 4-benzo[b]furyl, 5-benzo[b]furyl, 6-benzo[b]furyl, 7-benzo[b]furyl), benzothienyl(e.g., 2-benzo[b]thienyl, 3-benzo[b]thienyl, 4-benzo[b]thienyl, 5-benzo[b]thienyl, 6-benzo[b]thienyl, 7-benzo[b]thienyl), benzoimidazolyl (e.g., 1-benzoimidazolyl, 2-benzoimidazolyl, 4-benzoimidazolyl, 5-benzoimidazolyl), dibenzofuryl, benzooxazolyl, quinoxalinyl (e.g., 2-quinoxalinyl, 5-quinoxalinyl, 6-quinoxalinyl), cinnolinyl (e.g., 3-cinnolinyl, 4-cinnolinyl, 5-cinnolinyl, 6-cinnolinyl, 7-cinnolinyl, 8-cinnolinyl), quinazolinyl (e.g., 2-quinazolinyl, 4-quinazolinyl, 5-quinazolinyl, 6-quinazolinyl, 7-quinazolinyl, 8-quinazolinyl), quinolyl(e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), phthalazinyl (e.g., 1-phthalazinyl, 5-phthalazinyl, 6-phthalazinyl), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), purinyl, pteridinyl (e.g., 2-pteridinyl, 4-pteridinyl, 6-pteridinyl, 7-pteridinyl), carbazolyl, phenanthridinyl, acridinyl (e.g., 1-acridinyl, 2-acridinyl, 3-acridinyl, 4-acridinyl, 9-acridinyl), indolyl (e.g., 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), isoindolyl, phenandinyl (e.g., 1-phenandinyl,

2- phenandinyl) or phenothiadinyl (e.g., 1- phenothiadinyl, 2-phenothiadinyl, 3-phenothiadinyl, 4-phenothiadinyl).

"Heterocycle" means a cycle which can be lead to the above heterocyclic group.

"Heterocyclic group lower alkyl" or "Heterocycle lower alkyl" means lower alkyl substituted with the above heterocyclic group.

"Heterocyclic group oxy" or "Heterocycle oxy" means an oxy attached to the above heterocyclic group

"Heterocyclic group carbonyl" or "Heterocyclecarbonyl" means a carbonyl attached to the above heterocyclic group

"Lower alkoxy" or "alkoxy" means an oxy attached to the above lower alkyl, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy.

"Lower alkylcarbonyl", "cycloalkylcarbonyl", "cycloalkyl lower alkylcarbonyl", "lower alkoxycarbonyl", "arylcarbonyl", "aryl lower alkylcarbonyl", "aryloxycarbonyl", "heterocyclecarbonyl", "heterocycle lower alkylcarbonyl", and "heterocycle oxycarbonyl", each means a carbonyl attached to the above "lower alkyl", "cycloalkyl", "cycloalkyl lower alkyl", "lower alkoxy", "aryl", "aryl-lower alkyl", "aryloxy", "heterocycle", "heterocycle lower alkyl", and "heterocycleoxy", respectively

[0007]

When a substituent(s) is/are present on "optionally substituted lower alkyl", "optionally substituted cycloalkyl", "optionally substituted cycloalkyl lower alkyl", "optionally substituted lower alkenyl", "optionally substituted lower alkoxy", "optionally substituted aryl", "optionally substituted aryl lower alkyl", "optionally substituted aryloxy", "optionally substituted aryloxy lower alkyl", "optionally substituted heterocyle, "optionally substituted heterocyclic group", "optionally substituted heterocycle lower alkyl", "optionally substituted heterocycleoxy", "optionally substituted lower alkenyloxy", "optionally substituted lower alkylcarbonyl", "optionally substituted cycloalkylcarbonyl", "optionally substituted cycloalkyl lower alkylcarbonyl", "optionally substituted lower alkoxycarbonyl", "optionally substituted arylcarbonyl", "optionally substituted aryl lower alkylcarbonyl", "optionally substituted aryloxycarbonyl", "optionally substituted heterocyclecarbonyl", "optionally substituted heterocycle lower alkylcarbonyl", "optionally substituted heterocycleoxycarbonyl", "optionally substituted lower alkylene", "optionally substituted lower alkenylene", "optionally substituted phosphoric acid residue", "optionally substituted carbocycle" or "optionally

substituted heterocycle", each may be substituted with the same or different, 1 to 4 group(s) selected from Substituent group B at any position

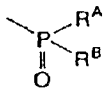
Examples of Substituent group B include hydroxy, carboxy, halogen (F,Cl,Br,I), halo lower alkyl (e.g., CF_3,CH_2CF_3, CH_2CCl_3), halo lower alkoxy (e g , OCF_3, OCH_2CF_3, OCH_2CCl_3), lower alkyl (e.g , methyl, ehtyl, isopropyl, tert-butyl), lower alkenyl (e g , vinyl), lower alkynyl (e g , ethynyl), cycloalkyl (e g , cyclopropyl), cycloalkenyl (e g , cyclopropenyl), lower alkoxy (e.g , methoxy, ethoxy, propoxy, butoxy), lower alkenyloxy (e.g., vinyloxy, allyloxy), lower alkoxycarbonyl (e.g , methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl), nitro, nitroso, optionally substituted amino (e g., alkylamino (e.g., methylamino, ethylamino, dimethylamino), acylamino (e.g., acetylamino, benzoylamino), aralkylamino (e.g., benzylamino, trithylamino), hydroxyamino), azido, aryl (e g., phenyl), aralkyl (e.g., benzyl), cyano, isocyano, isocyanate, thiocyanate, isothiocyanate, mercapt, alkylthio (e g , methylthio), alkylsulfonyl (e g., methansulfonyl, ethansulfonyl), optionally substituted alkylsulfonylamino (e.g , methanesulfonylamino, ethansulfonylamino, N-methylsulfonyl-N'-methylamino), optionally substituted carbamoyl (e g , alkylcarbamoyl (e g , methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl)), sulfamoyl, acyl (e.g., formyl, acetyl), formyloxy, haloformyl, oxal, thioformyl, thiocarboxy, dithiocarboxy, thiocarbamoyl, sulfino, sulfo, sulfoamino, hydrazino, azido, ureido, amizino, quanidino, phthalimide, oxo, phospheric acid residue, lower alkyl which is substituted with a phosphoric acid residue and may be intervened with a heteroatom group(s), aryl substituted with a phosphoric acid residue, aralkyl substituted with a phosphoric acid residue, hydroxyl lower alkyl, preferably hydroxy, carboxy, halogen(F,Cl,Br,I), halo lower alkyl (e.g., CF_3,CH_2CF_3, CH_2CCl_3), halo lower alkoxy (e g , OCF_3, OCH_2CF_3, OCH_2CCl_3), lower alkyl (e g , methyl, ethyl, isopropyl, tert-butyl), lower alkoxy (e g , methoxy, ethoxy, propoxy, butoxy), optionally substituted amino (e.g , alkylamino (e g , methylamino, ethylamino, dimethylamino), oxo, or phosphoric acid residue.

Examples of a substituent of "optionally substituted amino" or "optionally substituted carbamoyl" include mono- or di- lower alkyl, lower alkylcarbonyl, lower alkylsulfonyl, optionally substituted lower alkyl (e g., methyl, ethyl, isopropyl, benzyl, carbamoylalkyl (e.g., carbamoylmethyl), mono or di- lower alkylcarbamoyl lower alkyl (e.g., dimethylcarbamoylethyl), hydroxyl lower alkyl, heterocycle lower alkyl (e.g , morpholinoethyl, tetrahydropyranylethyl), alkoxycarbonyl lower alkyl (e.g., ethoxycarbonylmethyl, ethoxycarbonylethyl), mono- or di- lower alkylamino lower alkyl (e g , dimethylaminoethyl)), lower alkoxy lower alkyl (e g , methoxyethyl,

ethoxymethyl, ethoxyethyl, isopropoxyethyl), acyl (e.g., formyl, optionally substituted lower alkylcarbonyl (e.g., acetyl, propionyl, butylyl, isobutylyl, valeryl, isovaleryl, pivaroyl, hexanoyl, octanoyl, methoxyethylcarbonyl, 2,2,2-trifluoroethylcarbonyl, ethoxycarbonylmethylcarbonyl), lower alkoxy lower alkylcarbonyl (e.g., methoxyethylcarbonyl), lower alkylcarbamoyl lower alkylcarbonyl (e.g., methylcarbamoylehtylcarbonyl), alkoxycarbonylacetyl), optionally substituted arylcarbonyl (e.g., benzoyl, toloyl), optionally substituted aralkyl (e.g., benzyl, 4-fluorobenzyl), hydroxy, optionally substituted lower alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl, isopropylsulfonyl, 2,2,2-trifluoroethanesulfonyl, benzylsulfonyl, methoxyethylsulfonyl), lower alkyl, or arylsulfonyl optionally substituted with halogen (e.g., benzenesulfonyl, toluenesulfonyl, 4-fluorobenzenesulfonyl, fluorobenzenesulfonyl), cycloalkyl (e.g., cyclopropyl), aryl optionally substituted with lower alkyl (e.g., phenyl, trithyl), lower alkylaminosulfonyl (e.g., methylaminosulfonyl, dimethylaminosulfonyl), lower alkylaminocarbonyl (e.g., dimethylaminocarbonyl), lower alkoxycarbonyl (e.g., ethoxycarbonyl), cycloalkylcarbonyl (e.g., cyclopropylcarbonyl, cyclohexylcarbonyl), optionally substituted sulfamoyl (e.g., sulfamoyl, methylsulfamoyl, dimethylsulfamoyl), lower alkylcarbonylamino (e.g., methylcarbonylamino), heterocycle (e.g., morpholino, tetrahydropyranyl), optionally substituted amino (e.g., mono- or di-alkylamino (e.g., dimethylamino), formylamino).

As to amino of "optionally substituted amino", "optionally substituted carbamoyl", or "optionally substituted carbamoylcarbonyl", two substituents on the amino together with the neighboring N atom may form an N-containing heterocycle which optionally contains S and/or O in the ring (preferably 5- to 7- membered ring or saturated ring) and is optionally substituted with oxo or hydroxy. The optional S atom in the ring may be substituted with oxo. The N-containing heterocycle is preferably a 5- or 6-membered ring such as piperadinyl, piperidino, morpholino, pyrrolidino, 2-oxopiperidino, 2-oxopyrrolidino, 4-hydroxymorpholino.

"Phosphoric acid residue" means a group shown of the formula: $-PO(OH)_2$. "Optionally substituted phosphoric acid residue" means a phosphoric acid residue wherein the OH part and/or a hydrogen of the OH is optionally substituted with a phosphoric acid residue, preferably shown by the formula

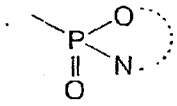


(P-1)

(wherein, R^A and R^B each is independently OR^C or NR^DR^E (wherein R^C, R^D and R^E are each independently hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclic group, or R^D and R^E taken together with the neighboring N atom may form an optionally substituted heterocycle (preferably 5- to 6- membered ring)) or R^A and R^B taken together with the neighboring P atom may form an optionally substituted heterocycle (preferably 5- to 6- membered ring)).

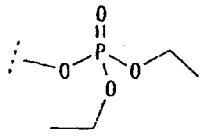
Preferably, R^A and R^B are both OR^C, or one of them is OR^C and the other is NR^DR^E. R^C, R^D and R^E each is preferably, independently, lower alkyl (e.g., methyl, ethyl).

The optionally substituted heterocycle formed by R^A and R^B taken together with the neighboring P atom may be the following structure:



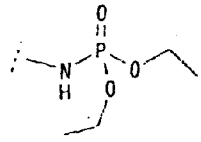
(wherein, the broken line means a part of the ring)

Hydroxy substituted with optionally substituted phosphoric acid residue is preferably hydroxy substituted with a phosphoric acid residue substituted with di lower alkyls, and more preferably a group of the formula:



Amino substituted with optionally substituted phosphoric acid residue is preferably amino substituted with a phosphoric acid residue substituted with di lower

alkyls, and more preferably a group of the formula



[0008]

(More preferable embodiments)

R^1 is hydrogen or lower alkyl, preferably hydrogen

X is a single bond, a heteroatom group selected from O, S, SO, SO_2 and NH (hereafter also referred to as "M"), or lower alkylene or lower alkenylene each may be intervened by the heteroatom The term of "intervened by" means the following cases.

1) The heteroatom group is present between carbon atoms which constitutes the alkylene or alkenylene

2) The heteroatom group is attached to the N atom of the carbamoyl group neighboring to X

3) The heteroatom group is attached to R^2 neighboring to X

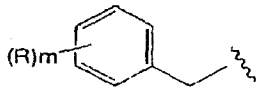
The heteroatom group (M) may be the same or different, and one or more atoms Examples of that lower alkylene is intervened by a heteroatom group include $\cdot M\cdot CH_2\cdot$, $\cdot CH_2\cdot M\cdot CH_2\cdot$, $\cdot CH_2\cdot M\cdot$, and $\cdot CH_2\cdot M\cdot M\cdot CH_2\cdot$

X is preferably a spacer consisting 1 to 3 joined atoms X is more preferably lower alkylene or lower alkenylene each may be intervened by a heteroatom group, or O. X is most preferably C1 to C3 alkylene, C2 to C3 alkenylene, or O. Especially preferred is methylene or O.

R^2 is optionally substituted aryl, preferably phenyl. A substituent on the aryl is the same or different, 1 to 3, preferably 1 to 2 substituent(s), including preferably halogen, hydroxy, amino, lower alkylamino, cyano, carboxy, formyl, oxo, lower alkyl, lower alkoxy, lower alkylthio, carbamoyl, and lower alkylcarbamoyl, and Substituent group SIC optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substitutedphosphoric acid residue, hydroxyl substituted with optionally substitutedphosphoric acid residue, amino substituted with optionally

substitutedphosphoric acid residue, lower alkyl substituted with optionally substitutedphosphoric acid residue (said lower alkyl may be intervened with a hetero atom group(s) selected from O, S, SO, SO_2, NR^5 (R^5 is independently selected from the same substituent group for R^1), -N= and =N-), lower alkoxy lower alkyl, amino lower alkyl optionally substituted with mono- or di-lower alkyl, halogenated lower alkyl, lower alkoxy, carbamoyl optionally substituted with mono- or di-lower alkyl, optionally substituted lower alkylsulfonylamino, halogenated lower alkoxy, hydroxyl lower alkyl), more preferably halogen,hydroxy,amino,cyano,lower alkyl, lower alkoxy or Substituent group S1, and most preferred is halogen (e.g., F) and/or a group selected from Substituent group S1. A substituent on the aryl is preferably at the 4-position. R^2 is more preferably phenyl or phenyl substituted with at least halogen, and most preferably 4-halogenophenyl (e.g., 4-F-phenyl) In another embodiment, R^2 is preferably phenyl optionally substituted with 1 to 3 R(s) mentioned below.

In all compounds of the present invention, the structure of "-X-R^2" is preferably shown by the formula below:



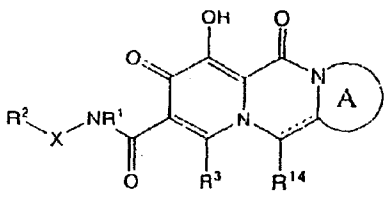
R each is independently a group selected from halogen and Substituent group S1

Substituent group S1 optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxyl substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, lower alkyl substituted with optionally substituted phosphoric acid residue (said lower alkyl may be intervened by a heteroatom group(s) selected from CO, O, S, SO, SO_2, NR^a (R^a is hydrogen or lower alkyl), -N= and =N-), lower alkoxy lower alkyl, optionally substituted amino lower alkyl (the substituent: mono- or di- lower alkyl, lower alkylcarbonyl, or lower alkylsulfonyl), halogenated lower alkyl, lower alkoxy, optionally substituted carbamoyl (the substituent: mono- or di- lower alkyl, lower alkylcarbonyl, or lower alkylsulfonyl), optionally substituted lower alkylsulfonylamino, halogenated lower alkoxy, and hydroxyl lower alkyl

m is an integer of 0 to 3, preferably 0 or 1 to 2 when m is 1, R is preferably halogen. When m is 2, R is more preferably the same or different group selected from halogen, lower alkyl, lower alkoxy, lower alkoxylower alkyl, halogenated lower alkyl, halogenated lower alkoxy, lower alkylsulfonylamino, carbamoyl, and lower alkylcarbamoyl. More preferably, R is two halogens, or halogen and another group R preferably locates at the 4-position and optional another position of the benzene ring.

R^4 can be a various substituent which does not bring a negative effect to the pharmacological activity, including hydrogen, halogen, hydroxy, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycleoxy, and optionally substituted amino Examples of substituent of "optionally substituted" include halogen, hydroxy, amino, lower alkylamino, cyano, carboxy, formyl, oxo, lower alkyl, lower alkoxy, lower alkylthio, carbamoyl, lower alkylcarbamoyl, aryl, heterocyclic group, lower alkylcarbonyl, lower alkylcarbonyloxy, lower alkoxycarbonyl, halogenated lower alkyl, halogenated lower alkoxy, and preferably halogen, hydroxy, amino, lower alkylamino, lower alkyl, and lower alkoxy R^4 is more preferably hydrogen, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy or optionally substituted amino, and most preferably hydrogen or lower alkyl (e.g., methyl), esp. hydrogen.

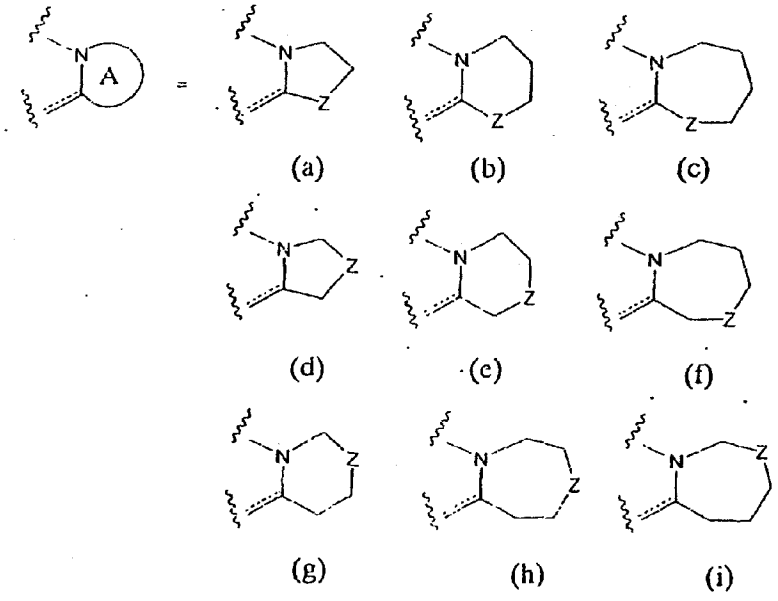
Z^2 shows C, CH, optionally substituted lower alkylene, lower alkenylene etc., and Z^2 and R^1 of Z^1 taken together form a ring, whereby compound (I) shows a tricyclic compound (I-1) or (I-11) shown below, or its derivative, tetracyclic compound.



(I-1)

A ring is optionally substituted heterocycle containing at least an N atom. The

heterocycle is a 5- to 7-membered ring which contains preferably 1 to 3, more preferably 2 to 3 atoms of O, S and/or N The heterocycle is preferably selected from the above heterocycle The arc optionally contains 1 to 2 heteroatom(s) at any possible position. One of preferable embodiments of A ring is an optionally substituted ring shown below.



(Z is CH_2, O, S, SO, SO_2 or NR^{19})

A ring is preferably a ring of (a), (b), or (c)

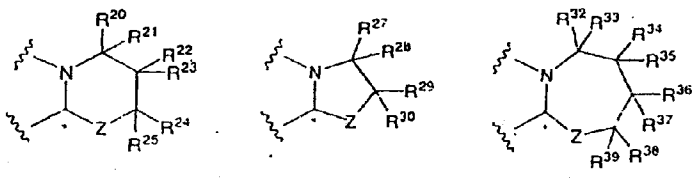
Z is preferably O or NR^{19}.

When Z is NR^{19}, examples of R^{19} include 1)hydrogen, 2)optionally substituted lower alkyl (the substituent is e.g., amino optionally substituted with mono- or di-lower alkyl, cycloalkyl, hydroxy, optionally substituted heterocyclic group (preferably 5- to 7-membered ring, e.g., furyl, thienyl, thiazolyl, pyridil, morpholino, imidazole; examples of the substituent include lower alkyl, halogen); optionally substituted heterocyclecarbonyl (the heterocycle is preferably 5- to 7-membered ring, e.g., morpholinocarbonyl), optionally substituted phenyl (the substituent is e g., lower alkyl, amino, lower alkylamino, hydroxy, halogen, halogenated lower alkyl, lower alkoxy, halogenated lower alkoxy, lower alkylthio, lower alkylsulfonyl), acetylamino, carbamoyl, carbamoyl substituted with mono- or di- lower alkyl, lower

alkylsulfonylamino, lower alkoxy, carbonyl, halogen, thiol, lower alkylthio), 3) lower alkenyl, 4) acyl (e.g., lower alkylcarbonyl), 5) lower alkylsulfonyl. R^{15} may be selected from Substituent group S2 shown below.

The other substituent on A ring may be selected from R^{15} to R^{18} or Substituent group S2, preferably lower alkyl. Substituents on A ring may form a condensed ring or a spiro ring as mentioned below, whereby compound (I) includes a tetracyclic compound.

A ring is more preferably any of the following rings:



Z = O or NR^{26} (A-1) Z = O or NR^{31} (A-2) Z = O or NR^{40} (A-3)

(wherein, R^{20} to R^{40} are each independently a group selected from Substituent group S2, or any two groups of R^{20} to R^{40}, which bonds to the same carbon atom, taken together with the carbon atom, may form a spiro ring, i.e., an optionally substituted carbocyle or optionally substituted heterocycle, or each combination of (R^{20} and R^{22}), (R^{23} and R^{24}), (R^{25} and R^{26}), (R^{27} and R^{29}), (R^{30} and R^{31}), (R^{32} and R^{34}), (R^{35} and R^{36}), (R^{37} and R^{38}), and (R^{39} and R^{40}), taken together with the neighboring atom, may form an optionally substituted carbocyle or optionally substituted heterocycle.

Substitution group S2: hydrogen, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocycle, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy, optionally substituted amino, optionally substituted lower alkylcarbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkylcarbonyl,

optionally substituted lower alkoxycarbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkylcarbonyl, optionally substituted aryl oxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkylcarbonyl, optionally substituted heterocycleoxycarbonyl, optionally substituted aminocarbonyl, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened with a heteroatom group(s) selected from CO, O, S, SO, SO_2, NR^5 (R^5 is independently selected from the same substitution group as R^4), -N= and =N-)

The stereochemistry of an asymmetric carbon represented by * shows the R- or S-configuration, or a mixture thereof)

In one embodiment, R^{20} to R^{40} each is preferably hydrogen, optionally substituted lower alkyl (examples of the substituent: OH, lower alkoxy, cycloalkyl, lower alkylthio, lower alkylsulfonyl, heterocyclic group, aryl, optionally substituted amino (examples of the substituent: lower alkyl, acyl)), cycloalkyl, optionally substituted aryl (examples of the substituent: OH, lower alkyl), and optionally substituted heterocyclic group

In one embodiment, R^{20} to R^{25}, R^{27} to R^{30}, and R^{32} to R^{39}, each is preferably hydrogen, C1-C8 alkyl, C6-C14 aryl C1-C8 alkyl, C6-C14 aryl, or alkoxy.

In one embodiment, R^{26}, R^{31}, and R^{40}, each is preferably hydrogen, C3-6 cycloalkyl, heterocycle, or C1-8 alkyl optionally substituted with hydroxy, C3-6 cycloalkyl, alkoxy, heterocycle, heteroaryl, C6-14 aryl, or amino, wherein said amino may be optionally substituted with -C(O)C1-8 alkyl or C1-8 alkyl.

More Preferred embodiments are shown below for example

1) When A ring is A-1, preferred is that 1) Z is NR^{26} and R^{26} and R^{21} taken together form heterocycle, and the others are hydrogens. 2) Z is O or NR^{26}, (R^{20} and R^{22}) or

(R^{23} and R^{24}) taken together form cycloalkyl which is substituted with phenyl, the others are hydrogens or optionally substituted lower alkyl.

II) When A ring is A-2, preferred is that 1) Z is O, R^{27} or R^{28} is lower alkyl, and the others are hydrogens; 2) Z is NR^{31} and R^{30} and R^{31} taken together form heterocycle and the others are hydrogens, or R^{27} and R^{29} taken together form cycloalkyl and the others are hydrogens . 3) Z is O, R^{27} and R^{29} taken together form cycloalkyl which may be condensed with phenyl, and the others are hydrogens

R^{14} and R^{x} are each independently hydrogen, optionally substitutedlower alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkyl lower alkyl, optionally substituted lower alkenyl, optionally substituted lower alkoxy, optionally substituted lower alkenyloxy, optionally substituted aryl, optionally substituted aryl lower alkyl, optionally substituted aryloxy, optionally substituted heterocyclic group, optionally substituted heterocycle lower alkyl, optionally substituted heterocycleoxy, hydroxy, optionally substituted amino,optionally substituted lower alkylcarbonyl, optionally substituted cycloalkylcarbonyl, optionally substituted cycloalkyl lower alkylcarbonyl, optionally substituted lower alkoxycarbonyl, optionally substituted arylcarbonyl, optionally substituted aryl lower alkylcarbonyl, optionally substituted aryloxycarbonyl, optionally substituted heterocyclecarbonyl, optionally substituted heterocycle lower alkylcarbonyl, optionally substituted heterocycleoxycarbonyl, optionally substituted aminocarbonyl, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy optionally substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, or lower alkyl substituted with optionally substituted phosphoric acid residue (the lower alkyl may be intervened with a heterotom group(s) selected from O, S, SO, SO_2, NR^a (R^a is hydrogen or lower alkyl), -N= and =N-)

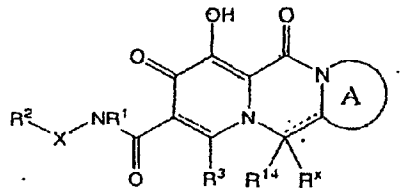
R^{14} and R^{x} are each independently, preferably, hydrogen, hydroxyl, optionally substituted lower alkyl (the substituent is preferably, e g., amino, lower alkyl amino, hydroxy, lower alkoxy) R^{14} and R^{x} are preferably hydrogens

A broken line in the compound (I-1) represents the presence or absence of a bond.

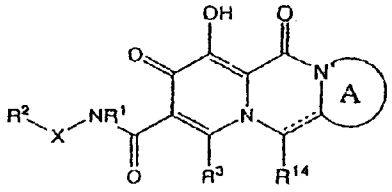
provided that when the broken line represents the presence of a bond, R^X is not present.

[0009]

The compound (I) includes the following compounds.

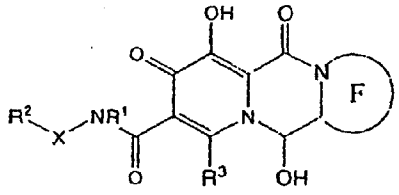


(I-1)



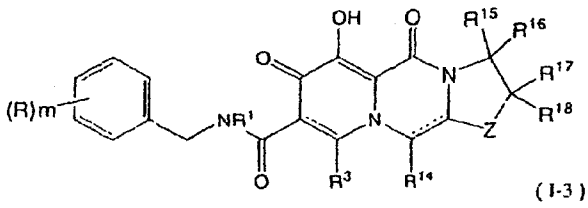
(I-1-1)

(wherein each symbol is as defined above)



(I-8)

F ring means the same heterocycle as A ring, preferably 5- to 7-membered ring, and the substituents on F ring are the same as those for A ring. The other symbols are as defined above.



(I-3)

(wherein each symbol is as defined above; Z is O or NR^{19}; R^{15} to R^{19} are each independently hydrogen or a group selected from the above Substituent group S2, or each combination of (R^{15} and R^{16}), (R^{17} and R^{18}), (R^{16} and R^{18}), and (R^{16} and R^{19}) taken together with the neighboring atom(s), may form an optionally substituted carbocycle (preferably 5- to 6-membered ring) or an optionally substituted heterocyle (preferably 5- to 6-membered ring); or each combination of (R^{15} and R^{16}) and (R^{17} and R^{18}) taken together may fom oxo)

Compound (I-3) is preferably as follows.

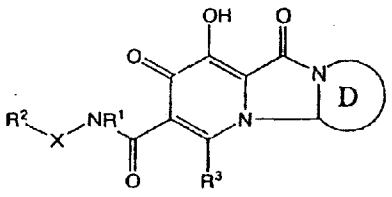
(1) R^1 is hydrogen; R^3 is hydrogen; m is 1 or 2; R^{14} is hydrogen.

(2) m is 1 or 2, R is each independently halogen, halogenated lower alkyl, lower alkoxy, halogenated lower alkoxy lower alkoxy lower alkyl, hydroxy lower alkyl, optionally substituted amino lower alkyl (the substituent is mono- or di- lower alkyl, lower alkylcarbonyl, or lower alkylsulfonyl), optionally substituted carbamoyl (the substituent is mono- or di- lower alkyl, lower alkylcarbonyl, or lower alkylsulfonyl), phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue or sulfonylamino optionally substituted with lower alkyl. R^1 is hydrogen; R^3 is hydrogen; R^{14} is hydrogen, hydroxyl or lower alkyl optionally substituted with mono- or di- lower alkylamino. Z is O or NR^{19} (R^{19} is hydrogen or lower alkyl, lower alkoxy lower alkyl, optionally substituted phosphoric acid residue, aryl substituted with optionally substituted phosphoric acid residue, aralkyl substituted with optionally substituted phosphoric acid residue, hydroxy substituted with optionally substituted phosphoric acid residue, amino substituted with optionally substituted phosphoric acid residue, or lower alkyl substituted with optionally substituted phosphoric acid residue).

(3)R is each independently, -F, $-CF_3$, -OMe, $-OCF_3$, $-CH_2OMe$, $-CH_2OH$, $-CH_2N(Me)_2$, -CONHMe, $-CON(Me)_2$, $-CH_2PO(OEt)_2$, $-PO(OEt)_2$, $-NHSO_2Me$, or $-NMeSO_2Me$;R^1 is hydrogen; R^3 is hydrogen; m is 1 or 2, R^{14} is hydrogen, hydroxyl or $-CH_2N(Me)_2$; Z is O or NR^{19} (R^{19} is hydrogen or $-CH(Me)_2$, $-(CH_2)_2OMe$,

-$(CH_2)_2PO(OEt)_2$).

(4) R^{15} and R^{16} are hydrogens; R^{17} and R^{18} are hydrogens or taken together with the neighboring atom form a 3- to 7-membered carbocycle; and/or Z is O or NH. This case preferably also satisfys the above (2) or (3).



(I-11)

D ring means the same heterocycle as A ring, preferably 5- to 7-membered ring, and the substituents on D ring are the same as those for A ring. The other symbols are as defined above.

The structure of compound (I) has at least the following characteristics.

(1) The main structure, condensed heterocycle, is substituted with oxo (=O), hydroxyl (OH) and oxo

(2) A substituted carbamoyl group (-$CONR^1XR^4$) is attached to the position neighboring to the oxo group on the condensed hereocycle.

The above structure contributes to a remarkably potent integrase inhibitory activity and/or cell-growth inhibitory activity against virus including HIV. In contrast, the structures of the other parts such as Z^1, Z^2, and R^3 each may be of variety, being optionally substituted or optionally condensed, and its condensed ring is also optionally substituted.

The present invention provides a pharmaceutically acceptable salt or a solvate of compound (I). All theoretically possible tautomer, geometrical isomer, optically active compound, and racemate thereof are within the scope of the invention.

Pharmaceutically acceptable salts of a compound of the present invention include, as basic salts, for example, alkali metal salts such as sodium or potassium salts; alkaline-earth metal salts such as calcium or magnesium salts; ammonium salts; aliphatic amine salts such as trimethylamine, triethylamine, dicyclohexylamine, ethanolamine, diethanolamine, triethanolamine or procaine salts; aralkyl amine salts

such as N, N-dibenzylethylenediamine salts; heterocyclic aromatic amine salts such as pyridin salts, picoline salts, quinoline salts or isoquinoline salts; quaternary ammonium salts such as tetramethylammonium salts, tetraethylammonium salts, benzyltrimethylammonium salts, benzyltriethylammonium salts, benzyltributylammonium salts, methyltrioctylammonium salts or tetrabutylammonium salts; and basic amino acid salts such as arginine salts or lysine salts. Acid salts include, for example, mineral acid salts such as hydrochloride, sulfates salts, nitrate salts, phosphates salts, carbonates salts, hydrogencarbonates or perchlorate; organic acid salts such as acetates, propionates, lactates, maleates, fumarates, tararic acid salts, malates, citrates salts, ascorbates, formic acid; sulfonates such as methanesulfonates, isethionates, benzenesulfonates, or p-toluenesulfonates; and acidic amino acid salts such as aspartates or glutamates.

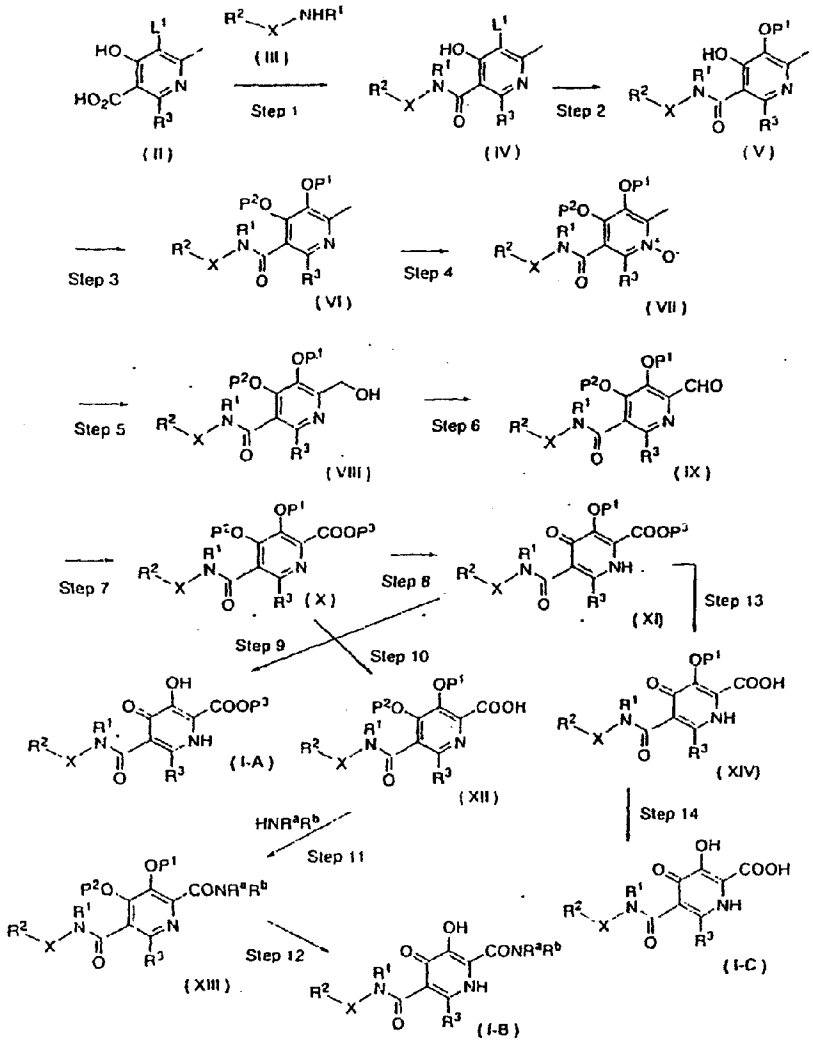
Solvates of a compound of the present invention include alcholates and hydrates.

[0012]

A general process for producing the present compound will be exemplified below.

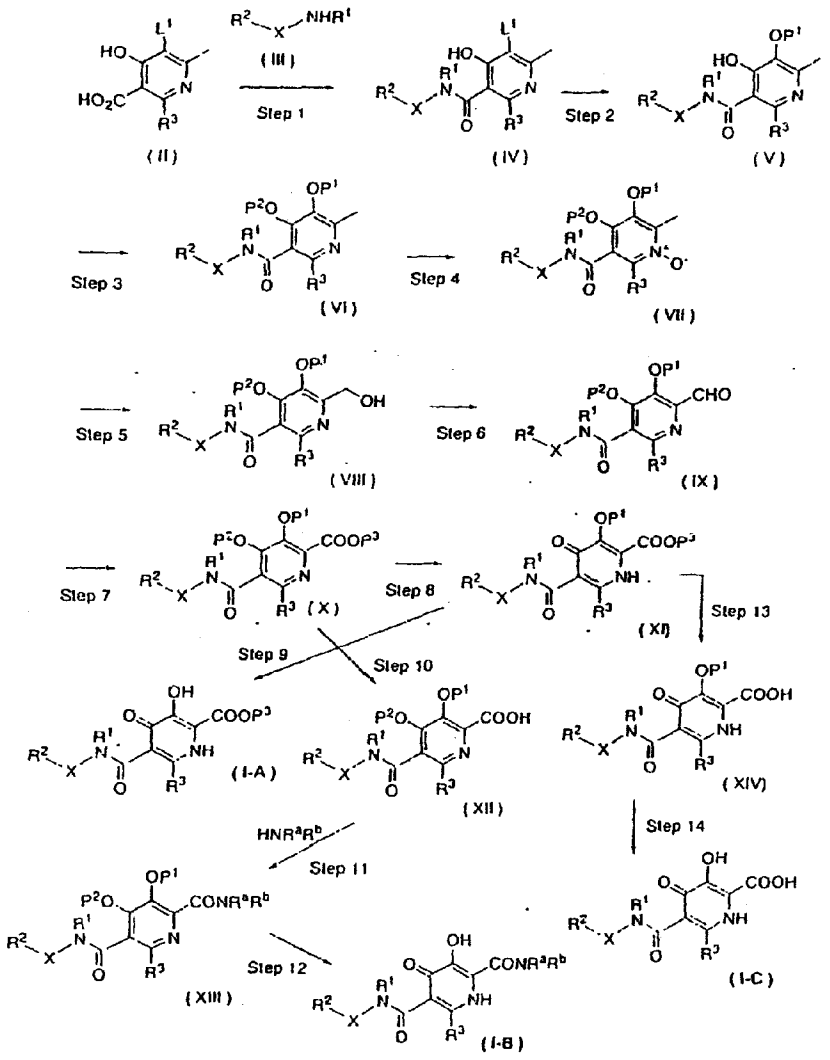
(Method of preparing raw material)

[Chemical formula 41]



(wherein L^1 is a leaving group (e.g.; halogen); P^1 and P^2 are a hydroxy protecting group; P^3 is a carboxy protecting group (e.g.: lower alkyl), R^a and R^b are hydrogen or a substituent on an amino group)

Examples of a hydroxy protecting group (P^1, P^2) include acyl (e.g.: acetyl, pivaloyl, benzoyl), aralkyl (e.g.: benzyl), lower alkyl (e.g.: methyl), alkoxyalkyl (e.g.: methoxymethyl, methoxyethyl), lower alkylsulfonyl (e.g.: methanesulfonyl), arylsulfonyl (e.g.: benzenesulfonyl, toluenesulfonyl), alkoxycarbonyl (e.g.:



(wherein L^1 is a leaving group (e.g.: halogen); P^1 and P^2 are a hydroxy protecting group; P^3 is a carboxy protecting group (e.g.: lower alkyl), R^a and R^b are hydrogen or a substituent on an amino group)

Examples of a hydroxy protecting group (P^1, P^2) include acyl (e.g.: acetyl, pivaloyl, benzoyl), aralkyl (e.g.: benzyl), lower alkyl (e.g.: methyl), alkoxyalkyl (e.g.: methoxymethyl, methoxyethyl), lower alkylsulfonyl (e.g.: methanesulfonyl), arylsulfonyl (e.g.: benzenesulfonyl, toluenesulfonyl), alkoxycarbonyl (e.g.:

methoxycarbonyl) and the like.

As a carboxy protecting group (P^1), lower alkyl (e.g.: methyl, ethyl), and aralkyl (e.g.: benzyl) are exemplified

[0013]

(First step)

The present step is a reaction for condensing a compound (II) and a compound (III) to synthesize a compound (IV). The reaction may be performed according to the condition for a reaction of amidating carboxylic acid which is generally performed A compound (II) may be reacted as it is, or may be reacted after converted into corresponding acid chloride or active ester Preferably, the reaction is performed in a suitable solvent in the presence of a condensing agent.

As a condensing agent, dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and the like may be used. If necessary, a reagent such as 1-hydroxybenzotriazole and N-hydroxysuccinimide, or a base such as triethylamine, N-methylmorpholine, and pyridine may be added

A reaction temperature is 0 to 150°C, preferably room temperature to 70°C.

As a reaction solvent, a non-protonic solvent can be broadly used, and tetrahydrofuran (THF), 1,4-dioxane, dimethylformamide (DMF), methylene chloride, chloroform and the like are preferable.

A reaction time is a few minutes to a few tens hours, preferably 9 to 17 hours.

(Second step)

The present step is a reaction for introducing a protected hydroxy group (OP^1) into a compound (IV) to produce a compound (V). The reaction may be performed according to the condition for an alkoxylating reaction which is generally performed.

For example, a compound (V) in which P^1 is methyl can be synthesized by reacting a compound (IV) with metal alkoxide (e.g.: sodium methoxide)

A reaction temperature is 0 to 200°C, preferably 80 to 120°C.

As a reaction solvent, alcohol, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 5 to 10 hours.

(Third step)

The present step is a reaction for protecting a hydroxy group of a compound

(V) to produce a compound (VI). The reaction may be performed according to the condition for a reaction of protecting a hydroxy group which is generally performed. For example, by using diisopropyl azodicarboxylate or diethyl azodicarboxylate together with an alcohol and various phosphines, a compound (VI) in which P^2 is alkyl can be synthesized.

A reaction temperature is 0 to 100°C, preferably 0°C to room temperature.

As a reaction solvent, THF, toluene, dichloromethane and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 1 to 3 hours.

(Fourth step)

The present step is a reaction of oxidizing a nitrogen atom of a compoung (VI) to produce a compound (VII). The reaction may be performed according to the condition for an oxidation reaction using an oxidizing agent which is generally performed.

A reaction temperature is 0 to 100°C, preferably under ice-cooling to room temperature.

As a reaction solvent, chloroform, methylene chloride, acetic acid and the like are exemplified

Examples of an oxidizing agent include metachloroperbenzoic acid, hydrogen peroxide and the like

A reaction time is a few minutes to a few tens hours, preferably 1 to 5 hours.

(Fifth step)

The present step is a reaction for hydroxylating a methyl group of a compound (VII). Preferably, after acetoxylation by a reaction with acetic anhydride (reaction temperature: 0 to 150°C, preferably 120 to 140°C), this may be hydrolyzed (e.g.: treatment with a base (e.g.: alkali metal hydroxide)).

A reaction time is a few minutes to a few tens hours, preferably 0.5 to 2 hours for acetoxylation, and 0.5 to 1 hour for hydrolysis.

(Sixth step)

The present step is a reaction for oxidizing a hydroxy group of a compound (VIII) to synthesize a compound (IX).

A reaction temperature is 0 to 150°C, preferably room temperature to 70°C.

As a reaction solvent, chloroform and the like are exemplified

As an oxidizing agent, dimethyl sulfoxide and the like are exemplified

A reaction time is a few minutes to a few tens hours, preferably 0.1 to 1 hour.

(Seventh step)

The present step is a reaction for oxidizing a formyl group of a compound (IX) to synthesize a compound (X).

A reaction temperature is 0 to 150°C, preferably under ice-cooling to room temperature.

As a reaction solvent, an alcohol and the like are exemplified

As an oxidizing agent, potassium hydroxide and iodine are exemplified

A reaction time is a few minutes to a few tens hours, preferably 0.5 to 3 hours.

(Eighth step)

The present step is a reaction for deprotecting an OP^2 part of a compound (X) to synthesize a compound (XI). The reaction may be performed according to the condition for a reaction of deprotecting a hydroxy protecting group which is generally performed.

A reaction temperature is 0 to 150°C, preferably under ice-cooling to room temperature.

As a reaction solvent, acetonitrile, methylene chloride, THF and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 1 to 3 hours

(Ninth step)

The present step is a reaction for deprotecting an OP^1 part of a compound (XI) to synthesize a compound (I-A) The reaction may be treated preferably with a Lewis acid (e g.: aluminum chloride)

A reaction temperature is 0 to 150°C, preferably 10 to 50°C.

As a reaction solvent, methylene chloride, THF and the like are exemplified

A reaction time is a few minutes to a few tens hours, preferably 1 to 3 hours.

(Tenth step)

The present step is a reaction for deprotecting an ester part ($COOP^3$) of a

compound (X) to synthesize carboxylic acid (XII). Preferably, hydrolysis with an alkali (e.g.: NaOH) may be performed.

A reaction temperature is 0 to 150°C, preferably 10 to 50°C

As a reaction solvent, methanol, water and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably a few minutes to 2 hours.

Carboxylic acid (XII) can be converted into various derivatives (e.g.: amide).

(Eleventh step)

The present step is a reaction for reacting a compound (XII) with various amines to synthesize a compound (XIII). The reaction may be performed according to the condition for a reaction of amidating carboxylic acid which is generally performed and, for example, the reaction may be performed as in the first step.

A reaction temperature is 0 to 150°C, preferably room temperature to 70°C

As a reaction solvent, a non-protonic solvent can be broadly used, and tetrahydrofuran (THF), 1,4-dioxane, dimethylformamide (DMF), methylene chloride, chloroform and the like are preferable.

A reaction time is a few minutes to a few tens hours, preferably a few minutes to 3 hours.

An amide part of the resulting compound (XIII) may be further chemically modified (e.g.: N-alkylation).

(Twelfth step)

The present step is a reaction for deprotecting OP^1 and OP^2 parts of a compound (XIII) to synthesize a compound (I-B). The reaction may be performed according to the condition for a reaction of deprotecting a hydroxy protecting group which is generally performed.

For example, when pyridine hydrochloride is used, a reaction temperature is 0 to 200°C, preferably 150 to 180 degree

A reaction time is a few minutes to a few tens hours, preferably 1 to 5 minutes.

(Thirteenth step)

The present step is a reaction for deprotecting an ester part ($COOP^3$) of a compound (XI) to synthesize carboxylic acid (XIV) Preferably, hydrolysis with an

alkali (e.g.: lithium hydroxide) may be performed

A reaction temperature is 0 to 150°C, preferably 10 to 50°C.

As a reaction solvent, methanol, water and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably a few minutes to 3 hours.

(Fourteenth step)

The present step is a reaction for deprotecting an OP^1 part of a compound (XIV) to synthesize a compound (I-C). The reaction may be treated preferably with a Lewis acid (e.g.: boron tribromide).

A reaction temperature is 0 to 150°C, preferably under ice-cooling to room temperature.

As a reaction solvent, dichloromethane and the like are exemplified.

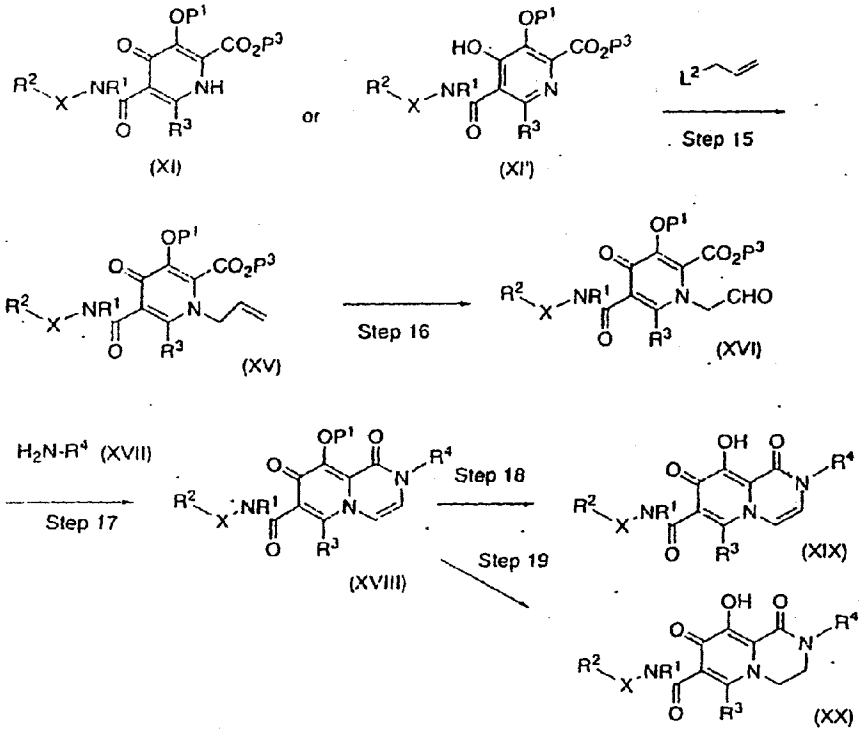
A reaction time is a few minutes to a few tens hours, preferably a few minutes to 5 hours.

[0014]

The monocyclic carbamoylpyridone derivative obtained above is derived into a bicyclic compound by the following method.

(Process 1)

[Chemical formula 42]



(wherein R^1, X, R^2, P^1, P^3 and R^3 are as define above, and L^2 is a leaving group such as halogen etc)

(Fifteenth step)

The present step is a reaction for reacting the compound (XI) or a compound (XI') which is a tautomer thereof with an allyl compound to synthesize a compound (XV) A compound (XI') can be synthesized, for example, according to the method of Example A-1.

The reaction is performed preferably in the presence of a base (e.g - cesium carbonate)

A reaction temperature is 0 to 100°C, preferably 10 to 40°C.

As a reaction solvent, dimethylformamide and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 1 to 10 hours

(Sixteenth step)

The present step is a reaction for oxidizing a compound (XV) to synthesize a compound (XVI) As an oxidizing agent, osmium tetraoxide and alkali metal osmium tetraoxide (e g. K_2OsO_4) are exemplified.

A reaction temperaturwe is 0 to 100°C, preferably 10 to 40°C.

As a reaction solvent, 1,4-dioxane, tetrahydrofuran and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 1 to 5 hours.

(Seventeenth step)

The present step is a reaction for reacting a compound (XVI) with amine (XVII) to perform dehydration condensation to synthesize a compound (XVIII).

A reaction temperature is 0 to 200°C, preferably 140 to 180°C.

As a reaction solvent, methylene chloride, acetonitrile and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 0.5 to 1.5 hours.

(Eighteenth step)

The present step is a reaction for deprotecting a compound (XVIII) preferably with an acid to synthesize a compound (XIX), and may be performed according to the condition for a conventional reaction of deprotecting a protected hydroxy group.

A reaction temperature is 0 to 200°C.

As an acid, pyridine hydrochloride, trifluoroacetic acid and the like are exemplified.

As a reaction solvent, the acid and trimethylsilyl iodide are exemplified

A reaction time is a few minutes to a few tens hours, preferably 15 minutes to 1 hour.

(Nineteenth step)

The present step is a reaction for reducing a compound (XVIII) to synthesize a compound (XX)

As a reducing agent, H_2/Pd · C and the like are exemplified.

A reaction temperatuer is 0 to 100°C, preferably 10 to 30°C.

As a reaction sovelnt, dimethylformamide, methanol, tetrahydrofuran and the like are exemplified.

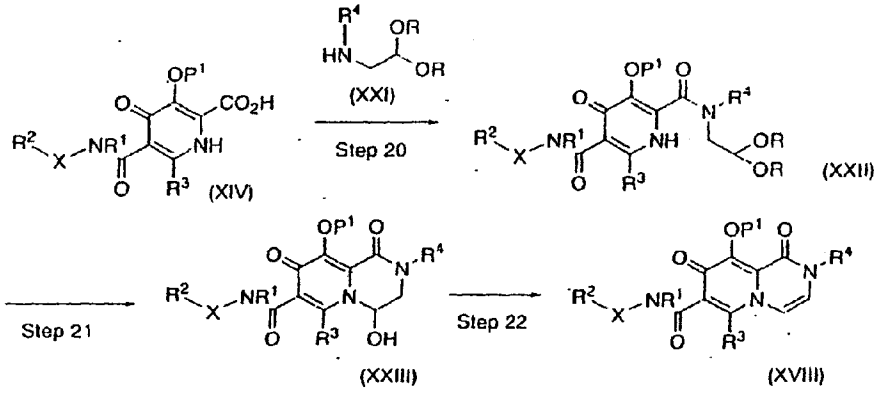
A reaction time is a few minutes to a few tens hours, preferably 5 to 20 hours

[0015]

(Process 2)

The intermediate (XVIII) may be also synthesized by a method shown below

[Chemical formula 43]



(Twentieth step)

The present step is a reaction for reacting a compound (XIV) with a compound (XXI) to synthesize a compound (XXII). The present reaction may be performed according to the condition for a conventional amidation reaction.

A reaction temperature is 0 to 100°C, preferably 0 to 50°C

As a reaction solvent, dimethylformiamide, methylene chloride, tetrahydrofuran and the like are exemplified

A reaction time is a few minutes to a few tens hours, preferably 1 to 10 hours.

(Twenty-first step)

The present step is a reaction for reacting a compound (XXII) with an acid to perform deprotection and intramolecular ring closure, to synthesize a compound (XXIII). The present reaction may be performed according to the condition for a conventional reaction of deprotecting acetal

A reaction temperature is 0 to 100°C, preferably room temperature to 80°C.

As a reaction solvent, dioxane, tetrahydrofuran and the like are exemplified

A reaction time is a few minutes to a few tens hours, preferably 0.5 to 1 hour.

As an acid, hydrochloric acid, and paratoluenesulfonic acid are exemplified

(Twenty-second step)

The present step is a reaction for dehydrating a compound (XXIII) to

synthesize a compound (XXIV) The present reaction may be peformed according to the condition for a conventional dehydration reaction

A reaction temperature is 0 to 100°C, preferably room temperature to 80°C

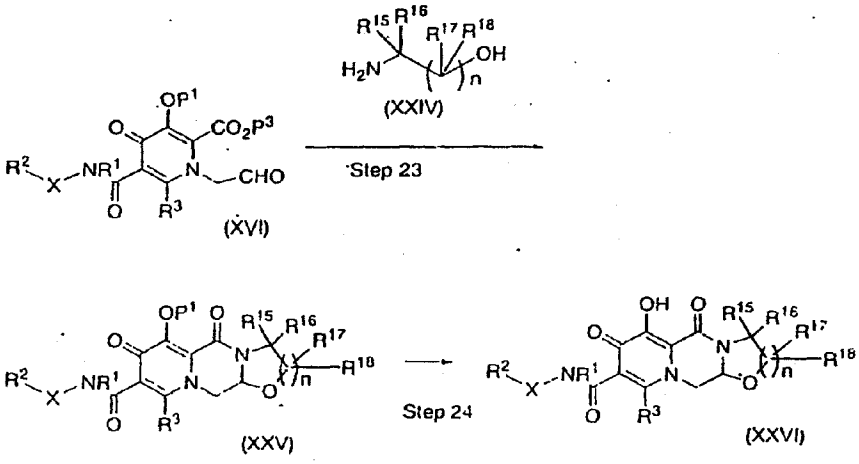
As a reaction solvent, acetonitrile, methylene chloride and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 1 to 5 hours.

[0016]

(Process 3)

[Chemical formula 44]



(Twenty-third step)

The present step is a reaction for reacting a compound (XVI) with amine (XXIV) to perform dehydration condensation to synthesize a compound (XXV) according to the seventeenth step or a method of synthesizing a compound 17-1. Preferably, as a reaction catalyst, an acid (e.g.: acetic acid) is added, and a microwave reaction apparatus is used.

A reaction temperature is 0 to 200°C, preferably 140 to 180°C.

As a reaction solvent, methylene chloride, acetonitrile and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 0.5 to 1.5 hours.

(Twenty-fourth step)

The present step is a reaction for deprotecting a compound (XXV) preferably with an acid to synthesize a compound (XXVI) according to the eighteenth step, and may be performed according to the condition for a conventional reaction of deprotecting a protected hydroxy group.

A reaction temprature is 0 to 200°C.

As an acid, pyridine hydrochloride, trifluoroacetic acid and the like are exemplified.

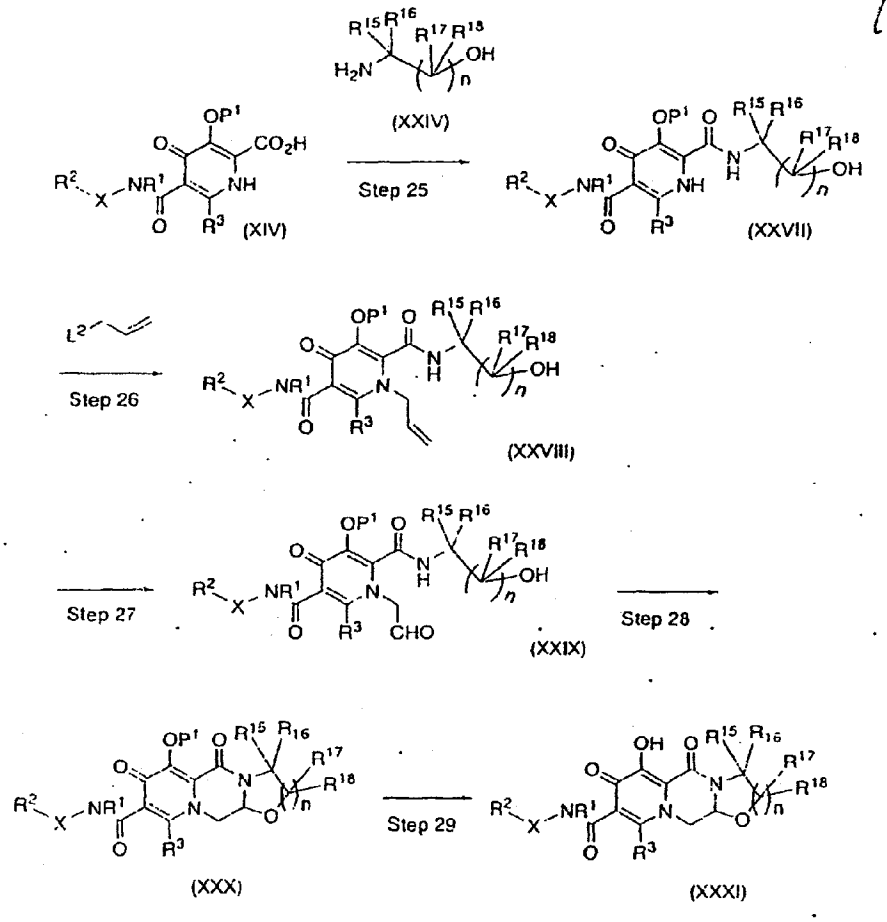
As a reaction solvent, the aforementioned acid and trimethylsilyl iodide are exemplified

A reaction time is a few minutes to a few tens hours, preferably 15 minutes to 1 hour.

[0017]

(Process 4)

[Chemical formula 45] .



(Twenty-fifth step)

The present step is a reaction for reacting a compound (XIV) with a compound (XXIV) to synthesize a compound (XXVII) according to the twentieth step. The present reaction may be performed according to the condition for a conventional amidation reaction.

A reaction temperature is 0 to 100°C, preferably 0 to 50°C.

As a reaction solvent, dimethylformamide, methylene chloride, tetrahydrofuran and the like are exemplified.

A reaction time is a few minutes to a few tens hours, preferably 1 to 10 hours

(Twenty-sixth step)

The present step is a reaction for reacting a compound (XXVII) or a tautomer

thereof with an allyl compound to synthesize a compound (XXVIII) according to the fifteenth step.

A reaction is performed preferably in the presence of a base (e.g : cesium carbonate).

A reaction temperature is 0 to 100°C, preferably 10 to 40°C.

As a reaction solvent, dimethylformamide and the like are exemplified

A reaction time is a few minutes to a few tens hours, preferably 1 to 10 hours.

(Twenty-seventh step)

The present step is a reaction for oxidizing a compound (XXVIII) to synthesize a compound (XXIX) according to the sixteenth step

As an oxidizing agent, osmium tetraoxide and alkali metal osmium tetraoxide (e.g.: K_2OsO_4) are exemplified.

A reaction temperature is 0 to 100°C, preferably 10 to 40°C.

As a reaction solvent 1,4-dioxane, tetrahydrofuran and the like are exemplified

A reaction time is a few minutes to a few tens hours, preferablky 1 to 5 hours

(Twenty-eighth step)

The present step is a reaction for dehydration-condensing a compound (XXIX) to synthesize a compound (XXX) according to the seventeenth step or a method of synthesizing a compound 17-1. Preferably, as a reaction catalyst, an acid (e.g.: acetic acid) is added, and a microwave reaction apparatus is used.

A reaction temperature is 0 to 200°C, preferably 140 to 180°C.

As a reaction solvent, methylene chloride, acetonitrile and the like are exemplified

A reaction time is a few minutes to a few tens hours, preferably 0.5 to 1.5 hours.

(Twenty-ninth step)

The present step is a reaction for deprotecting a compound (XXX) preferably with an acid to synthesize a compound (XXXI) according to the eighteenth step, and may be peformed according to the condition for a conventional reaction of deprotecting a protected hydroxy group.

A reaction temperature is 0 to 200°C.

As an acid, pyridine hydrochloride, trifluoroacetic acid and the like are exemplified.

As a reaction solvent, the aforementioned acid and trimethylsilyl iodide are exemplified.

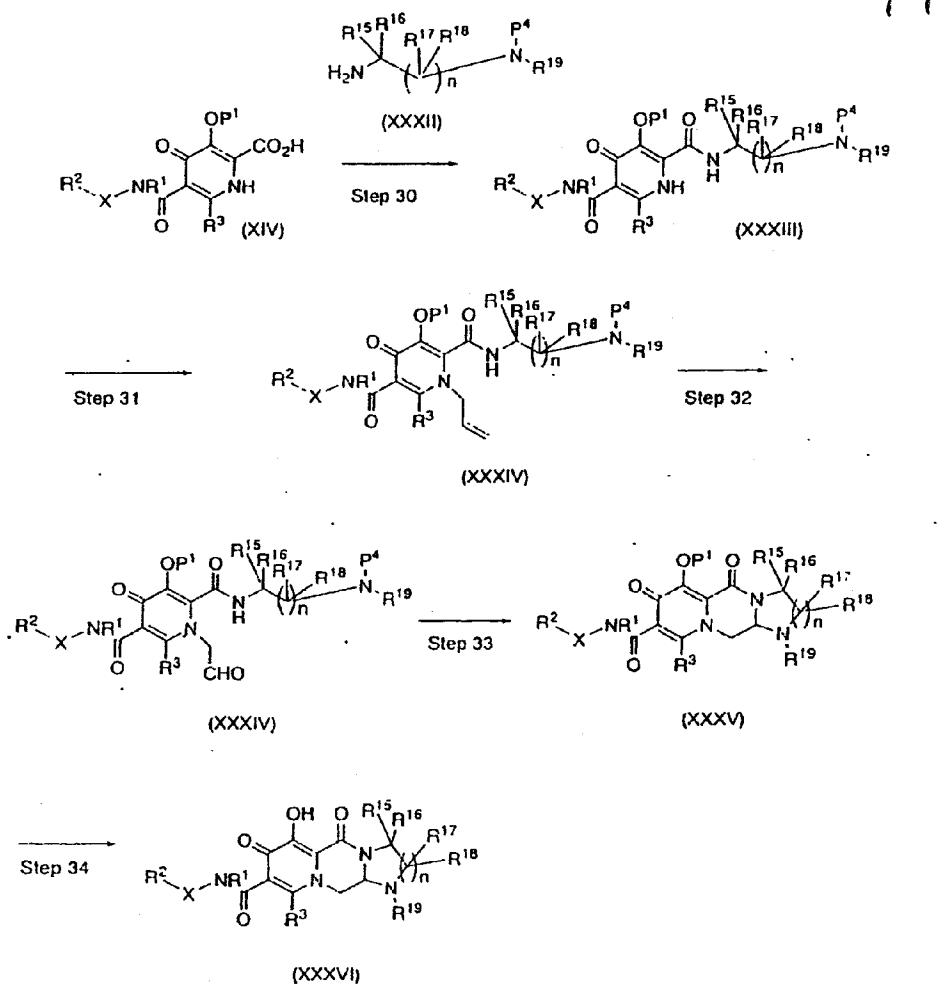
A reaction time is a few minutes to a few tens hours, preferably 15 minutes to 1 hour

[0018]

(Process 5)

A compound (1-3) in which Z is NR^{19} can be synthesized according to the following reaction scheme, according to Process 4.

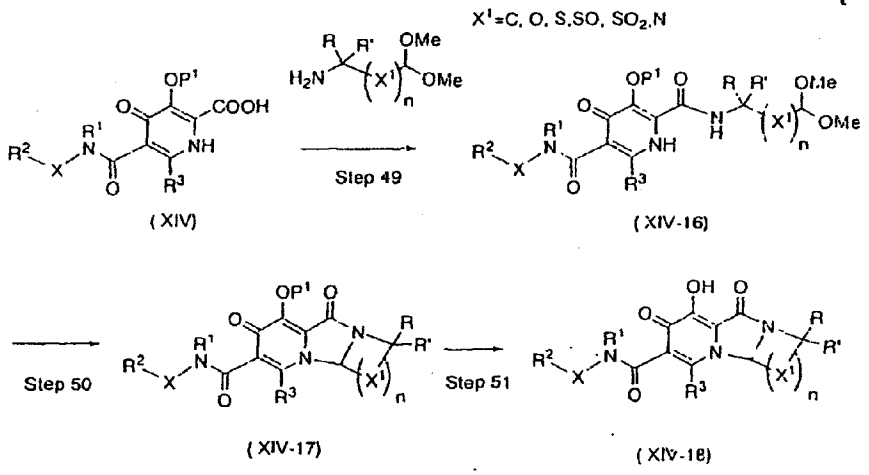
[Chemical formula 46]



[0019]

(Process 10)

[Chemical formula 51]



(wherein respective symbols are as defined above)

(Forty-ninth step)

A compound (XIV-16) is obtained by reacting a compound (XIV) with an amine reagent, according to the thirty-fifth step.

(Fiftieth step)

A compound (XIV-17) is obtained by subjecting a compound (XIV-16) to a general acetal deprotecting reaction according to the forty-fourth step

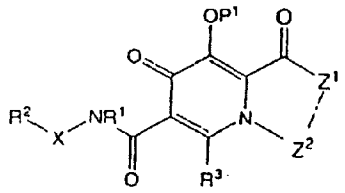
(Fifty-first step)

A compound (XIV-18) is obtained (D ring formation) by deprotecting a P^1 part of a compound (XIV-14) according to the thirty-eighth step

[0020]

The present invention further provides various intermediates (I-P) shown below and a process for preparing the same, as well as a process for preparing the above mentioned compound (I) comprising the deprotection of the intermediate

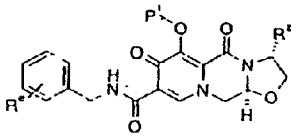
(Intermediates)



(I-P)

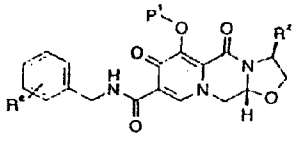
(P^1 is a hydroxyl-protecting group; the other symbols are as defined above)

Preferred compounds are shown below. Each P^1 is a hydroxyl-protecting group, such as C_{6-14}arylC_{1-8}alkyl (e.g., benzyl (=Bn)).



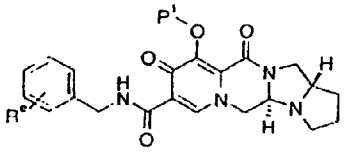
(I-20a)

Preferably, wherein R^e is one or two halogen; R^4 is C_{1-8}alkyl, C_{6-14}arylC_{1-8}alkyl, C_{6-14}aryl, or alkoxy, and P^1 is C_{6-14}arylC_{1-8}alkyl;



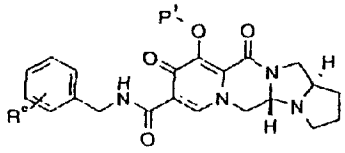
(I-20b)

Preferably, wherein R^e is one or two halogen; R^4 is C_{1-8}alkyl, C_{6-14}arylC_{1-8}alkyl, C_{6-14}aryl, or alkoxy; and P^1 is C_{6-14}arylC_{1-8}alkyl;



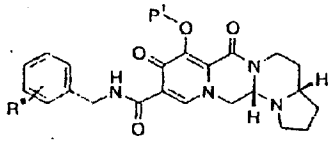
(I-21a)

Preferably, wherein R^e is one or two halogen, and P^1 is C_{6-14}arylC_{1-8}alkyl;



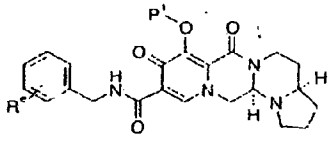
(I-21b)

Preferably, wherein R^e is one or two halogen; and P^1 is C_{6-14}arylC_{1-8}alkyl;



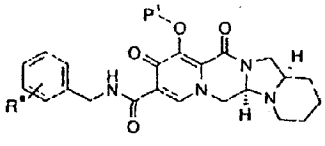
(I-22a)

Preferably, wherein R^e is one or two halogen; and P^1 is C_{6-14}arylC_{1-8}alkyl.



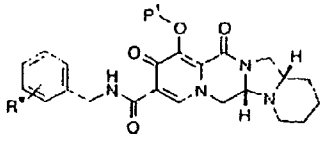
(I-22b)

Preferably, wherein R^e is one or two halogen; and P^1 is C_{6-14}arylC_{1-8}alkyl.



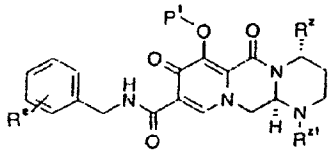
(I-23a)

Preferably, wherein R^e is one or two halogen; and P^1 is C_{6-14}arylC_{1-8}alkyl.



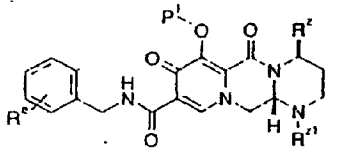
(I-23b)

Preferably, wherein R^e is one or two halogen, and P^1 is C_{6-14}arylC_{1-8}alkyl.



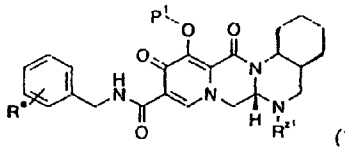
(I-24a)

Preferably, wherein R^e is one or two halogen; R^z is C_{1-8}alkyl; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;



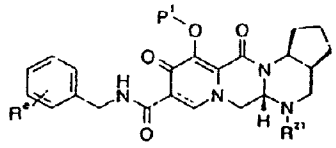
(I-24b)

Preferably, wherein R^e is one or two halogen; R^z is C_{1-8}alkyl; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl;



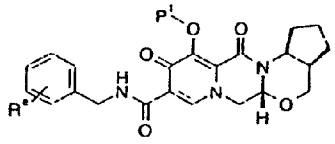
(I-25)

Preferably, wherein R^e is one or two halogen; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;and P^1 is C_{6-14}arylC_{1-8}alkyl;



(I-26)

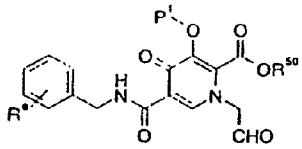
Preferably, wherein R^e is one or two halogen; R^{21} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with –C(O)C_{1-8}alkyl or C_{1-8}alkyl; and P^1 is C_{6-14}arylC_{1-8}alkyl.



(I-27)

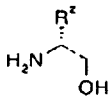
Preferably, wherein R^e is halogen; and P^1 is C_{6-14}arylC_{1-8}alkyl.

The above intermediates, compound (I-20a), (I-20b), (I-21a), (I-21b), (I-22a), (I-22b), (I-23a), (I-23b), (I-24a), (I-24b), (I-25), (I-26), or (I-27), can be prepared by condensing a compound of the formula

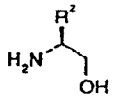


wherein R^e is one or two halogen; and R^{50} is C_{1-8}alkyl.

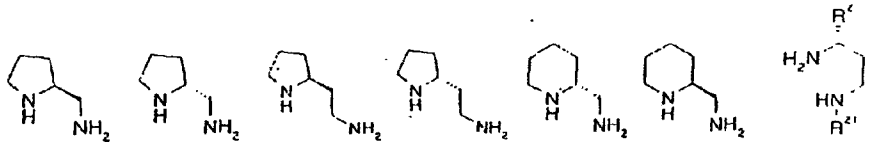
with each amine shown below, respectively.



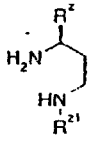
wherein R^z is C_{1-8}alkyl, C_{6-14}arylC_{1-8}alkyl, C_{6-14}aryl, or alkoxy.



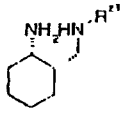
wherein R^z is C_{1-8}alkyl, C_{6-14}arylC_{1-8}alkyl, C_{6-14}aryl, or alkoxy.



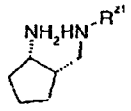
wherein R^z is C_{1-8}alkyl; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;



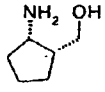
wherein R^z is C_{1-8}alkyl; R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl;



wherein R^{z1} is hydrogen, C_{3-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl.



wherein R^{21} is hydrogen, C_{1-6}cycloalkyl, , heterocycle, or C_{1-8}alkyl optionally substituted with hydroxy, C_{3-6}cycloalkyl, alkoxy, heterocycle, heteroaryl, C_{6-14}aryl, or amino, wherein said amino may be optionally substituted with $-C(O)C_{1-8}$alkyl or C_{1-8}alkyl.



The condition for the above condensation is illustrated below for example.

Examples of the solvent include halocarbons such as dichloromethane, dichloroethane, and acetic acid.

The reaction temperature is preferably, 0 to 200 ℃, more preferably, 50 to 170℃

The reaction time is usually several minutes to several hours.

The above intermediates, compound (I-20a), (I-20b), (I-21a), (I-21b), (I-22a), (I-22b), (I-23a), (I-23b), (I-24a), (I-24b), (I-25), (I-26), or (I-27), can be deprotected to give each corresponding deprotected compound wherein P^1 is hydrogen, or its pharmaceutically acceptable salt, which are encompassed within the scope of compound (I) of the present invention.

In addition, the present compound obtained above may be further chemically modified to synthesize another compound. In addition, when there is a reactive functional group (e.g.: OH, COOH, NH_2) on a side chain part etc. in the above reaction, the group may be protected before the reaction and may be deprotected after the reaction, if desired.

The present compound is useful, for example, as a drug such as an anti-virus drug. The present compound has the remarkable inhibitory action on integrase of a virus. Therefore, the present compound can be expected to have the preventive or

therapeutic effect for various diseases derived from a virus which produces at least integrase, and is grown at infection in an animal cell, and is useful as an integrase inhibiting agent for retrovirus (e g. HIV-1, HIV-2, HTLV-1, SIV, FIV etc.), and is useful as an anti-HIV drug etc.

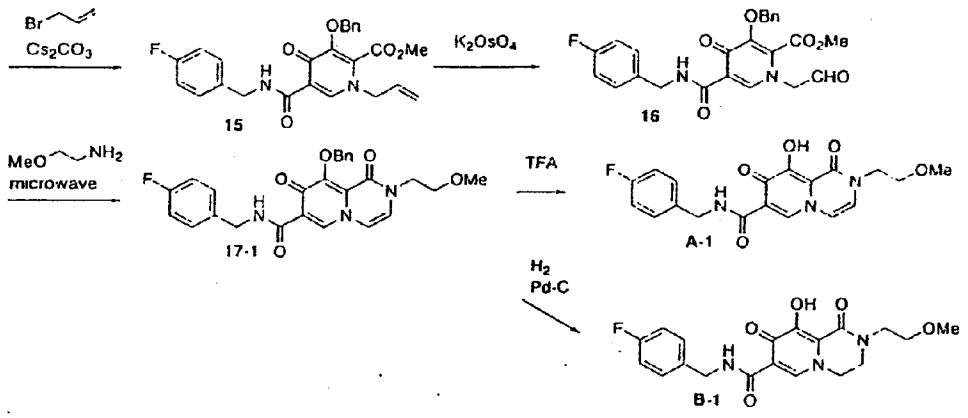
In addition, the present compound may be used in joint use therapy by combining an anti-HIV drug having the different action methanism such as a reverse trascriptase inhibiter and/or a protease inhibiting agent. Particularly, currently, an integrase inhibiter is not marketed, and it is useful to use in joint use therapy by combining the present compound with a reverse transcriptase inhibiter and/or a protease inhibiter.

Further, the above use includes not only use as a medical mixture for anti-HIV, but also use as a joint use agent for increasing the anti-HIV activity of other anti-HIV drug such as cocktail therapy.

In addition, the present compound can be used in order to prevent infection with a retrovirus vector from spreading into a tissue other than an objective tissue, upon use of a retrovirus vector based on HIV or MLV in the field of gene therapy. Particularly, when a cell is infected with a vector in vitro, and the cell is returned into a body, if the present compound is administered in advance, extra infection can be prevented in a body

The present compound can be adminitetered orally or parenterally In the case of oral administration, the present compound can be also used as a conventional preparation, for example, as any dosage form of a solid agent such as tablets, powders, granules, capsules and the like; an aqueous agent; an oily suspension; or a liquid agent such as syrup and elixir In the case of parenteral administration, the present compound can be used as an aqueous or oily suspension injectable, or a nasal drop. Upon preparation of it, conventional excipients, binders, lubricants, aqueous solvents, oily solvents, emulsifiers, suspending agents, preservatives, stabilizers and the like may be arbitrarily used. As an anti-HIV-drug, particularly, an oral agent is preferable A preparation of the present invention is prepared by combining (e.g. mixing) a therapeutically effective amount of the present compound with a pharmaceutically acceptable carrier or diluent

A dose of the present invention is different depending on an administration method, an age, a weight and conditions of a patient, and a kind of a disease and, usually, in the case of oral administraton, about 0 05mg to 3000mg, preferably about 0.1mg to 1000mg may be administered per adult a day, if necessary, by dividing the



1) Maltol 1 (189g, 1.5mol) was dissolved in dimethylformamide (1890ml), and benzyl bromide (184ml, 1.5mol) was added After the solution was stirred at 80°C for 15 minutes, potassium carbonate (228g, 1.65mol) was added, and the mixture was stirred for 1 hour. After the reaction solution was cooled to room temperature, an inorganic salt was filtered, and the filtrate was distilled off under reduced pressure. To the again precipitated inorganic salt was added tetrahydrofuran (1000ml), this was filtered, and the filtrate was distilled off under reduced pressure to obtain the crude product (329g, >100%) of 3-benzyloxy-2-methyl-pyran-4-one 2 as a brown oil.
NMR ($CDCl_3$)δ: 2.09(3H, s), 5.15(2H, s), 6.36(1H, d, J=5.6Hz), 7.29-7.41(5H, m), 7.60(1H, d, J=5.6Hz).

2) The compound 2 (162.2g, 750mmol) was dissolved in ethanol (487ml), and aqueous ammonia (28%, 974ml) and a 6N aqueous sodium hydroxide solution (150ml, 900mmol) were added After the reaction solution was stirred at 90 °C for 1 hour, this was cooled to under ice-cooling, and ammonium chloride (58g, 1080mmol) was added. To the reaction solution was added chloroform, this was extracted, and the organic layer was washed with an aqueous saturated sodium bicarbonate solution, and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, isopropyl alcohol and diethyl ether were added to the residue, and precipitated crystals were filtered to obtain 3-benzyloxy-2-methyl-1H-pyridine-4-one 3 (69.1g, 43%) as a pale yellow crystal.
NMR (DMSO-d_6)δ: 2.05(3H, s), 5.04(2H, s), 6.14(1H, d, J=7.0Hz), 7.31-7.42(5H, m), 7.46(1H, d, J=7.2Hz), 11.29(1H, brs).

3) The above compound 3 (129g, 599mmol) was suspended in acetonitrile (1300ml), and N-bromosuccinic acid imide (117g, 659mmol) was added, followed by stirring at room temperature for 90 minutes. Precipitated crystals were filtered, and washed with acetonitrile and diethyl ether to obtain
3-benzyloxy-5-bromo-2-methyl-pyridine-4-ol 4(154g, 88%) as a colorless crystal.
NMR (DMSO-d_6)δ: 2.06(3H, s), 5.04(2H, s), 7.32-7.42(5H, m), 8.03(1H, d, J=5.5Hz), 11.82(1H, brs)

4) To a solution of the compound 4 (88g, 300mmol), palladium acetate (13.4g, 60mmol) and 1,3-bis(diphenylphosphino)propane (30.8g, 516mmol) in dimethylformamide (660ml) were added methanol (264ml) and triethylamine (210ml, 1.5mol) at room temperature. The interior of a reaction vessel was replaced with carbon monoxide, and the material was stirred at room temperature for 30 minutes, and stirred at 80 degree for 18 hours. A vessel to which ethyl acetate (1500ml), an aqueous saturated ammonium chloride solution (1500ml) and water (1500ml) had been added was stirred under ice-cooling, and the reaction solution was added thereto. Precipitates were filtered, and washed with water (300ml), ethyl acetate (300ml) and diethyl ether (300ml) to obtain 5-benzyloxy-4-hydroxy-6-methyl-nicotinic acid methyl ester 5 (44.9g, 55%) as a colorless crystal.
NMR (DMSO-d_6)δ: 2.06(3H, s), 3.72(3H, s), 5.02(2H, s), 7.33-7.42(5H, m), 8.07(1H, s).

5) After a solution of the compound 5 (19.1g, 70mmol) in acetic anhydride (134ml) was stirred at 130 °C for 40 minutes, the solvent was distilled off under reduced pressure to obtain 4-acetoxy-5-benzyloxy-6-methyl-nicotinic acid methyl ester 6 (19.9g, 90%) as a flesh colored crystal.
NMR ($CDCl_3$)δ: 2.29(3H, s), 2.52(3H, s), 3.89(3H, s), 4.98(2H, s), 7.36-7.41(5H, m), 8.85(1H, s)

6) To a solution of the compound 6 (46.2g, 147mmol) in chloroform (370ml) was added metachloroperbenzoic acid (65%) (42.8g, 161mmol) in portions under ice-cooling, and this was stirred at room temperature for 90 minutes. To the reaction solution was added a 10% aqueous potassium carbonate solution, and this was stirred for 10 minutes, followed by extraction with chloroform. The organic layer was washed with successively with a 10% aqueous potassium carbonate solution, an aqueous saturated ammonium chloride solution, and an aqueous saturated sodium chloride solution, and

dried with anhydrous sodium sulfate The solvent was distilled off under reduced pressure, and the residue was washed with diisopropyl ether to obtain 4-acetoxy-5-benzyloxy-6-methyl-1-oxy-nicotinic acid methyl ester 7 (42.6g, 87%) as a colorless crystal.

NMR ($CDCl_3$)δ: 2.30(3H, s), 2.41(3H, s), 3.90(3H, s), 5.02(2H, s), 7.37-7.39(5H, m), 8.70(1H, s)

7) To acetic anhydride (500ml) which had been heated to stir at 130 °C was added the compound 7 (42.6g, 129mmol) over 2 minutes, and this was stirred for 20 minutes. The sovent was distilled off under reduced pressure to obtain 4-acetoxy-6-acetoxymethyl-5-benzyloxy-nicotinic acid methyl ester 8 (49.6g, >100%) as a black oil.

NMR ($CDCl_3$)δ: 2.10(3H, s), 2.28(3H, s), 3.91(3H, s), 5.07(2H, s), 5.20(2H, s), 7.35-7.41(5H, m), 8.94(1H, s).

8) To a solution of the compound 8 (46.8g, 125mmol) in methanol (140ml) was added a 2N aqueous sodium hydroxide solution (376ml) under ice-cooling, and this was stirred at 50 °C for 10 minutes. To the reaction solution were added diethyl ether and 2N hydrochloric acid under ice cooling, and precipitated crystals were filtered. Resulting crystals were washed with water and diethyl ether to obtain 5-benzyloxy-4-hydroxy-6-hydroxymethyl-nicotinic acid 9 (23.3g, 68%) as a colorless crystal.

NMR (DMSO-d_6)δ: 4.49(2H, s), 5.19(2H, s), 5.85(1H, brs), 7.14-7.20(2H, m), 7.33-7.43(7H, m), 8.30(1H, s), 10.73(1H, t, J=5.8Hz), 11.96(1H, brs).

9) To a solution of the compound 9 (131g, 475mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (219g, 1140mmol) and 1-hydroxybenzotriazole (128g, 950mmol) in dimethylformamide (1300ml) was added 4-fluorobenzylamine (109ml, 950mmol), and this was stirred at 80°C for 1.5 hours After the reaction solution was cooled to room temperature, hydrochloric acid was added, followed by extraction with ethyl acetate The extract was washed with a 5% aqueous potassium carbonate solution, an aqueous saturated ammonium chloride solution, and an aqueous saturated sodium chloride solution, and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain a mixture (175g) of 10 and 11. the resulting mixture was dissolved in acetic

acid (1050ml) and water (1050ml), and zinc (31 1g, 475mmol) was added, followed by heating to reflux for 1 hour. After the reaction solution was cooled to room tempreture, a 10% aqueous potassium carbonate solution was added, followed by extraction with ethyl acetate. The extract was washed with an aqueous saturated ammonium chloride solution, and an aqueous saturated sodium chloride solution, and dried with anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, this was washed with diethyl ether to obtain 5-benzyloxy-N-(4-fluoro-benzyl)-4-hydroxy-6-hydroxymethyl-nicotinic acid amide 10 (107g, 59%) as a colorless crystal.
NMR (DMSO-d_6)δ: 4.45(2H, d, J=4.3Hz), 4.52(2H, d, J=5.3Hz), 5.09(2H, s), 6.01(1H, brs), 7.36-7.43(5H, m), 8.31(1H, s), 12.63(1H, brs).

10) After manganese dioxide (49g) was added to a suspension of the compound 10 (9 8g, 25.6mmol) in chloroform (490ml), the mixture was stirred at room temperature for 1 hour After the reaction solution was stirred at 60 °C for 20 minutes, Celite filtration was performed, and this was washed with chloroform heated at 50 °C The filtrate was distilled off under reduced pressure to obtain 5-benzyloxy-N-(4-fluoro-benzyl)-6-formyl-4-hydroxy-nicotinic acid amide 12 (8.2g, 84%) as a pale yellow crystal
NMR (DMSO-d_6)δ: 4.53(2H, d, J=5.8Hz), 5 38 (2H, s), 7.15-7 21(2H, m), 7 35 7 46(7H, m), 8.33(1H, s), 9.90(1H, s), 10.35(1H, t, J=5.8Hz), 12.49(1H, brs)

11) To an aqueous solution (105ml) of sodium chlorite (7.13g, 78.8mmol), and sulfamic acid (7.65g, 78.8mmol) was added a solution of the compound 12 (15.0g, 39.4mmol) in tetrahydrofuran (630ml) under ice-coling, and the mixture was stirred at room temperature for 1 hour After water (2500ml) was added to the reaction solution, precipitated crystals were filtered. Washing with diethyl ether afforded 3-benzyloxy-5-(4-fluoro-benzylcarbamoyl)-4-hydroxy-pyridine-2-carboxylic acid 13 (14 0g, 90%) as a colorless crystal
NMR (DMSO-d_6)δ: 4.52(2H, d, J=5.8Hz), 5.13 (2H, s), 7 14-7.19(2H, m), 7.31 7.40(5H, m), 7.47-7.49(2H, m), 8 31(1H, d, J=4 5Hz), 10.44(1H, t, J=5.9Hz), 12 47(1H, brs)

12) A solution of the compound 13 (198mg, 0.500mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (115mg, 0 600mmol) and 1-hydroxybenzotriazole (81mg, 0.600mmol) in dimethylformamide (3ml) was

stirred at room temperature for 1.5 hours. Then, methanol (3ml) and triethylamine (153ul, 1 10mmol) were added, and the mixture was heated to reflux for 1.5 hours The reaction solution was diluted with ethyl acetate, washed with an aqueous saturated sodium bicarbonate solution, a 10% aqueous citric acid solution, and an aqueous saturated sodium chloride solution, and dried with anhydrous sodium sulfate The solvent was distilled off under reduced pressure, and the residue was washed with diethyl ether to obtain
3-benzyloxy-5-(4-fluoro-benzylcarbamoyl)-4-hydroxy-pyridine-2-carboxylic acid methyl ester 14 (141mg, 69%) as a colorless crystal.
NMR (DMSO-d_6)δ 3.85(3H, s), 4.52(2H, d, J=6.0Hz), 5.15(2H, s), 7.13-7.21(2H, m), 7.31-7.47(7H, m), 8.33(1H, s), 10.41(1H, t, J=6 0Hz), 12.59(1H, brs).

13) After 3-bromopropene (2 15ml, 24 8mmol) was added to a solution of the compound 14 (6.79g, 16.5mmol), and cesium carbonate (8.09g, 24.8mmol) in dimethylformamide (54ml), the mixture was stirred at room temperature for 4.5 hours To the reaction solution was added an aqueous ammonium chloride solution, and this was extracted with ethyl acetate, washed with water and an aqueous saturated sodium chloride solution, and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was washed with diethyl ether to obtain
1-allyl-3-benzyloxy-5-(4-fluoro-benzylcarbamoyl)-4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methyl ester 15 (6.15g, 83%) as a colorless crystal.
NMR ($CDCl_3$) δ 3.76(3H, s), 4.54(2H, d, J=6.0Hz), 4.60(2H, d, J=6.0Hz), 5.20-5.37(2H, m), 5 25(2H, s), 5.80-5.93(1H, m), 6.98-7.04(2H, m), 7.31-7.35(7H, m), 8.45(1H, s), 10.41(1H, m).

14) To a solution of the compound 15 (7.6g, 16 9mmol) in 1,4-dioxane (228ml) was added an aqueous solution (38ml) of potassium osmate dihydrate (372mg, 1.01mmol), and sodium metaperiodate (14.5g, 67.6mmol) was further added, followed by stirring at room temperature for 2 hours The reaction solution was added to a vessel to which ethyl acetate (300ml) and water (300ml) had been added, while stirring. The organic layer was washed with water, a 5% aqueous sodium hydrogen sulfite solution and an aqueous saturated sodium chloride solution, and dried with anhydrous sodium sulfate The solvent was distilled off under reduced pressure, and the residue was washed with diethyl ether to obtain

3-benzyloxy-5-(4-fluoro-benzylcarbamoyl)-4-oxo-1-(2-oxo-ethyl)-1,4-dihydro-pyridine-2-carboxylic acid methyl ester 16 (5.39g, 71%) as a colorless crystal.
NMR ($CDCl_3$)δ: 3.74(3H, s), 4.60(2H, d, J=5.9Hz), 4.87(2H, s), 5.27(2H, s), 6.98-7.04(2H, m), 7.30-7.40(7H, m), 8.39(1H, s), 9.58(1H, s), 10.38(1H, s).

15) To a solution of the compound 16 (400mg, 0.884mmol) in methylene chloride (12ml) were added 2-methoxyethylamine (77ul, 0.884mmol) and acetic acid (18ul), and the mixture was stirred at room temperature for 5 minutes. Thereafter, the reaction was performed at 140 °C for 30 minutes in a microwave reaction apparatus. The solvent was distilled off under reduced pressure, the residue was subjected to silica gel column chromatography, and fractions eluting with toluene-acetone were concentrated under reduced pressure to obtain 9-benzyloxy-2-(2-methy-ethyl)-1,8-dioxo-1,8-dihydro-2H-pyrid[1,2-a]pyrazine-7-carboxylic acid 4-fluoro-benzylamide 17-1 (226mg, 54%) as a yellow solid.
NMR ($CDCl_3$)δ: 3.35(3H, s), 3.65(2H, t, J=5.1Hz), 3.97(2H, t, J=4.5Hz), 4.63(2H, d, J=5.7Hz), 5.28(2H, s), 6.56(2H, m), 7.01(2H, t, J=8.7Hz), 7.38-7.30(5H, m), 7.65(2H, d, J=6.6Hz), 10.63(1H, s).

16) To the compound 17-1 (140mg, 0.293mmol) was added trifluoroacetic acid (1.4ml) under ice-cooling, and the mixture was stirred at 0 °C for 5 minutes and, then, at room temperature for 1.5 hours. The solvent was distilled off under reduced pressure, and this was diluted with chloroform, and added to ice water. This was washed with an aqueous saturated sodium bicarbonate solution, a 10% aqueous citric acid solution and water, and dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was recrystallized with methylene chloride-ethanol to obtain Example A-1 (89mg, 79%) as a yellow crystal.
melting point 223-224 °C
NMR (DMSO-d_6)δ: 3.25(3H, s), 3.58(2H, t, J=5.4Hz), 3.92(2H, t, J=5.1Hz), 4.53(2H, d, J=5.7Hz), 6.87(1H, d, 6.3Hz), 7.14(2H, t, J=9.0Hz), 7.33-7.38(2H, m), 7.47(1H, d, J=6.0Hz), 8.77(1H, s), 10.56(1H, t, J=6.0Hz), 12.00(1H, brs).

17) The compound 17-1 (157mg, 0.329mmol) was dissolved in dimethylformamide (18ml) and methanol (1ml), 10% palladium-carbon powder (31mg) was added, and the mixture was stirred at room temperature for 20 hours under the hydrogen atmosphere. The reaction solution was filtered with Celite, and the filtrate was

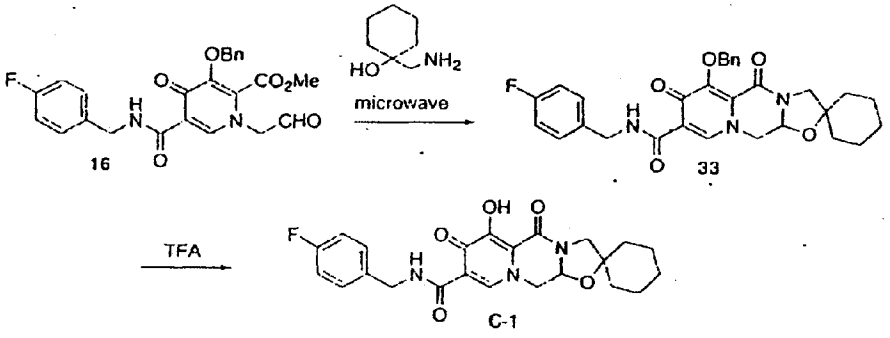
concentrated under reduced pressure. The residue was dissolved in chloroform, this was filtered with Celite again, and the filtrate was concentrated under reduced pressure The residue was recrystallized with methylene chloride-methanol to obtain Example B-1 (66mg, 52%) as a brown crystal.

melting point: 197-199 °C

NMR (DMSO-d_6)δ 3.27(3H, s), 3.55(2H, t, J=5.1Hz), 3.68(2H, t, J=5.1Hz), 3.79(2H, s), 4.36(2H, s), 4.51(2H, d, J=5 7Hz), 7.15(2H, t, J=8.7Hz), 7.32-7 37(2H, m), 8.38(1H, s), 10.46(1H, t, J=5.4Hz), 12.41(1H, s).

Example C-1

[Chemical formula 55]



1) A compound 33 was synthesized using 1 aminomethylcyclopentanol hydroxyethylamine according to the method of synthesizing a compound 17-1

1H-NMR ($CDCl_3$)δ: 1.30-1.80(10H, m), 3.47(1H, d, J=11.4Hz), 3.61(1H, d, J=11.4Hz), 3.80-3.95(1H, m), 4.30(1H, dd, J=14.7, 3.0Hz), 4.60(2H, d, J=5.7Hz), 5.17-5.23(2H, m), 5.39(1H, d, J=9.9Hz), 6.95-7 10(2H, m), 7.20-7.40(5H, m), 7.58(2H, d, J=7.2Hz), 8.41(1H, s), 10 40(1H, s).

2) A compound 33-2 was synthesized using hydroxyethylamine according to the similar method.

Compound 33-2)

5-Benzyloxy-4,6-dioxo-2,3,4,6,9,9a-hexahydro-1-oxa-3a,8a-diaza-cyclopenta[b]naphthalene-7-carboxylic acid 4-fluorobenzylamide

1H-NMR (DMSO-d_6)δ: 3.48-3.58(1H, m), 3.73-3 86(1H, m), 3.97-4.10(2H, m), 4.20-4.30(1H, m), 4.46-4.60(2H, m), 4 85(1H, dd, J=12 3, 3.5Hz), 5.40(1H, d, J=10.2Hz),

5.18(1H, d, J=10.2Hz), 5.28(1H, dd, J=10.2, 3.2Hz), 7 10-7.20(2H, m), 7.23-7.40(5H, m), 7.50-7.73(2H, m), 8.60(1H, s), 10.22(1H, m).

3) Example C-1 was synthesized using a compound 33, according to the method of synthesizing Example A-1

Melting point: >300°C

1H-NMR (DMSO-d_6)δ: 1.10-1.60(10H, m), 3.25(1H, d, J=11.4Hz), 3.37(1H, d, J=11.4Hz), 3.76(1H, t, J=10.5Hz), 4.30(2H, d, J=5.8Hz), 4.66(1H, dd, J=12.2, 3.8Hz), 5.22(1H, dd, J=3.8, 10.4Hz), 6.90-6.96(2H, m), 7.10-7.15(2H, m), 8.25(1H, s), 10.10(1H, brs), 11 32(1H, brs).

The following compounds were synthesized using the similar method.

Example C-2)

5-Hydroxy-4,6-dioxo-2,3,4,6,9,9a-hexahydro-1-oxa-3a,8a-diaza-cyclopenta[b]naphthalene-7-carboxylic acid 4-fluorobenzylamide

Melting point: 272-274 °C

1H-NMR (DMSO-d_6)δ: 3.59-3 67(1H, m), 3.72-3.81(1H, m), 3.98-4.10(2H, m), 4.27-4 35(1H, m), 4 52(2H, d, J=7.2Hz), 4.92(1H, dd, J=12.3, 12.3Hz), 5.27(1H, dd, J=3.6, 9.9Hz), 7.11-7.20(2H, m), 7.30-7.40(2H, m), 8 49(1H, s), 10 32(1H, t, J=5.6Hz), 11.53(1H, s).

Example C-3)

5-Hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-1a,8a-diazaanthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 259 °C

1H-NMR (DMSO-d_6)δ: 1.60-1.67(1H, m), 1 72-1 85(1H, m), 3 25(1H, td, J=12.8, 3.5Hz), 3.86-3.93(1H, m), 4.06(1H, dd, J=11 4, 4 2Hz), 4 44-4.57(5H, m), 5 28(1H, t, J=3 8Hz), 7.13-7.18(2H, m), 7.33-7.37(2H, m), 8 51(1H, s), 10.36(1H, t, J=6.0Hz), 12.47(1H, s).

Example C-4)

5-Hydroxy-1-isopropyl-4,6-dioxo-2,3,4,6,9,9a-hexahydro-1H-1,3a,8a-triaza-cyclopenta[b]naphthalene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 232-234°C

NMR (DMSO-d_6)δ: 1.03(3H, d, 6.6Hz), 1 14(3H, d, 6.6Hz), 2.79-3.66(5H, m), 3 82(1H, t, 10.8Hz), 4.51(3H, m), 4 90(1H, m), 7.15(2H, t, 9 0Hz), 7.34(2H, m), 8.45(1H, s),

10.39(1H, t, 5.4Hz), 11.60(1H, s).

Example C-5)

5-Hydroxy-4,6-dioxo-2,3,4,6,9,9a-hexahydro-1H-1,3a,8a-triaza-cyclopenta[b]naphthalene 7-carboxylic acid 4-fluoro-benzylamide

melting point: 256-258 °C

NMR (DMSO-d_6)δ: 3.00-3.55(5H, m), 3.96(1H, t, 11.4Hz), 4.52(2H, d, 11.7Hz), 4.76(2H, m), 7.16(2H, t, 8.7Hz), 7.36(2H, m), 8.48(1H, s), 10.42(1H, t, 5.4Hz), 11.91(1H, s).

Example C-6)

5-Hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 255°C

NMR (DMSO-d_6)δ: 1.60(1H, s), 2.75-3.16(4H, m), 4.52(2H, d, 6.0Hz), 4.13-4.68(4H, m), 7.16(2H, 9.0Hz, t), 7.34(2H, m), 10.42(1H, s), 10.44(1H, 6.0Hz, t), 12.81(1H, s).

Example C-7)

1-(2-Diethylamino-ethyl)-5-hydroxy-4,6-dioxo-2,3,4,6,9,9a-hexahydro-1H-1,3a,8a-triaza-cyclopenta[b]naphthalene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 186-187 °C

NMR (DMSO-d_6)δ 0.97(6H, t, 7.2Hz), 2.42-2.91(10H, m), 3.44-3.87(5H, m), 4.23(1H, m), 4.51(2H, d, 5.7Hz), 5.00(1H, m), 7.16(2H, t, 9.0Hz), 7.33-7.37(2H, m), 8.43(1H, s), 10.39(1H, t, 5.7Hz), 11.81(1H, s).

Example C-8)

1-Hydroxy-2,11-dioxo-2,5,5a,7,8,9,10,11-octahydro-6-oxa-4a,10a-diaza-cyclohepta[b]naphthalene-3-carboxylic acid 4-fluoro-benzylamide

melting point: 242-244 °C

NMR (DMSO-d_6)δ: 1.40-2.00(4H, m), 3.20-3.30(1H, m), 3.66-3.77(2H, m), 4.14-4.23(1H, m), 4.38-4.41(1H, m), 4.52(2H, d, 6.3Hz), 4.58-4.63(1H, m), 5.34(1H, brs), 7.15(2H, t, 9.0Hz), 7.33-7.37(2H, m), 8.50(1H, s), 10.39(1H, brs), 12.14(1H, s).

Example C-9)

5-Hydroxy-1-(2-hydroxy-ethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

NMR (DMSO-d_6)δ: 1.58-1.80(1H, m), 2.70-3.60(7H, m), 4 40-4.54(6H, m), 4.77-4.82(1H, m), 7.15(2H, t, 9.0Hz), 7.33-7.38(2H, m), 8.52(1H, s), 10.43(1H, brs), 12.57(1H, s).

Example C-10)

1-Hydroxy-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 4-fluoro-benzylamide

melting point: 256°C.

NMR (DMSO-d_6)δ: 1.47-1.77(4H, m), 2.69-2.81(2H, m), 3.34-3 41(1H, m), 4.08-4.12(1H, m), 4.26-4.40(2H, m), 4.52(2H, d, J=6.0Hz), 7.15(2H, t, 8.8Hz), 7.33-7.36(2H, m), 8 43(1H, s), 10 46(1H, t, J=6.0Hz), 12.68(1H, s).

Example C-11)

5-Hydroxy-1-(2-methoxy-ethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 147°C

NMR (DMSO-d_6)δ: 1.56-1.74(2H, m), 2.53-2.58(1H, m), 2.66-3.10(4H, m), 3.18(3H, s), 3.41-3.39(2H, m), 4.37-4.52(5H, m), 4.73-4.80(1H, m), 7.15(2H, t, 8.8Hz), 7.33-7.37(2H, m), 8.56(1H, s), 10 40(1H, t, J=6.0Hz), 12 62(1H, s).

Example C-12)

5-Hydroxy-1-(2-isopropoxy-ethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene 7-carboxylic acid 4-fluoro-benzylamide

melting point: 151 °C

NMR (DMSO-d_6)δ 1.02(6H, dd, J=4.0, 6.0Hz), 1.56-1.67(2H, m), 2.53-2.58(1H, m), 2.74-3.04(1H, m), 3.18(3H, s), 3.41-3.52(3H, m), 4.41-4.59(5H, m), 4.79-4.83(1H, m), 7.15(2H, t, 8.8Hz), 7.34-7 36(2H, m), 8.56(1H, s), 10.40(1H, t, J=6.0Hz), 12.56(1H, s)

Example C-13)

5-Hydroxy 3,3-dimethyl 6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H 1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 275-277 °C

NMR (DMSO-d_6)δ: 2.97(3H, s), 3.01(3H, s), 3.00-3 18(3H, m), 4.45-4.56(5H, m), 5.16(1H, s), 7 15(2H, t, J=9Hz), 7.35(2H, dd, J=5.4Hz, 8.7Hz), 8.51(1H, s), 10.36(1H, t, J=5.7Hz), 12.4(1H, s).

Example C-14)

1-Cyclohexyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid-4-fluoro-benzylamide

melting point: 275-277 °C

NMR (DMSO-d_6)δ 1.22-1.70(2H, m), 2.50-3.02(3H, m), 4.45(4H, m), 4.52(2H, s), 4.78(1H, d, J=13.2Hz), 7.16(2H, t, J=8.7Hz), 7.35(2H, dd, J=5.7Hz, 8.4Hz), 8.62(1H, s), 10.52(1H, s), 12.55(1H, s)

Example C-15)

5-Hydroxy-1-isopropyl-6,10-dioxo-1,2,3,4,6,9,9a,10-oxtahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid-4-fluoro-benzylamide

melting point: 220 °C

NMR (DMSO-d_6)δ: 0.94(6H, d, J=9.6Hz), 1.53-1.67(2H, m), 2.92-3.30(3H, m), 4.32-4.40(4H, m), 4.52(2H, d, J=5.7Hz), 4.89(1H, d, J=14.1Hz), 7.16(2H, t, J=9.0Hz), 7.35(2H, dd, J=6.3Hz, 9.0Hz), 8.61(1H, s), 10.46(1H, s), 12.55(1H, s).

Example C-16)

5-Hydroxy-3,3-dimethyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 280 °C

NMR (DMSO-d_6)δ: 0.87(3H, s), 0.93(3H, s), 2.59-3.15(6H, m), 4.09-4.57(6H, m), 7.14(2H, d, J=9.0Hz), 7.34(2H, dd, J=5.4Hz, 8.4Hz), 8.42(1H, s), 10.46(1H, s), 12.77(1H, s).

Example C-17)

5-Hydroxy-1-(2-morpholin-4-yl-2-oxo-ethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 140 °C

NMR (DMSO-d_6)δ: 1.60(2H, m), 2.91-3.62(13H, m), 4.41(2H, m), 4.51(2H, d, J=4.8Hz), 4.80(2H, m), 7.15(2H, t, J=8.7Hz), 7.34(2H, m), 8.44(1H, s), 10.43(1H, s), 12.54(1H, s).

Example C-18

1-(3-Acetylamino-propyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 177-178 °C

NMR (DMSO-d_6)δ: 1.74(3H, s), 1.49-2.98(9H, m), 3.60(1H, s), 4.25-4.65(7H, m), 7.14(2H, t, J=8.4Hz), 7.34(2H, m), 7.71(1H, s), 8.26(1H, s), 10.60(1H, s).

Example C-19)

1-Dimethycarbamoylmethyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 190 °C

NMR (DMSO-d_6)δ: 1.60(2H, m), 2.76(3H, s), 2.83(3H, s), 2.90-3.59(5H, s), 4.40(2H, m), 4.51(2H, d, 5.7Hz), 4.80(1H, d, d=14.4Hz), 4.98(1H, s), 7.16(2H, t, J=8.4Hz), 7.34(2H, m), 8.54(1H, s), 10.42(1H, s).

Example C-20)

5-Hydroxy-1-(3-methanesulfonylamino-propyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 176 °C

NMR (DMSO-d_6)δ: 1.54-1.75(4H, m), 2.80(3H, s), 2.30-3.04(8H, m), 4.45(2H, m), 4.52(2H, d, J=5.6Hz), 4.75(1H, d, J=13.2Hz), 6.91(1H, t, J=5.6Hz), 7.16(2H, t, J=8.8Hz), 7.36(2H, m), 8.61(1H, s), 10.41(1H, t, J=5.6Hz), 12.58(1H, s).

Example C-21)

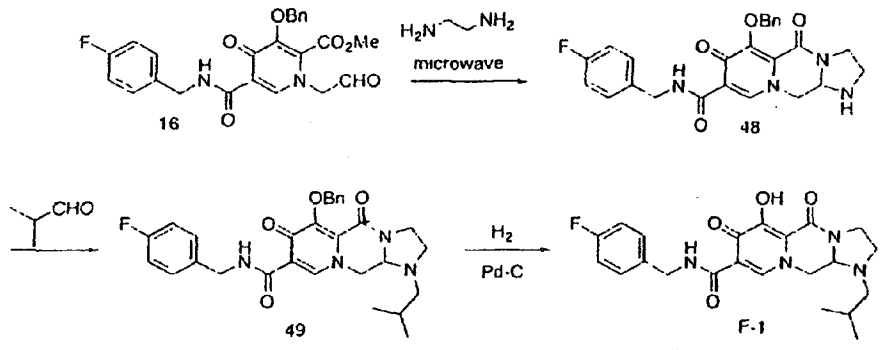
5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-dizazaanthracene-7-carboxylic acid 4-fluorobenzylamide

NMR (CDCl3)δ: 1.27(3H, d, J=6.0Hz), 1.55-1.78(2H, m), 3.11(1H, td, J=12.9, 3.7Hz), 3.89-4.00(1H, m), 4.16(1H, dd, J=13.8, 3.9Hz), 4.31(1H, dd, J=13.8, 3.9Hz), 4.60(2H, d, J=6.0Hz), 4.71(1H, ddd, J=13.5, 4.8, 1.8Hz), 5.08(1H, t, J=3.9Hz), 6.96-7.04(2H, m), 7.26-7.35(2H, m), 8.32(1H, s), 10.41(1H, br s), 12.41(1H, br s).

Example F-1)

5-Hydroxy-1-isobutyl-4,6-dioxo-2,3,4,6,9,9a-hexahydro-1H-1,3a,8a-triazacyclopenta[b]naphthalene-7-carboxylic acid-4-fluorobenzylamide

[Chemical formula 59]



1) According to the method of synthesizing a compound 17-1, the crude purified product (503mg) of a compound 48 was obtained at a yield of 82% from a compound 16 (600mg)

2) To a solution of a compound 48 (100mg, 0 22mmol), isobutylaldehyde (39μl, 0.432mmol) and acetic acid (25μl, 0.432mmol) in dichloromethane (4ml) was added sodium triacetoxyborohydride (92mg, 0.432mmol) under ice-cooling, and the mixture was stirred at room temperature for 2 hours Further, isobutylaldehyde (20μl) and sodium triacetoxyborohydride (46mg) were added, and the mixture was stirred for 30 minutes. To the reaction solution was added water, this was extracted with chloroform, and the organic layer was washed with an aqueous saturated sodium bicarbonate solution. After drying, the solvent was distilled off under reduced pressure, and this was purified by silica gel column chromatography. A compound 49 (87mg) was obtained as a colorless crystal at a yield of 78%.
1H-NMR ($CDCl_3$)δ: 0.96(3H, d, J=6.6Hz), 0.97(3H, d, J=6.3Hz), 1.72-1.86(1H, m), 2.25-2.41(2H, m), 2.47-2.58(1H, m), 3.39-3.46(1H, m), 3.69-3.76(2H, m), 3.85-3.93(1H, m), 4.06(1H, dd, J=9.9, 2.7Hz), 4.16-4 22(1H, m), 4 57(1H, dd, J=15.3, 5.1Hz), 4.64(1H, dd, J=14.7, 5 1Hz), 5.20(1H, d, J=9.9Hz), 5 38(1H, d, J=9.9Hz), 6.96-7.05(2H, m), 7.28-7 36(5H, m), 7.58-7.62(2H, m), 8.40(1H, s), 10.44(1H, br s).

3) According to the method of a step 17) of Example B-1, a compound F-1 (43mg) was obtained at a yield of 64% from a compound 49 (81mg).
1H-NMR (DMSO-d_6)δ: 0 90(3H, d, J=6.4Hz), 0.91(3H, d, J=6.0Hz), 1.75-1.84(1H, m), 2.24-2.39(1H, m), 2.39-2.54(2H, m), 3.36-3.43(1H, m), 3.52-3.60(1H, m), 3.67-3 73(1H, m), 3 81-3 88(1H, m), 4.19-4.23(1H, m), 4.52(2H, d, J=6.0Hz), 4.94-4.99(1H, m),

7 12-7.20(2H, m), 7.32-7.38(2H, m), 8.45(1H, s), 10.37(1H, t, J=2.0Hz), 11.74(1H, s).

According to the same manner as that of Example F-1, the following Example compounds F-2 to F-63 were synthesized

Example F-2)

5-Hydroxy-1-isobutyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 146-148 °C

1H-NMR (DMSO-d_6)δ: 0.63(3H, d, J=6.6Hz), 0.79(3H, d, J=6.6Hz), 1.56-1.66(2H, m), 1.67-1.75(1H, m), 1 94-1.99(1H, m), 2.41-2.54(2H, m), 2.96-3.06(2H, m), 4.41-4.59(5H, m), 4.76-4.81(1H, m), 7.14-7 21(2H, m), 7.33-7.38(2H, m), 8.61(1H, s), 10.40(1H, d, J=5.8Hz), 12.56(1H, s).

Example F-3)

1-Cyclopropylmethyl-5-hydroxy 6,10 dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 182-184 °C

NMR (DMSO-d_6)δ: 0 06(2H, m), 0.43(2H, d, 8.4Hz), 0.80(1H, m), 1.66(2H, m), 2 28-3 30(4H, m), 4 40-4 50(4H, m), 4 52(2H, d, 6.0Hz), 4.78(2H, m), 7.15(2H, t, 8 7Hz), 7.34(2H, m), 8.55(1H, s), 10.47(1H, s), 12.55(1H, s)

Example F-4)

1-Cyclopentylmethyl-5-hydroxy-6,1-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 184-185 °C°C

NMR (DMSO-d_6)δ: 0 88-2.10(1H, m), 2.60(2H, m), 2.95-3.28(2H, m), 4.38-4.53(6H, m), 4.82(1H, m), 7.15(2H, t, 9 0Hz), 7 34(2H, m), 8.57(1H, s), 10.42(1H, s), 12.45(1H, s).

Example F-5)

5-Hydroxy-1-(1-methylsulfanylbenzyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

(DMSO-d_6)δ: 1.51-1.56(1H, m), 1.69-1.74(1H, m), 2.42(3H, s), 2.55-2.62(1H, m), 2.80-2.84(1H, m), 3.00-3 08(1H, m), 3.32-3 36(1H, m), 3.93(1H, d, J=13.6Hz), 4.45-4.53(4H, m), 4 58(1H, s), 4 83(1H, d, J=15.2Hz), 7 11-7.19(6H, m), 7 33-7 40(2H, m), 8 34(1H, s), 10.38(1H, t, J=6.0Hz), 12.58(1H, s).

Example F-6)

1-(5-Chloro-1,3-dimethyl-1H-pyrazol-4-ylmethyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

(DMSO-d_6)δ: 1.56-1.59(2H, m), 1.88(3H, s), 2.37-2.45(1H, m), 2.76-2.80(1H, m), 3.00-3.06(2H, m), 3.64(3H, s), 3.87(1H, d, J=13.2Hz), 4.40-4.55(5H, m), 4.97(1H, d, J=14.4Hz), 7.13-7.19(2H, m), 7.33-7.38(2H, m), 8.56(1H, s), 10.39(1H, t, J=6.0Hz), 12.46(1H, s).

Example F-7)

5-Hydroxy-1-(3-methoxybenzyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

(DMSO-d_6)δ: 1.52-1.57(1H, m), 1.70-1.80(1H, m), 2.60-2.68(1H, m), 2.84-2.90(1H, m), 3.01-3.09(1H, m), 3.36(1H, d, J=14.0Hz), 3.61(3H, s), 3.91(1H, d, J=14.0Hz), 4.45-4.52(4H, m), 4.58(1H, s), 4.76(1H, d, J=14.8Hz), 6.68-6.73(2H, m), 6.77(1H, d, J=7.6Hz), 7.13-7.19(3H, m), 7.33-7.38(2H, m), 8.17(1H, s), 10.38(1H, t, J=6.0Hz), 12.57(1H, s).

Example F-8)

5-Hydroxy-1-(4-methanesulfonylbenzyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

(DMSO-d_6)δ: 1.54-1.58(1H, m), 1.74-1.80(1H, m), 2.67-1.74(1H, m), 2.83-2.87(1H, m), 3.05-3.12(1H, m), 3.18(3H, s), 3.52(1H, d, J=14.8Hz), 4.09(1H, d, J=14.8Hz), 4.46-4.52(4H, m), 4.67(1H, s), 4.73(1H, d, J=14.8Hz), 7.12-7.18(2H, m), 7.32-7.36(2H, m), 7.46(2H, m), 7.80(2H, d, J=8.0Hz), 8.17(1H, s), 10.37(1H, t, J=5.8Hz), 12.59(1H, s).

Example F-9)

5-Hydroxy-1-(6-methoxypyridin-3-ylmethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

(DMSO-d_6)δ: 1.51-1.56(1H, m), 1.71-1.77(1H, m), 2.58-2.66(1H, m), 2.80-2.86(1H, m), 3.01-3.09(1H, m), 3.38(1H, d, J=13.6Hz), 3.78(3H, s), 3.87(1H, d, J=13.6Hz), 4.45-4.52(4H, m), 4.60(1H, s), 4.82(1H, d, J=13.6Hz), 6.71(1H, d, J=8.6Hz), 7.12-7.19(2H, m), 7.33-7.38(2H, m), 7.49(1H, d, J=8.6Hz), 7.98(1H, s), 8.30(1H, s), 10.37(1H, t, J=6.0Hz), 12.58(1H, s).

Example F-10)

5-Hydroxy-1-isobutyl-3,3-dimethyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

(DMSO-d_6)δ: 0.64(3H, d, J=6.4Hz), 0.82(3H, d, J=6.8Hz), 0.90(3H, s), 0.91(3H, s), 1.59-1.67(1H, m), 1.92-1.97(1H, m), 2.11-2.15(1H, m), 2.51-2.57(1H, m), 2.67(1H, d, J=12.0Hz), 2.77(1H, d, J=12.8Hz), 4.13(1H, s), 4.21(1H, d, J=12.8Hz), 4.47-4.59(3H, s), 4.80(1H, dd, J=14.4, 2.8Hz), 7.14-7.19(2H, m), 7.34-7.38(2H, m), 8.66(1H, s), 10.41(1H, t, J=6.0Hz), 12.44(1H, s).

Example F-11)

5-Hydroxy-1,3,3-trimethyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

(DMSO-d_6)δ: 0.89(6H, s), 2.14-2.18(1H, m), 2.24(3H, s), 2.54-2.58(1H, m), 2.74-2.78(1H, s), 3.88(1H, s), 4.21(1H, d, J=13.2Hz), 4.45-4.53(3H, m), 4.72-4.76(1H, m), 7.13-7.19(2H, m), 7.33-7.38(2H, m), 8.64(1H, s), 10.40(1H, t, J=6.0Hz), 12.46(1H, s)

Example F-12)

4-[7-(4-Fluorobenzylcarbamoyl)-5-hydroxy-6,10-dioxy-3,4,6,9,9a,10-hexahydro-2H-1,4a,8a-triazaanthracene-1-yl]butanoic acid ethyl ester

($CDCl_3$)δ: 1.23(3H, t, J=7.1Hz), 1.70-1.79(1H, m), 1.86-2.00(1H, m), 2.17-2.34(2H, m), 2.46-2.57(1H, m), 2.61-2.77(2H, m), 2.85-2.92(1H, m), 3.13-3.18(1H, m), 4.13(2H, q, J=7.1Hz), 4.27-4.34(2H, m), 4.57-4.63(3H, m), 4.66-4.73(1H, m), 6.95-7.03(2H, m), 7.29-7.36(2H, m), 8.36(1H, s), 10.48(1H, t, J=4.8Hz), 12.50(1H, s)

Example F-13)

1-(3-Dimethylcarbamoylpropyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

($CDCl_3$)δ: 1.62-1.82(3H, m), 1.83-2.00(1H, m), 2.10-2.35(2H, m), 2.57-2.65(2H, m), 2.75-2.95(2H, m), 2.92(3H, s), 2.96(3H, s), 3.07-3.14(1H, m), 4.23-4.30(2H, m), 4.60(2H, d, J=6.0Hz), 4.68(1H, dd, J=13.2, 4.5Hz), 5.12(1H, d, J=12.6Hz), 6.95-7.02(2H, m), 7.28-7.35(2H, m), 8.42(1H, s), 10.54(1H, t, J=5.4Hz), 12.51(1H, s)

Example F-14)

5-Hydroxy-1-(4-morpholin-4-yl-4-oxobutyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

($CDCl_3$)δ: 1.61-1.83(3H, m), 1.84-2.00(1H, m), 2.12-2.23(1H, m), 2.25-2.36(1H, m), 2.56-2.64(2H, m), 2.75-2.95(2H, m), 3.09-3.15(1H, m), 3.37(2H, t, J=4.8Hz), 3.61-3.66(6H, m), 4.26-4.32(2H, m), 4.59(2H, d, J=5.7Hz), 4.68(1H, dd, J=13.2, 4.5Hz), 4.95-5.01(1H, m), 6.95-7.03(2H, m), 7.28-7.35(2H, m), 8.40(1H, s), 10.52(1H, t, J=5.7Hz), 12.51(1H, s)

Example F-15)

5-Hydroxy-1-methyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 252-253°C

(DMSO-d_6)δ: 1.56-1.75(2H, m), 2.22(3H, s), 2.50-2.55(1H, m), 2.90-3.10(2H, m), 4.17(1H, brs), 4.39-4.42(2H, m), 4.52(2H, d, J=6.0Hz), 4.74-4.78(1H, m), 7.13-7.17(2H, m), 7.33-7.37(2H, m), 8.61(1H, s), 10.40(1H, t, J=6.0Hz), 12.54(1H, s).

Example F-16)

5-Hydroxy-6,10-dioxo-1-thiophen-3-ylmethyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 242-243°C

(DMSO-d_6)δ: 1.52-1.73(2H, m), 2.59-2.62(1H, m), 2.87-3.03(2H, m), 3.52(1H, d, J=13.6Hz), 3.90(1H, d, J=14.4Hz), 4.40-4.56(5H, m), 4.83-4.90(1H, m), 6.92(1H, d, J=5.2Hz), 7.13-7.17(2H, m), 7.28-7.37(3H, m), 7.42-7.44(1H, m), 8.46(1H, s), 10.39(1H, t, J=6.0Hz), 12.58(1H, s)

Example F-17)

5-Hydroxy-6,10-dioxo-1-thiazol-2-ylmethyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

melting point 214-215°C

(DMSO-d_6)δ: 1.54-1.72(2H, m), 2.75-2.81(1H, m), 2.95-3.07(2H, m), 3.80(1H, d, J=16.0Hz), 4.37(1H, d, J=16.4Hz), 4.44-4.51(4H, m), 4.69(1H, brs), 4.89-4.93(1H, m), 7.13-7.17(2H, m), 7.32-7.35(2H, m), 7.55(1H, d, J=3.2Hz), 7.69(1H, d, J=3.2Hz), 8.37(1H, s), 10.36(1H, t, J=6.0Hz), 12.50(1H, s).

Example F-18)

5-Hydroxy-(3-methylsulfanyl-propyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 162-164°C

(DMSO-d_6)δ 1.50-1.82(4H, m), 2.27(3H, s), 2.32-2.44(3H, m), 2.60-2.82(2H, m), 3.00-3.14(2H, m), 4.37-4.59(5H, m), 4.75-4.79(1H, m), 7.13-7.17(2H, m), 7.33-7.35(2H, m), 8.60(1H, s), 10.40(1H, t, J=6.0Hz), 12.57(1H, s)

Example F-19)

5-Hydroxy-6,10-dioxo-1-pyridin-4-ylmethyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 180-183°C

(DMSO-d_6)δ: 1.52-1.76(2H, m), 2.62-2.80(2H, m), 3.01-3.07(1H, m), 3.42(1H, d, J=15.2Hz), 4.05(1H, d, J=15.2Hz), 4.49-4.50(4H, m), 4.64(1H, brs), 4.78-4.81(1H, m), 7.12-7.21(4H, m), 7.32-7.36(2H, m), 8.33(1H, s), 8.42(2H, d, J=4.4Hz), 10.39(1H, t, J=6.0Hz), 12.55(1H, s)

Example F-20)

1-Cyclohexylmethyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 201-202°C

(DMSO-d_6)δ: 0.56-0.59(1H, m), 0.87-0.84(1H, m), 1.02-1.13(3H, m), 1.23-1.29(1H, m), 1.49-1.70(6H, m), 1.92-1.97(1H, m), 2.52-2.55(1H, m), 2.96-3.03(2H, m), 4.40-4.43(3H, m), 4.52(2H, d, J=6.0Hz), 4.73-4.77(1H, m), 7.12-7.16(2H, m), 7.32-7.36(2H, m), 8.59(1H, s), 10.40(1H, t, J=5.2Hz), 12.58(1H, s)

Example F-21)

5-Hydroxy-6,10-dioxo-1-pyridin-2-ylmethyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 216-219°C

(DMSO-d_6)δ: 1.52-1.76(2H, m), 2.66-2.80(1H, m), 2.90-3.07(2H, m), 3.67(1H, d, J=15.2Hz), 4.01(1H, d, J=13.2Hz), 4.37-4.97(4H, m), 4.62(1H, brs), 4.85-4.88(1H, m), 7.07-7.25(4H, m), 7.33-7.36(2H, m), 7.61-7.68(1H, m), 8.26(1H, s), 8.45(1H, s), 10.36(1H, t, J=6.0Hz), 12.57(1H, s)

Example F-22)

1-(2-Ethyl-butyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 137-140°C

(DMSO d_6)δ: 0.62(3H, t, J=7.2Hz), 0.77(3H, t, J=7.2Hz), 0.99-1.30(5H, m), 1.57-1.71(2H, m), 1.97-2.02(1H, m), 2.44-2.58(2H, m), 3.02-3.32(2H, m), 4.34-4.57(5H, m), 4.78-4.82(1H, m), 7.13-7.17(2H, m), 7.32-7.36(2H, m), 8.60(1H, s), 10.39(1H, t, J=5.2Hz), 12.54(1H, s).

Example F-23)

5-Hydroxy-1-(2-morpholin-4-ylethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 254-256°C

(DMSO-d_6)δ: 1.55-1.68(2H, m), 2.28-2.39(8H, m), 2.59-2.65(1H, m), 2.82-3.09(3H, m), 3.33-3.58(5H, m), 4.34-4.50(3H, m), 4.52(2H, d, J=5.2Hz), 4.79-4.84(1H, m), 7.12-7.17(2H, m), 7.32-7.36(2H, m), 8.52(1H, s), 10.45(1H, t, J=5.2Hz), 12.55(1H, s)

Example F-24)

1-Hydroxy-6-methyl-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 4-fluorobenzylamide

melting point: 255°C

(DMSO-d_6)δ: 1.48-1.55(1H, m), 1.67-1.80(3H, m), 2.29(3H, s), 2.75-2.80(2H, m), 3.23-3.31(1H, m), 4.07-4.09(1H, m), 4.36-4.40(1H, m), 4.45-4.59(3H, m), 4.68-4.69(1H, m), 7.13-7.17(2H, m), 7.30-7.37(2H, m), 8.50(1H, s), 10.42(1H, t, J=6.0Hz), 12.42(1H, s).

Example F-25)

1-Hydroxy-6-isobutyl-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 4-fluorobenzylamide

melting point: 221-223°C

DMSO-d_6)δ 0.81(3H, d, J=6.8Hz), 0.84(3H, d, J=6.4Hz), 1.45-1.78(5H, m), 2.36-2.54(2H, m), 2.27-2.93(2H, m), 3.17-3.23(1H, m), 4.03-4.06(1H, m), 4.32-4.56(1H, m), 4.82-4.85(1H, m), 7.13-7.17(2H, m), 7.30-7.37(2H, m), 8.48(1H, s), 10.42(1H, t, J=6.0Hz), 12.53(1H, s)

Example F-26)

6-Cyclopropylmethyl-1-hydroxy-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 4-fluorobenzylamide

melting point 213°C

DMSO d_6)δ: 0.15-0.26(2H, m), 0.16-0.48(2H, m), 0.86-1.06(1H, m), 1.45-1.75(4H, m), 2.45-2.65(1H, m), 2.68-2.83(1H, m), 2.91-2.98(2H, m), 3.17-3.26(1H, m), 4.03-4.14(1H, m), 4.43-4.45(2H, m), 4.54(2H, d, J=5.6Hz), 4.89-4.91(1H, m), 7.15-7.19(2H, m), 7.35-7.39(2H, m), 8.50(1H, s), 10.47(1H, t, J=6.0Hz), 12.52(1H, s).

Example F-27)

1-Furan-2-ylmethyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 193-197°C

DMSO-d_6)δ: 1.67(2H, m), 2.61(1H, s), 2.93(2H, m), 3.75(1H, d, J=14.8Hz), 3.84(1H, d, J=14.8Hz), 4.34-4.47(3H, m), 4.52(2H, d, J=6.0Hz), 4.96(1H, d, J=14.8Hz), 6.36(2H, s), 7.16(2H, t, J=8.8Hz), 7.35(2H, m), 7.59(1H, s), 8.97(1H, s), 10.43(1H, s), 12.51(1H, s)

Example F-28)

1-(4-Dimethylamino-benzyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 221-223°C

DMSO-d_6)δ: 1.55-1.99(2H, m), 2.87(6H, s), 2.87-3.06(4H, m), 3.80(1H, d, J=14.0Hz), 4.50(5H, m), 4.83(1H, d, J=14.0Hz), 6.58(2H, d, J=9.6Hz), 6.98(2H, d, J=8.8Hz), 7.15(2H, t, J=8.8Hz), 7.35(2H, m), 8.31(1H, s), 10.39(1H, s), 12.58(1H, s)

Example F-29)

5-Hydroxy-6,10-dioxo-1-(4-trifluoromethyl-benzyl)-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 273-277°C

DMSO-d_6)δ: 1.52-1.70(2H, m), 2.63-3.04(3H, m), 3.50(1H, d, J=14.8Hz), 4.10(1H, d, J=14.8Hz), 4.54(5H, m), 4.79(1H, d, J=14.8Hz), 7.14(2H, t, J=8.8Hz), 7.33(2H, m), 7.55(2H, d, J=6.8Hz), 7.61(2H, d, J=8.0Hz), 8.22(1H, s), 10.40(1H, s), 12.56(1H, s).

Example F-30)

5-Hydroxy-6,10-dioxo-1-pyridin-3-ylmethyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 210-212°C

DMSO-d_6)δ: 1.51-1.76(2H, m), 2.63(1H, t, J=12.8Hz), 2.80(1H, d, J=12.0Hz), 3.07(1H, t,

J=12.8Hz), 3.44(1H, d, J=13.2Hz), 4.00(1H, d, 11.0Hz), 4 47(4H, m), 4.62(1H, s), 4.84(1H, d, J=14 0Hz), 7.16(2H, t, J=8.8Hz), 7.33(2H, m), 7.58(1H, d, J=7.6Hz), 8.30(1H, s), 8 45(2H, s), 10 41(1H, s), 12.57(1H, s)

Example F-31)

1-(2-Chloro-6-fluoro-benzyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 213-215°C

DMSO-d_6)δ:1.58(2H, 2H), 2 55-3.09(3H, m), 3.45(1H, d, J=12.4Hz), 4.16(1H, d J=12.4Hz), 4 40-4.58(4H, m), 5.12(1H, d, J=14 4Hz), 7.15-7 38(7H, m), 8 66(1H, s), 10.41(1H, t, J=6.4Hz), 12.46(1H, s).

Example F-32)

5-Hydroxy-1-(4-methoxy benzyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 191-193°C

NMR (DMSO-d_6)δ:1.50-1 77(2H, m), 2 58 3 06(3H, m), 3 68(3H, s), 3 88(1H, d, J=13.6Hz), 4.41-1.55(4H, m), 4.80(2H, d, J=14 4Hz), 6.80(2H, d, J=8.8Hz), 7.09(2H, d, J=8.4Hz), 7.15(2H, t, J=8.8Hz), 7 35(2H, m), 8.28(1H, s), 10.48(1H, s), 12.58(1H, s).

Example F-33)

1-(3,5-Bis-trifluoromethyl-benzyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluorobenzylamide

melting point: 275-277°C

NMR (DMSO-d_6)δ:1 58-1 88(2H, m), 2.51-3 14(3H, m), 3 33-4.10(3H, m), 4 51(2H, m), 4.73(1H, m), 7.15(2H, m), 7.34(2H, m), 7.82-7 93(4H, m), 10.31(1H, s), 12.57(1H, s)

Example F-34)

1-(4-Diethylamino-benzyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluorobenzylamide

melting point 182°C

NMR (DMSO-d_6)δ- 1 04(6H, t, J=6 8Hz), 1 50-1 69(2H, m), 2 55-3 05(3H, m), 3 26(4H, q, J=7.2Hz), 3.80(1H, d, J=13.6Hz), 4.44-4.57(4H, m), 4.91(1H, d, J=12 4Hz), 6.52(2H, d, J=8.8Hz), 6 94(2H, d, J=8.4Hz), 7.15(2H, t, J=8.4Hz), 7 35(2H, m), 8.46(1H, s), 10 41(1H, s), 12.60(1H, s)

Example F-35)

5-Hydroxy-1-((E)-2-methyl-but-2-enyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 175-177°C

NMR (DMSO-d_6)δ: 1.35(3H, s), 1.51(3H, d, J=6.0Hz), 1.52-1.69(3H, m), 2.60-3.15(3H, m), 4.31-4.52(5H, m), 4.67-4.76(1H, m), 5.30-5.40(1H, m), 7.15(2H, t, J=8.4Hz), 7.28-43(2H, m), 8.46(1H, s), 10.39(1H, brs), 12.60(1H, s).

Example F-36)

1-(3-Dimethylamino-2-methyl-propyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

NMR (DMSO-d_6)δ: 0.63-0.68(2H, m), 1.57-1.82(3H, m), 2.11-2.49(10H, m), 2.98-3.11(2H, m), 4.41-4.54(5H, m), 4.73-4.80(1H, m), 7.14-7.18(2H, m), 7.31-7.38(2H, m), 8.58(1H, s), 10.40(1H, s), 12.57(1H, s).

Example F-37)

1-(3,3-Dimethyl-butyl)-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point 175-177°C

NMR (DMSO-d_6)δ: 1.19-1.36(2H, m), 1.57-1.70(2H, m), 2.23-2.30(1H, m), 2.51-2.69(2H, m), 2.97-3.04(2H, m), 4.42-4.54(5H, m), 4.78(1H, d, J=14.0Hz), 7.13-7.17(2H, m), 7.33-7.36(2H, m), 8.63(1H, s), 10.39(1H, t, J=6.0Hz), 12.56(1H, s).

Example F-38)

1-Ethyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 221°C

NMR (DMSO-d_6)δ: 0.94(3H, t, J=6.8Hz), 1.56-1.71(2H, m), 2.45-2.50(1H, m), 2.59-2.76(2H, m), 2.96-3.03(2H, m), 4.40-4.44(3H, m), 4.52(2H, d, J=6.0Hz), 4.77-4.82(1H, m), 7.14-7.18(2H, m), 7.34-7.38(2H, m), 8.62(1H, s), 10.41(1H, t, J=6.0Hz), 12.59(1H, s)

Example F-39)

5-Hydroxy-6,10-dioxo-1-(2-oxo propyl) 1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anth

racene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 244-246°C

NMR (DMSO-d_6)δ 1.54-1.61(1H, m), 1.67-1.76(1H, m), 2.22(3H, s), 2.50-2.56(1H, m), 2.91-3.02(2H, m), 4.18(1H, s), 4.38-4.45(2H, m), 4.52(2H, d, J=6.0Hz), 4.76(1H, d, J=14.4Hz), 7.13-7.18(2H, m), 7.34-7.37(2H, m), 8.61(1H, s), 10.40(1H, t, J=6.0Hz), 12.54(1H, s).

Example F-40)

5-Hydroxy-6,10-dioxo-1-(4,4,4-trifluoro-butyl)-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 220°C

NMR (DMSO-d_6)δ 1.53-1.62(2H, m), 1.67-1.75(1H, m), 2.07-2.18(2H, m), 2.40-2.47(1H, m), 2.64-2.78(2H, m), 2.96-3.04(2H, m), 4.42-4.49(2H, m), 4.53(2H, d, J=5.2Hz), 4.74(1H, d, J=12.8Hz), 7.13-7.17(2H, m), 7.33-7.37(2H, m), 8.61(1H, s), 10.40(1H, t, J=6.0Hz), 12.57(1H, s).

Example F-41)

5-Hydroxy-1-(3-methyl-butyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

melting point: 151°C

NMR (DMSO-d_6)δ 0.78(6H, dd, J=7.6, 16.2Hz), 1.21-1.28(2H, m), 1.41-1.48(1H, m), 1.56-1.71(2H, m), 2.22-2.31(1H, m), 2.51-2.59(1H, m), 2.66-2.73(1H, m), 2.96-3.05(2H, m), 4.41-4.55(5H, m), 4.80(1H, d, J=13.2Hz), 7.13-7.18(2H, m), 7.33-7.37(2H, m), 8.64(1H, s), 10.40(1H, t, J=6.0Hz), 12.57(1H, s).

Example F-42)

5-Hydroxy-1-isobutyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 3-chloro-2-fluoro-benzylamide

melting point: 180-182°C

NMR (DMSO-d_6)δ 0.62(3H, d, J=6.0Hz), 0.78(3H, d, J=6.4Hz), 1.55-1.69(3H, m), 1.93-1.99(1H, m), 2.97-3.08(2H, m), 1.39-1.46(3H, m), 4.59-4.64(2H, m), 4.75-4.81(1H, m), 7.16-7.23(1H, m), 7.27-7.34(1H, m), 7.47-7.53(1H, m), 8.59(1H, s), 10.44(1H, s), 12.57(1H, s)

Example F-43)

1-Cyclopropylmethyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 3-chloro-2-fluoro-benzylamide

melting point: 189-192°C

NMR (DMSO-d_6)δ: 0.00-0.10(2H, m), 0.35-0.41(2H, m), 0.70-0.77(1H, m), 1.57-1.69(2H, m), 2.52-2.65(1H, m), 2.67-2.85(1H, m), 2.91-2.99(1H, m), 4.30-4.41(2H, m), 4.48-4.52(2H, m), 4.71-4.80(1H, m), 7.06-7.10(1H, m), 7.18-7.22(1H, m), 7.36-7.40(1H, m), 8.52(1H, s), 10.30(1H, s), 12.26(1H, s).

Example F-44)

1-Furan-2-ylmethyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 3-chloro-2-fluoro-benzylamide

melting point: 190-192°C

NMR (DMSO-d_6)δ: 1.56-1.68(2H, m), 2.54-2.63(1H, m), 2.89-2.99(2H, m), 3.80(2H, dd, J=18.4, 33.2Hz), 4.37-4.51(3H, m), 4.62(2H, d, J=6.0Hz), 4.97(1H, d, J=15.2Hz), 6.39(2H, s), 7.18-7.22(1H, m), 7.31-7.34(1H, m), 7.48-7.51(1H, m), 7.58(1H, s), 8.64(1H, s), 10.45(1H, t, J=6.0Hz), 12.55(1H, s).

Example F-45)

5-Hydroxy-6,10-dioxo-1-thiazol-2-ylmethyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 3-chloro-2-fluoro-benzylamide

melting point: 217-219°C

NMR (DMSO-d_6)δ: 1.59-1.74(2H, m), 2.76-2.83(1H, m), 2.97-3.08(2H, m), 3.90(1H, d, J=16.0Hz), 4.36(1H, d, J=16.0Hz), 4.45-4.69(5H, m), 4.89(1H, d, J=14.8Hz), 7.18-7.22(1H, m), 7.28-7.31(1H, m), 7.47-7.53(1H, m), 7.54(1H, d, J=3.2Hz), 7.68(1H, d, J=3.2Hz), 8.34(1H, s), 10.40(1H, d, J=6.0Hz), 12.52(1H, s)

Example F-46)

5-Hydroxy-6,10-dioxo-1-pyridin-2-ylmethyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 3-chloro-2-fluoro-benzylamide

melting point: 190-193°C

NMR (DMSO-d_6)δ: 1.54-1.61(1H, m), 1.69-1.75(1H, m), 2.66-2.74(1H, m), 2.91-3.08(2H, m), 3.68(1H, d, J=14.4Hz), 4.02(1H, d, J=14.8Hz), 4.40-4.67(5H, m), 4.85(1H, d, J=12.4Hz), 7.16-7.35(3H, m), 7.46-7.52(1H, m), 7.61-7.69(1H, m), 8.20(1H, s), 8.43-8.47(1H, m), 10.41(1H, d, J=6.0Hz), 12.58(1H, s)

Example F-47)

5-Hydroxy-1-isobutyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 2,4 difluoro-benzylamide

melting point: 194°C

NMR (DMSO-d_6)δ: 0 62(3H, d, J=6.4Hz), 0.78(3H, d, J=6.4Hz), 1.55-1 69(3H, m), 1.93-1 99(1H, m), 2.97-3.08(2H, m), 4.39-4.46(3H, m), 4.50-4 59(2H, m), 4 77(1H, d, J=14.4Hz), 7.03-7.09(1H, m), 7.20-7.28(1H, m), 7.36-7.43(1H, m), 8.59(1H, s), 10.39(1H, s), 12.56(1H, s).

Example F-48)

1-Cyclopropylmethyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

melting point: 169-171°C

NMR (DMSO-d_6)δ: 0.00-0.10(2H, m), 0.42-0.44(2H, m), 0.77-0 81(1H, m), 1.59-1 74(2H, m), 2.27-2 32(1H, m), 2.62-2.72(1H, m), 3.05-3.12(1H, m), 4.30-4.58(5H, m), 4.69(1H, d, J=14.8Hz), 7.03-7.11(1H, m), 7 22-7.26(1H, m), 7.37-7.40(1H, m), 8.62(1H, s), 10 40(1H, t, J=6.0Hz), 12.57(1H, s)

Example F-49)

1-Furan-2-ylmethyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a triaza a nthracene-7-carboxylic acid 2,4-difluoro-benzylamide

melting point: 186-188°C

NMR (DMSO-d_6)δ: 1.55-1.68(2H, m), 2.55-2.64(1H, m), 2.88-2.99(2H, m), 3.80(2H, dd, J=15 6, 34.8Hz), 4 36-4 56(5H, m), 4.97(1H, d, J=16 0Hz), 6 39(2H, s), 7.05 7 08(1H, m), 7 21-7.26(1H, m), 7.37-7.44(1H, m), 7.58(1H, s), 8 64(1H, s), 10.38(1H, t, J=5 6Hz), 12.53(1H, s).

Example F-50)

5-Hydroxy-6,10-dioxo-1-thiazol-2-ylmethyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

melting point: 168-170°C

NMR (DMSO-d_6)δ: 1 59-1.74(2H, m), 2.76-2.83(1H, m), 2 97-3.08(2H, m), 3 89(1H, d, J=16.4Hz), 4.36(1H, d, J=16.0Hz), 4.44-4.55(4H, m), 4.69(1H, s), 4.89(1H, d, J=14.8Hz), 7 03-7.09(1H, m), 7.20-7.27(1H, m), 7.34-7.41(1H, m), 7.54(1H, d, J=3 2Hz), 7.68(1H, d, J=3 2Hz), 8.34(1H, s), 10.35(1H, d, J=6.0Hz), 12.50(1H, s)

4.36-4.40(2H, m), 4.59(2H, d, J=5.6Hz), 4.84-4.86(1H, m), 7.16-7 20(1H, m), 7.28-7.32(1H, m), 7.46-7.50(1H, m), 8 45(1H, s), 10.46(1H, t, J=6.0Hz), 12.50(1H, s)

Example F-51)

5-Hydroxy-6,10-dioxo-1-pyridin-2-ylmethyl-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

melting point: 200-203°C

NMR (DMSO-d_6)δ: 1.54-1.61(1H, m), 1.69-1.78(1H, m), 2.71-2.79(1H, m), 2.91-3.09 (2H, m), 3.72(1H, d, J=14.4Hz), 4.07(1H, d, J=14.4Hz), 4.44-4.54(4H, m), 4.70(1H, s), 4.82(1H, d, J=14.4Hz), 7.04-7.10(1H, m), 7.21-7.42(4H, m), 7.74-7.80(1H, m), 8.17(1H, s), 8.47-8.49(1H, m), 10.35(1H, d, J=6.0Hz), 12.57(1H, s)

Example F-52)

1-Hydroxy-6-methyl-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cycloheptа[b]naphthalene-3-carboxylic acid 3-chloro-2-fluoro-benzylamide

melting point: 230-231°C

NMR (DMSO-d_6)δ: 1.47-1.53(1H, m), 1.62-1.78(3H, m), 2.29(3H, s), 2.77-2.81 (2H, m), 4.05-4.10(1H, m), 4.35-4.40(1H, m), 4.54-4.64(3H, m), 4.70(1H, s), 7.18-7.22(1H, m), 7.30-7.34(1H, m), 7.47-7.52(1H, m), 8.49(1H, s), 10.47(1H, d, J=6.0Hz), 12.44(1H, s)

Example F-53)

1-Hydroxy-6-isobutyl-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclo heptа[b]naphthalene-3-carboxylic acid 3-chloro-2-fluoro-benzylamide

melting point: 215-216°C

NMR (DMSO-d_6)δ: 0.83(6H, dd, J=6.8, 13.6Hz), 1.45-1.80(5H, m), 2.36-2.41(1H, m), 2.77-2.93(2H, m), 3.17-3.24(1H, m), 4.02-4.09(1H, m), 4.32-4.40(2H, m), 4.61(2H, d, J=5.6Hz), 4.82-4.84(1H, m), 7.18-7.22(1H, m), 7.30-7.33(1H, m), 7.48-7.51(1H, m), 8.47(1H, s), 10.48(1H, t, J=6.0Hz), 12.55(1H, s).

Example F-54)

6-Cyclopropylmethyl-1-hydroxy-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 3-chloro-2-fluoro-benzylamide

melting point: 212°C

NMR (DMSO-d_6)δ: 0.00-0.10(2H, m), 0.40-45(2H, m), 0.80-0.87(1H, m), 1.45-1.77(3H, m), 2.64-2.69(1H, m), 2.85-2.95(2H, m), 3.13-3.20(1H, m), 4.03-4.09(1H, m), 4.36-4.40(2H, m), 4.59(2H, d, J=5.6Hz), 4.84-4.86(1H, m), 7.16-7.20(1H, m), 7.28-7.32(1H, m), 7.46-7.50(1H, m), 8.45(1H, s), 10.46(1H, t, J=6.0Hz), 12.50(1H, s)

Example F-55)

6-Furan-2-ylmethyl-1-hydroxy-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 3-chloro-2-fluoro-benzylamide

Melting point: 189-190°C

NMR (DMSO-d_6)δ: 1.48-1.63(3H, m), 1.70-1.77(1H, m), 2.79-2.83(2H, m), 3.90(2H, dd, J=14.8, 39.6Hz), 4.05-4.11(1H, m), 4.40-4.51(2H, m), 4.61(2H, d, J=5.6Hz), 4.89-4.91(1H, m), 6.30-6.33(1H, m), 6.38-6.40(1H, m), 7.18-7.22(1H, m), 7.30-7.34(1H, m), 7.48-7.53(1H, m), 7.57(1H, s), 8.45(1H, s), 10.45(1H, t, J=6.0Hz), 12.44(1H, s).

Example F-56)

1-Hydroxy-6-methyl-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 2,4-difluoro-benzylamide

melting point: 241°C

NMR (DMSO-d_6)δ: 1.47-1.53(1H, m), 1.62-1.78(3H, m), 2.29(3H, s), 2.77-2.81 (2H, m), 4.05-4.10(1H, m), 4.35-4.40(1H, m), 4.53-4.61(3H, m), 4.69(1H, s), 7.03-7.08(1H, m), 7.20-7.27(1H, m), 7.37-7.43(1H, m), 8.49(1H, s), 10.42(1H, d, J=6.0Hz), 12.43(1H, s).

Example F-57)

1-Hydroxy-6-isobutyl-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 2,4-difluoro-benzylamide

melting point: 203°C

NMR (DMSO-d_6)δ: 0.82(6H, dd, J=6.4, 13.2Hz), 1.45-1.80(5H, m), 2.36-2.42(1H, m), 2.77-2.93(2H, m), 3.15-3.23(1H, m), 4.02-4.08(1H, m), 4.32-4.41(2H, m), 4.54(2H, d, J=5.6Hz), 4.82-4.84(1H, m), 7.02-7.09(1H, m), 7.20-7.27(1H, m), 7.36-7.43(1H, m), 8.47(1H, s), 10.41(1H, t, J=6.0Hz), 12.54(1H, s).

Example F-58)

6-Cyclopropylmethyl-1-hydroxy-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 2,4-difluoro-benzylamide

melting point: 182-183°C

NMR (DMSO-d_6)δ: 0.00-0.10(2H, m), 0.40-45(2H, m), 0.80-0.87(1H, m), 1.43-1.77(3H, m), 2.60-2.69(1H, m), 2.85-2.95(2H, m), 3.11-3.19(1H, m), 4.00-4.06(1H, m), 4.36-4.40(2H, m), 4.51(2H, d, J=5.6Hz), 4.83-4.87(1H, m), 7.00-7.07(1H, m), 7.16-7.23(1H, m), 7.34-7.38(1H, m), 8.44(1H, s), 10.39(1H, t, J=6.0Hz), 12.47(1H, s)

Example F-59)

6-Furan-2-ylmethyl-1-hydroxy-2,11-dioxo-2,5a,6,7,8,9,10,11-octahydro-5H-4a,6,10a-triaza-cyclohepta[b]naphthalene-3-carboxylic acid 2,4-difluoro-benzylamide

melting point: 171-173°C

NMR (DMSO-d_6)δ 1.47-1.64(3H, m), 1.70-1.77(1H, m), 2.79-2.83(2H, m), 3.90(2H, dd, J=15.6, 39.6Hz), 4.05-4.11(1H, m), 4.41-4.57(4H, m), 4.90-4.92(1H, m), 6.30-6.33(1H, m), 6.38-6.40(1H, m), 7.03-7.09(1H, m), 7.20-7.27(1H, m), 7.37-7.45(1H, m), 7.57(1H, s), 8.44(1H, s), 10.41(1H, t, J=6.0Hz), 12.43(1H, s).

Example F-60)

5-Hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 3-chloro-2-fluoro-benzylamide

melting point: 276°C

NMR (DMSO-d_6)δ: 1.60-1.68(1H, m), 1.77-1.84(1H, m), 3.85-3.93 (1H, m), 4.03-4.07(1H, m), 4.43-4.62(5H, m), 5.28(1H, s), 7.17-7.22(1H, m), 7.29-7.34(1H, m), 7.47-7.52(1H, m), 8.49(1H, s), 10.41(1H, d, J=6.0Hz), 12.48(1H, s).

Example F-61)

5-Hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

melting point: 258°C

NMR (DMSO-d_6)δ 1.60-1.69(1H, m), 1.77-1.85(1H, m), 3.86-3.92 (1H, m), 4.04-4.08(1H, m), 4.43-4.55(5H, m), 5.28(1H, s), 7.03-7.09(1H, m), 7.21-7.27(1H, m), 7.36-7.43(1H, m), 8.50(1H, s), 10.35(1H, d, J=6.0Hz), 12.47(1H, s)

Example F-62)

5-Hydroxy-1-(2-methoxy-ethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7 carboxylic acid 3-chloro-2-fluoro-benzylamide

melting point: 193°C

NMR (DMSO-d_6)δ: 1.53-1.73(2H, m), 2.51-2.58(1H, m), 2.71-2.78(1H, m), 2.81-2.87 (1H, m), 2.95-3.08(2H, m), 3.17(3H, s), 4.40-4.52(3H, m), 4.62(1H, d, J=5.6Hz), 4.78(1H, d, J=14.4Hz), 7.18-7.22(1H, m), 7.30-7.34(1H, m), 7.47-7.52(1H, m), 8.55(1H, s), 10.45(1H, d, J=6.0Hz), 12.59(1H, s).

Example F-63)

5-Hydroxy-1-(2-methoxy-ethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

melting point: 166-168°C

NMR (DMSO-d_6)δ: 1.55-1.72(2H, m), 2.51-2.58(1H, m), 2.70-2.77(1H, m), 2.80-2.87(1H, m), 2.97-3.07(2H, m), 3.18(3H, s), 4.39-4.52(3H, m), 4.54(1H, d, J=5.2Hz), 4.78(1H, d, J=13.6Hz), 7.03-7.09(1H, m), 7.20-7.27(1H, m), 7.37-7.43(1H, m), 8.55(1H, s), 10.40(1H, d, J=6.0Hz), 12.58(1H, s).

Example F-64)

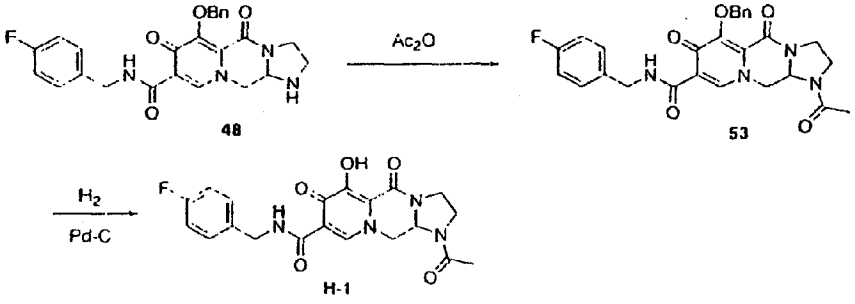
5-Hydroxy-1-(1H-imidazol-4-ylmethyl)-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triazaanthracene-7-carboxylic acid 4-fluorobenzylamide

(DMSO-d_6)δ: 1.55-1.59(1H, m), 1.64-1.70(1H, m), 2.58-2.66(1H, m), 2.87-2.95(2H, m), 3.67(1H, d, J=15.2Hz), 3.73(1H, d, J=15.2Hz), 4.34(1H, s), 4.38-4.43(1H, m), 4.47-4.54(3H, m), 5.05(1H, d, J=14.0Hz), 7.00(1H, s), 7.13-7.19(2H, m), 7.33-7.38(1H, m), 7.59(1H, s), 8.55(1H, s), 10.41(1H, t, J=5.6Hz), 11.95(1H, br s), 12.59(1H, s).

Example H-1)

1-Acetyl-5-hydroxy-4,6-dioxo-2,3,4,6,9,9a-hexahydro-1H-1,3a,8a-triaza-cyclopenta[b]naphthalene-7-carboxylic acid 4-fluoro-benzylamide

[Chemical formula 61]



1) To a solution of a compound 48 (120mg, 0.26 mmol) in methylene chloride (1.2 ml) were added triethylamine (43 μl, 0.31 mmol), acetic anhydride (29 μl, 0.31 mmol), and 4-dimethylaminopyridine (cat.) at room temperature, and the mixture was stirred for 30 minutes. Further, triethylamine (18 μl, 0.13 mmol) and acetic anhydride (12 μl, 0.13 mmol) were added, and the mixture was stirred for 4 hours. 2N hydrochloric

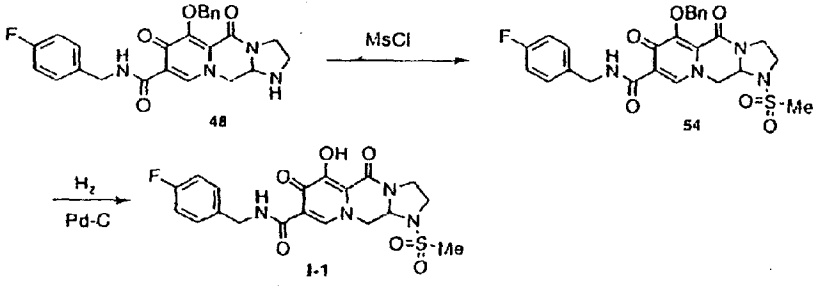
acid was added, this was extracted with chloroform, and the organic layer was washed with water, dried with sodium sulfate, and concentrated under reduced pressure Diisopropyl ether was added to crystallize the material, which was filtered to obtain 53 (112 mg) as a pale orange crystal at a yield of 86 %.

2) An Example compound H-1 (71 mg) was obtained at a yield of 82 % from a compound 53 (106 mg), according to the method of Example B-1 17).
melting point 290°C
NMR (DMSO-d_6)δ 2.08(3H, s), 3.44-4.21(5H, m), 4.51(2H, d, 5.7Hz), 4.93(1H, m), 5.46-5.62(1H, m), 7.15(2H, t, 9.0Hz), 7.34(2H, m), 8.49(1H, s), 10.40(1H, t, 5.7Hz), 11 48(1H, s)

An Example compound H-2 was synthesized according to the same manner as that of Example H-1

Example H-2)
1-Acetyl-5-hydroxy-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza-anthracene-7-carboxylic acid 4-fluoro benzylamide
melting point: 290°C
NMR (DMSO-d_6)δ- 1.95(2H, m), 2.14(3H, s), 2 85(2H, m), 4.45(4H, m), 4.51(2H, d, 5.7Hz), 5 99(1H, s), 7 15(2H, t, 9.0Hz), 7.34(2H, m), 8.37(1H, s), 10.46(1H, s), 12.28(1H, s).

Example I-1)
5-Hydroxy-1-methanesulfonyl-4,6-dioxo-2,3,4,6,9,9a-hexahydro-1H-1,3a,8a-triaza-cyclopenta[b]naphthalene-7-carboxylic acid 4-fluoro-benzylamide
[Chemical formula 62]



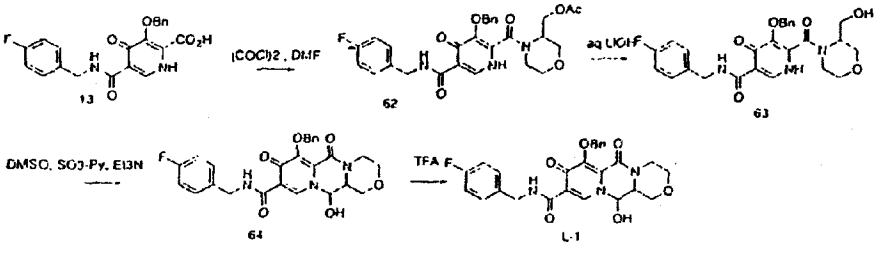
1) To a solution of a compound 48 (140 mg, 0.30 mmol) in pyridine (1.4 ml) were added methanesulfonyl chloride (28 μl, 0.36 mmol), and 4-dimethylaminopyridine (cat.) at room temperature, and the mixture was stirred for 3 hours. After 2N hydrochloric acid was added, this was extracted with ethyl acetate, and the organic layer was washed with water, dried with sodium sulfate, and concentrated under reduced pressure. Diisopropylether was added to crystallize the material, which was filtered to obtain 54 (127 mg) as a pale orange crystal at a yield of 78 %

2) According to the method of Example B-1 17), an Example compound I-1 (21 mg) was obtained at a yield of 21 % from a compound 54 (123 mg).
melting point: 260°C
NMR (DMSO-d_6)δ: 3.16(3H, s), 3.30-4.15(5H, m), 4.45(2H, d, 5.7Hz), 4.27(2H, m), 5.36(1H, m), 7.14(2H, t, 8.7Hz), 7.33(2H, m), 8.22(1H, s), 10.53(1H, s).

According to the same manner as that of Example I-1, an Example compound I-2 was synthesized.

Example I-2)
5-Hydroxy-1-methanesulfonyl-6,10-dioxo-1,2,3,4,6,9,9a,10-octahydro-1,4a,8a-triaza anthracene-7 carboxylic acid 4-fluoro-benzylamide
melting point: 257-259°C
NMR (DMSO-d_6)δ: 1.80-1.96(2H, m), 3.02-3.58(2H, m), 3.16(3H, s), 4.76(2H, m), 5.56(1H, s), 7.16(2H, t, 9.0Hz), 7.35(2H, m), 8.36(1H, s), 10.39(1H, s).

Example L-1)
5,9-Dihydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-1H-2-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide
[Chemical formula 65]



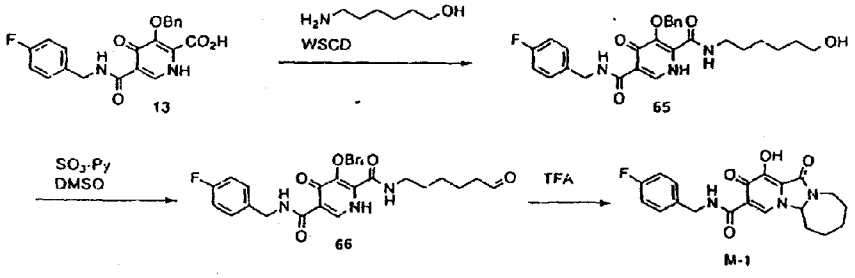
1) According to the method of synthesizing a compound 66, a compound 62 (278 mg, 57%) was obtained from a compound 13 (357 mg).

2) According to the method of synthesizing a compound 57, a compound 63 (202 mg, 79 %) was obtained from a compound 62 (278 mg)

3) To a solution of a compound 63 (200 mg, 0.403 mmol) in chloroform (2 ml) were added dimethyl sulfoxide (286 μl, 4.03 mmol), and triethylamine (337 μl, 2.42 mmol), the mixture was stirred for 10 minutes under ice-cooling, a sulfur trioxide-pyridine complex (321 mg, 2 02 mmol) was added, and the mixture was stirred at room temperature for 2 hours. To the reaction solution was added water (3 ml), and chloroform was distilled off under reduced pressure, followed by extraction with ethyl acetate. The organic layer was washed with water, dried with anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure The crystalline residue was washed with ethyl acetate to obtain a compound 64 (60 mg) at a yield of 30 %.

4) Using a compound 64, and according to the method of synthesizing Example A-1, an Example compound L-1 was synthesized.
NMR (DMSO-d_6)δ: 2.98-3.10(1H, m), 3.38-3.60(2H, m), 3.80-4.20(5H, m), 4.40 4.55(2H, m), 5 48(1H, brs), 5.85(1H, s), 7 15(2H, t, J=8.4Hz), 7 33 7 37(2H, m), 8.45(1H, s), 8 60(1H, s), 10 27-10.42(1H, m), 12.61(1H, brs)

Example M-1)
1-Hydroxy-2,10 dioxo-2,4b,5,6,7,8,9,10-octahydro-4a,9a-diaza-benzo[a]azulene-3-carboxylic acid 4-fluoro-benzylamide
[Chemical formula 66]

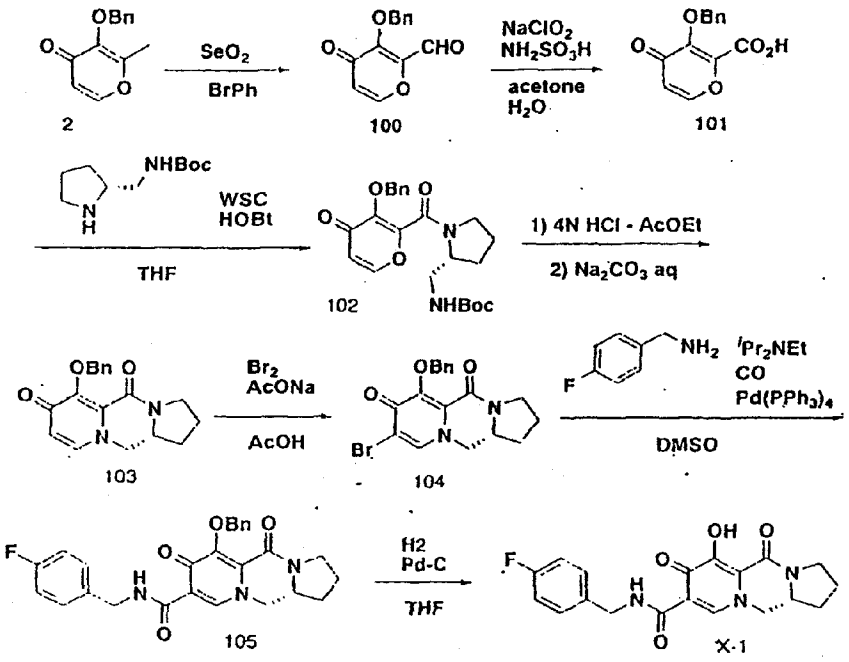


1) According to the method of synthesizing a compound 21, a compound 65 (207 mg) was obtained at a yield of 24 % from a compound 13 (250 mg)

2) According to the method of synthesizing a compound 64, a compound 66 (313 mg. 67 %) was obtained from a compound 65 (470 mg).

3) After trifluoroacetic acid (10 ml) was added to a compound 66 (100 mg, 0.020 mmol), the mixture was stirred at 75°C for 4 hours. The solvent was distilled off under reduced pressure, and this was diluted with chloroform, and added to ice water This was washed with an aqueous saturated sodium bicarbonate solution, a 10 % aqueous citric acid solution, and water, and dried with anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was subjected to silica gel column chromatography, and fractions eluted with chloroform-methanol were concentrated under reduced pressure, and recrystallized with ethyl acetate-diisopropyl ether to obtain an Example compound M-1 (23 mg, 16 %)
melting point 281-283°C
NMR (DMSO-d_6)δ: 1.43-1.52(2H, m), 1.62-1.83(3H, m), 2.04-2.18(1H, m), 2.23-2.35(1H, m), 4.08-4.16(1H, m), 4.48-4.53(2H, m), 5.58-5.61(1H, m), 7.11-7.20(2H, m), 7.30-7.38(2H, m), 8.29(1H, s), 10.30-10.36(1H, m), 12.78(1H, brs).

Example X-1)
(R)-6-Hydroxy-5,7-dioxo-2,3,5,7,11,11a hexahydro 1H-pyrido[1,2-a]pyrrolo[1,2-d]pyrazine-8-carboxylic acid 4-fluoro-benzylamide
[Chemical formula 67]



1) Selenium dioxide (666mg, 6.0mmol) was added to the solution of compound 2 (216mg, 1.0mmol) in bromobenzene (2ml). Then the mixture was heated up to 160°C, and stirred for 16h. After celite filtration the solvent was evaporate. The precipitate was purified by silicagel column chromatography, and fractions eluting with n-hexan/EtOAc were concentrated under reduced pressure to obtain compound 100 (164mg, 71%) as a yellow oil.

1H-NMR ($CDCl_3$)δ: 5.52(1H, s), 6.50(1H, d, J=6.0Hz), 7.36(5H, m), 7.74(1H, d, J=6.3Hz), 9.88(1H, s).

2) Sulfamic acid (1.50g, 15.4mmol) and $NaClO_2$ (1.05g, 11.6mmol) was added to the solution of compound 100 (2.54g, 11.0mmol) in acetone (20ml) and water (30ml). Then the mixture was stirred for 3h. The solvent was evaporated under reduced pressure to obtain compound 101 (2.18mg, 80%) as a white solid.

1H-NMR (DMSO-d_6)δ: 5.11(2H, s), 6.55(1H, d, J=5.4Hz), 7.32-7.46(5H, m), 8.21(1H, d, J=5.7Hz).

3) (R)-2-N-BOC aminomethyl pyrrolidine (391mg, 1.95mmol) was added to the solution of compound 101 (400mg, 1.62mmol),

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (373mg, 1.95mmol), and 1-hydroxybenzotriazole (219mg, 1.62mmol) in THF (6ml) After stiring for 16h $NaHCO_3$ aqueous solution was added to the mixture. The mixture was extracted with EtOAc, which was washed with NH_4Cl aqueous solution and brine. The organic phase was dried over $MgSO_4$. After a filtration the solvent was removed under reduced pressure to obtain compound 102 (694mg, 100%) as a white solid
1H-NMR ($CDCl_3$)δ: 1.46(9H, s), 1.56-2.14(4H, m), 3.29(4H, m), 4.18(1H, m), 5.24(1H, s), 5.27(1H, s), 6.46(1H, d, J=5.7Hz), 7.35(5H, m), 7.69(1H, d, J=5.7Hz).

4) The solution of compound 102 (694mg, 1.95mmol) in HCl/EtOAc (4mol/l, 8ml) was stirred for 30 min. The soluvant was removed under reduced pressur, diluted with EtOH (16ml) then. A saturated $NaHCO_3$ aqueous solution was added to the solution to control pH at 9. The mixture was strred at 50 °C for 2h, then diluted with water. The mixture was extracted with $CHCl_3$, washed with brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to obtain compound 103 (413mg, 68%) as a yellow solid.
1H-NMR ($CDCl_3$)δ: 1.54-2.22(4H, m), 3.60(2H, m), 3.80(1H, t, J=12.0Hz), 4.18(1H, d, J=12.0Hz), 5.15(1H, d, J=9.9Hz), 5.35(1H, d, J=9.9Hz), 6.71(1H, d, J=5.4Hz), 7.33(3H, m), 7.50(1H, d, J=5.1Hz), 7.63(2H, d, J=7.2Hz).

5) NaOAc (118mg, 1.44mmol) and bromine (0.234ml, 2.62mmol) were added to the solution of compound 103 (408mg, 1.31mmol) in acetic acid (8ml), stirred for 30 min then. An aqueous solution of NaOH (2M) was added to the mixture, and extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give compound 104 (390mg, 77%) as a white solid.
1H-NMR ($CDCl_3$)δ: 1.55-2.19(4H, m), 3.55-4.02(5H, m), 5.12(1H, d, J=9.6Hz), 5.35(1H, d, J=9.9Hz), 7.29-7.38(3H, m), 7.61(1H, s), 7.67(2H, d, J=6.6Hz)

6) Tetrakis triphenylphosphine paradium (0) (77mg, 0.067mmol) and N,N-diisopropylethylamine (0.29ml, 1.67mmol) were added to the solution of compound 104 (130mg, 0,334mmol) in DMSO (2.6ml), the mixture was stirred under CO atmosphere for 2h at 80°C . The reaction mixture was diluted with a saturated NH_4Cl aqueous solution, extracted with EtOAc then. And the organic phase was washed with brine, and dried over Na_2SO_4 The precipitate was purified by silicagel column chromatography, and fractions eluting with MeOH/EtOAc were concentrated

under reduced pressure to obtain compound 105 (115mg, 75%) as a white oil.
1H-NMR ($CDCl_3$)δ: 1.56-2.33(4H, m), 3.66(2H, m), 3.90(2H, m), 4.19(1H, s), 4.66(2H, m), 5.20(1H, d, J=9.9Hz), 5.37(1H, d, J=9.9Hz), 7.00(2H, t, J=8.7Hz), 7.33(5H, m), 7.61(2H, m), 8.39(1H, m), 10.50(1H, s).

7) A mixture of compound 105 (111mg, 0.241mmol) and paradium carbon (10%, 22mg) in THF (8ml) and MeOH (2ml) was stirred under hydrogen atmosphere for 3h. After celite filteration the solvent was removed under reduced pressure to give the example X-1 (57mg, 64%) as a white solid
Melting point: 274°C
1H-NMR (DMSO-d_6)δ: 1.56-2.25(4H, m), 3.48-3.65(2H, m), 4.01(2H, m), 4.51(2H, d, J=5.7Hz), 4.71(1H, d, J=9.9Hz), 7.14(2H, t, J=9.0Hz), 7.33(2H, dd, J=5.7, 8.7Hz), 8.41(1H, s), 10.44(1H, t, J=6.0Hz), 12.18(1H, s).

The following compounds were synthesized using the similar method

Example X-2)
(R)-6-Hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro-1H-pyrido[1,2-a]pyrrolo[1,2-d]pyrazine-8-carboxylic acid 2,4-difluoro-benzylamide
Melting point: 300°C
1H-NMR (DMSO-d_6)δ: 1.03-2.20(4H, m), 3.39-3.66(2H, m), 4.02(2H, m), 4.54(2H, d, J=6.0Hz), 4.71(1H, d, J=9.9Hz), 7.06(1H, m), 7.23(1H, m), 7.38(1H, m), 8.41(1H, s), 10.43(1H, t, J=6.0Hz), 12.19(1H, s)

Example X-3)
(R)-6-Hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro-1H-pyrido[1,2-a]pyrrolo[1,2-d]pyrazine-8-carboxylic acid 3-chloro-2-fluoro-benzylamide
Melting point: 304°C
1H-NMR (DMSO-d_6)δ: 3.44-3.66(2H, m), 4.01(2H, m), 4.61(2H, d, J=5.4Hz), 4.70(1H, d, J=9.0Hz), 7.20(1H, m), 7.31(1H, m), 7.49(1H, m), 8.41(1H, s), 10.49(1H, t, J=5.7Hz), 12.20(1H, s).

Example X-4)
1-Hydroxy-2,9-dioxo-2,5,6,7,8,9,10,10a-octahydro-4a,8a-diaza-anthracene-3-carboxylic acid 4-fluoro-benzylamide

Melting point: 259°C

1H-NMR (DMSO-d_6)δ:1.33-1.79(6H, m), 2.51(1H, m), 3.88(1H, m), 4.12(1H, dd, J=9 3, 14.1Hz), 4.38(1H, d, J=12.9Hz), 4.53(3H, m), 7.16(2H, t, J=9.0Hz), 7.34(2H, dd, J=5 7, 8.7Hz), 8.39(1H, s), 10 44(1H, t, J=6.3Hz), 12.84(1H, s).

According to the same manner as that of Example C-21, the following Example compounds Y-1 to Y-18 were synthesized.

Example Y-1)

(3S,9aS)-5-Hydroxy-3-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

Example Y-9)

(3R,9aR)-5-Hydroxy-3-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

1H-NMR ($CDCl_3$)δ: 0.90(3H, d, J=6.9Hz), 2.00-2.10(1H, m), 2.70(1H, dd, J=11.6, 13 4Hz), 3.41(1H, dd, J=11.2, 12.9Hz), 4.05-4.45(2H, m), 4 30-4.38(1H, dd, J=4 0, 14.1Hz), 4.63(2H, d, J=5.9Hz), 4.65-4.75(1H, m), 4.98(1H, t, J=3.7Hz), 6.80-6.84(2H, m), 7.32-7.40(1H, m), 8.31(1H, s), 10.38(1H, brs), 12 37(1H, s).

Example Y-2)

(4S,9aR)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

Example Y-3)

(4R,9aS)-5-Hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

1H-NMR ($CDCl_3$)δ 1 42(3H, d, J=7.0Hz), 1.56(1H, dd, J=2.0, 14.0Hz), 2.19-2.30(1H, m), 4 02(1H, d, J=2.2Hz), 4 05(1H, t, J=2 3Hz), 4 12(1H, dd, J=6.0, 13.6Hz), 4.27(1H, dd, J=4.2, 13.4Hz), 4.64(2H, d, J=5.9Hz), 4.95-5.05(1H, m), 5.26(2H, d, J=4 1, 5 8Hz), 6.75 6.85(2H, m), 7.30-7.40(1H, m), 8.30(1H, s), 10 38(1H, brs), 12.45(1H, s).

Example Y-4)

(2R,9aR)-5-Hydroxy-2-methoxymethyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

Example Y-8)

(2S,9aS)-5-Hydroxy-2-methoxymethyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a

,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
1H-NMR ($CDCl_3$)δ: 1.60-1.80(2H, m), 3.09-3.21(1H, m), 3.37(3H, s), 3.35-3.50(2H, m), 4.00-4.11(1H, m), 4.24(1H, d, J=13.1Hz), 4.36(1H, d, J=10.1Hz), 4.64(1H, d, J=5.9Hz), 4.70-4.80(1H, m), 5.12(1H, s), 6.75-6.85(2H, m), 7.30-7.40(1H, m), 8.30(1H, s), 10.38(1H, brs), 12.33(1H, brs)

Example Y-5)
(6aR,6aS,10aR)-1-Hydroxy-2,12-dioxo-2,5,5a,7,8,9,10,10a,11,12-decahydro-6aH-6-oxa-4a,11a-diaza-naphthacene-3-carboxylic acid 2,4-difluoro-benzylamide [racemate]
1H-NMR (DMSO-d6)δ: 1.00-1.85(9H, m), 2.90(1H, t, J=4.2Hz), 4.36(1H, dd, J=4.2, 12.9Hz), 4.44-4.57(4H, m), 5.32(1H, t, J=3.9Hz), 7.03-7.09(1H, m), 7.20-7.27(1H, m), 7.35-7.43(1H, m), 8.49(1H, s), 10.34(1H, brs).

Example Y-6)
(2S,9aR)-2-Ethyl-5-hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
Example Y-7)
(2R,9aS)-2-Ethyl-5-hydroxy-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
1H-NMR (DMSO-d6)δ: 0.87(3H, d, J=5.4Hz), 1.40-1.51(3H, m), 1.75(1H, d, J=10.8Hz), 3.22(1H, t, J=10.2Hz), 3.73-3.78(1H, m), 4.41-4.57(4H, m), 5.29(1H, s), 7.03-7.07(1H, m), 7.21-7.26(1H, m), 7.37-7.42(1H, m), 8.50(1H, s), 10.34(1H, brs), 12.48(1H, s).

Example Y-10)
(2S,9aS)-5-Hydroxy-6,10-dioxo-2-phenyl-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
1H-NMR ($CDCl_3$)δ: 1.70-1.82(1H, m), 1.98(1H, d, J=9.6Hz), 3.49(1H, t, J=9.6Hz), 4.54-4.68(5H, m), 4.98(1H, d, J=8.7Hz), 5.51(1H, s), 7.04-7.08(1H, m), 7.21-7.42(7H, m), 8.50(1H, s), 10.38(1H, s), 12.45(1H, s)

Example Y-11)
(2S,9aS)-5-Hydroxy-2-isopropyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide
Example Y-12)
(2R,9aR)-5-Hydroxy-2-isopropyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-di

aza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

1H-NMR (DMSO-d6)δ: 0.86(6H, dd, J=4.8, 13.5Hz), 1.41-1.49(1H, m), 1.57-1.69(1H, m), 1.72-1.78(1H, m), 3.20(1H, t, J=8.4Hz), 3.52-3.59(1H, m), 4.41-4.46(5H, m), 5.29(1H, s), 7.01-7.08(1H, m), 7.21-7.26(1H, m), 7.37-7.43(1H, m), 8.50(1H, s), 10.35(1H, brs), 12.48(1H, s).

Example Y-13)

(3S,9aS)-5-Hydroxy-3-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

Example Y-14)

(3R,9aR)-5-Hydroxy-3-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

1H-NMR (DMSO-d6)δ: 0.81(3H,d, J=6.6Hz), 1.84-1.93(1H, m), 2.86(1H, t, J=12.5Hz), 3.48(1H, t, J=11.1Hz), 3.97-4.03(1H, m), 4.41-4.60(3H, m), 4.52(2H, d, J=5.9Hz), 5.20(1H, t, J=3.8Hz), 7.12-7.20(2H, m), 7.32-7.38(2H, m), 8.52(1H, s), 10.36(1H, t, J=5.9Hz), 12.45(1H, s).

Example Y-15)

(2R,9aS)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

Example Y-16)

(2S,9aR)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 2,4-difluoro-benzylamide

1H-NMR (DMSO-d6)δ: 1.14(3H, d, J=6.0Hz), 1.38(1H, m), 1.75(1H, d, J=13.8Hz), 3.18-3.29(1H, m), 3.95-4.06(1H, m), 4.42-4.58(3H, m), 4.54(2H, d, J=5.7Hz), 5.30(1H, t, J=3.9Hz), 7.03-7.10(1H, m), 7.20-7.29(1H, m), 7.35-7.44(1H, m), 8.50(1H, s), 10.35(1H, t, J=5.7Hz), 12.48(1H, s)

Example Y-17)

(2S,9aR)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

Example Y-18)

(2R,9aS)-5-Hydroxy-2-methyl-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid 4-fluoro-benzylamide

1H-NMR (DMSO-d6)δ: 1.15(3H, d, J=6.0Hz), 1.35-1.50(1H, m), 1.75(1H, d, J=12.9Hz),

3.23(1H, td, J=13.0, 2.8Hz), 3 95-4.03(1H, m),4.41-4 59(3H, m), 4 52(2H, d, J=6 0Hz), 5.30(1H, t, J=3.9Hz), 7.12-7.19(2H, m), 7 32-7.38(2H, m), 8.52(1H, s), 10.36(1H, t, J=6 0Hz), 12.48(1H, s)

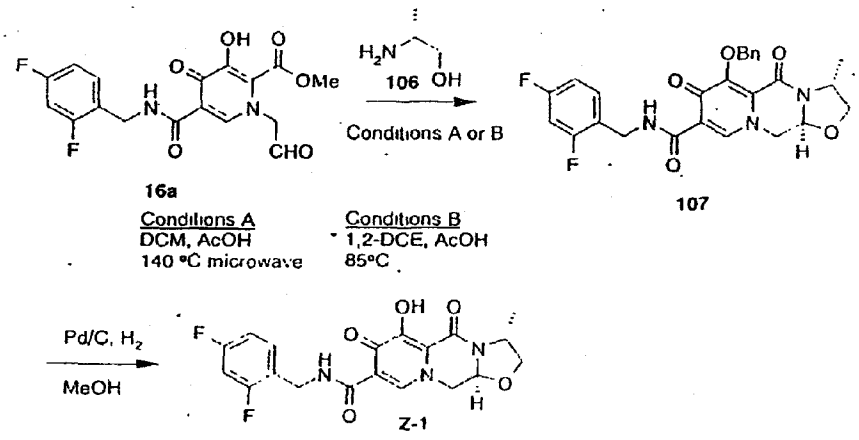
Corresponding amino-alcohol derivatives used in syntheses of Y-1 to Y-18 were prepared as optically pure version using methods similar to those described in the following reports

3-Amino-2-methyl-propan-1-ol, and 4-Amino-butan-2-ol were prepared according to the method of Russell A Barrow (J. Am. Chem Soc. 1995, 117, 2479-2490).
3-Amino-butan-1-ol were prepared according to the method of P. Besse (Tetrahedron Asymmetry 10(1999) 2213-2224).
1-Amino pentan-3-ol, 1-Amino-4-methyl-pentan-3-ol, 4-Amino-1-methoxy-butan-2-ol, and 3 Amino-1-phenyl-propan-1-ol were prepared according to the method described in the following literatures, U.S Pat. Appl. Publ , 2004133029, 08 Jul 2004, PCT Int. Appl., 2002012173, 14 Feb 2002.

All examples below consist of >95% ee and >6:1 diastereomeric purity unless indicated otherwise. The compounds shown in table ZZ consist of mixtures of diastereomers at the depicted stereocenter in ratios of 1:1 to >10:1 Stereocenters that were formed during the process' below have been assigned using NMR techniques well know in the art (1D and 2D method) and/or using vibrational circular dichroism techniques. Stereochemical assignment determinatons were performed on representative examples and closely related compounds were assigned by analogy in some cases. The schemes below are meant to be general guidance to how examples were synthesized. It will be possible that one skilled in the art may rearrange the order of steps or change substituents to apply the method described below and in the examples to construct compounds of the general formula Additional methods known to those skilled in the art or commonly present in the literature may also be applied

to perform similar transformations and arriving at the same compounds of the general formula or amino alcohol and diamine precursors.

[Chemical formula 68]



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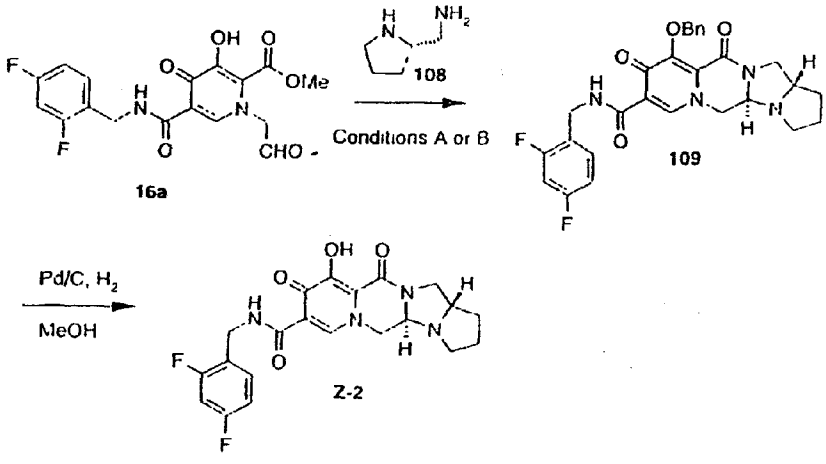

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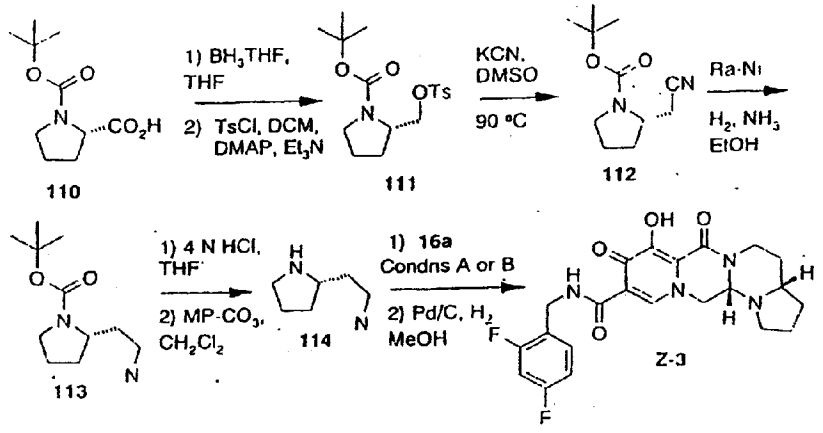

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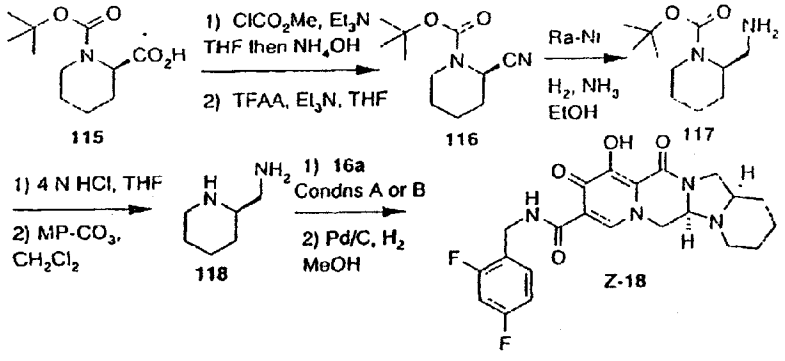

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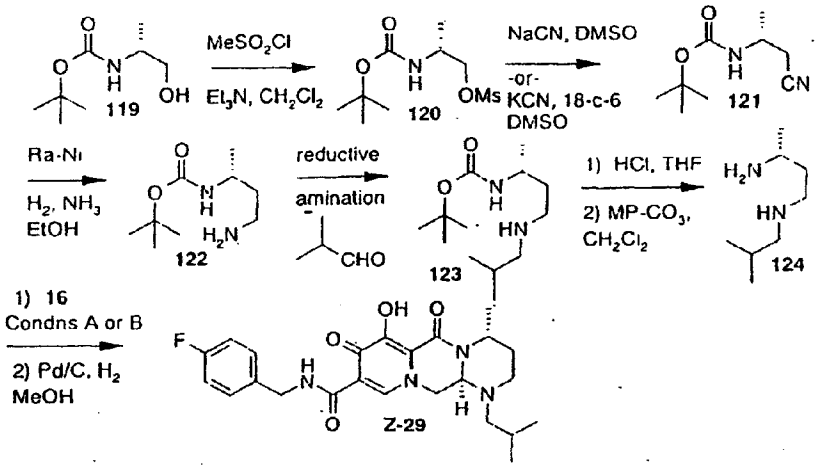

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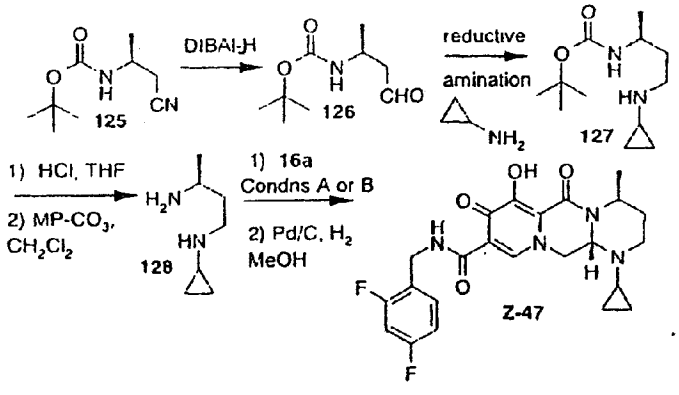

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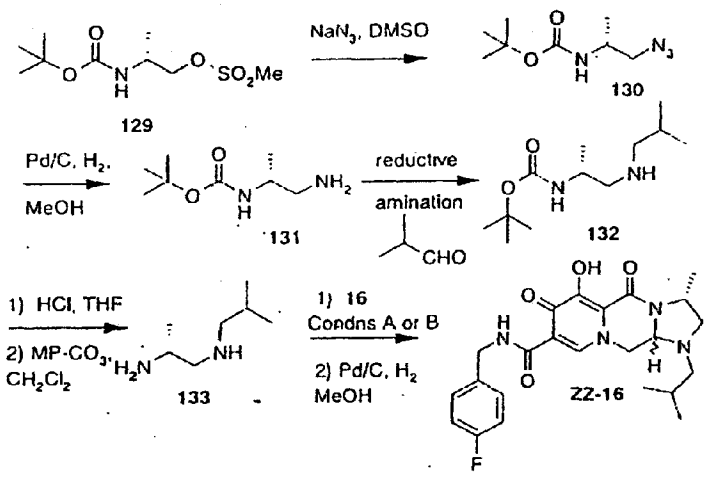

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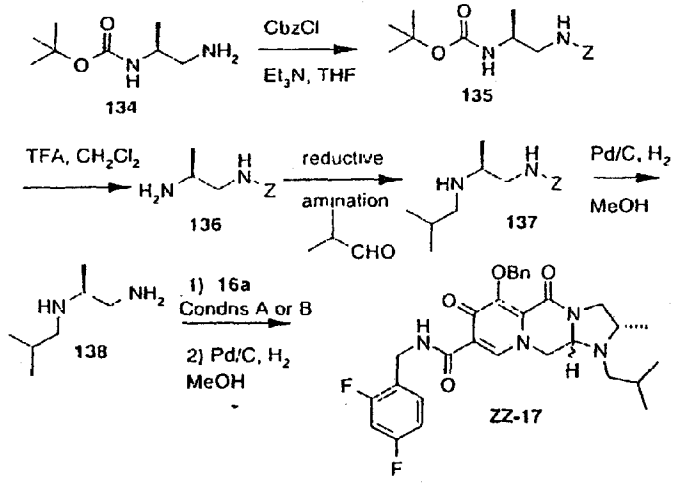

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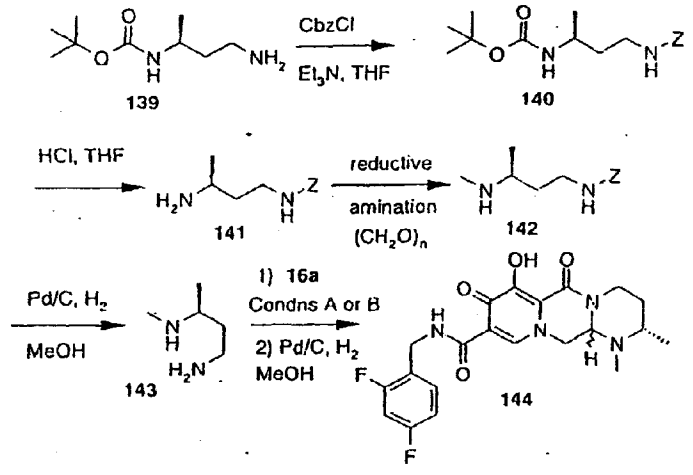

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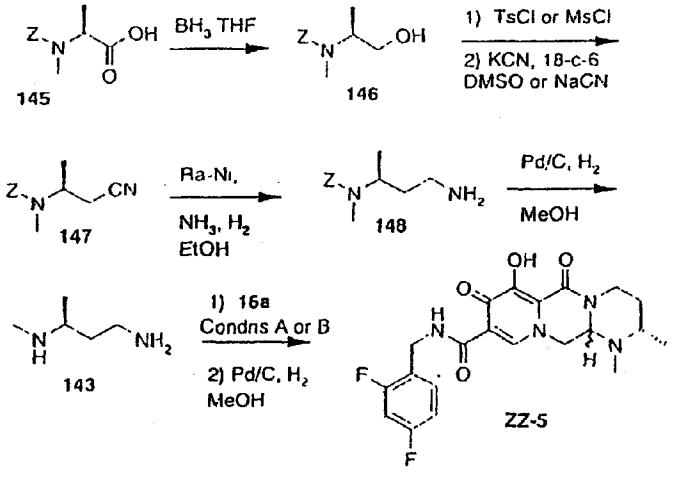

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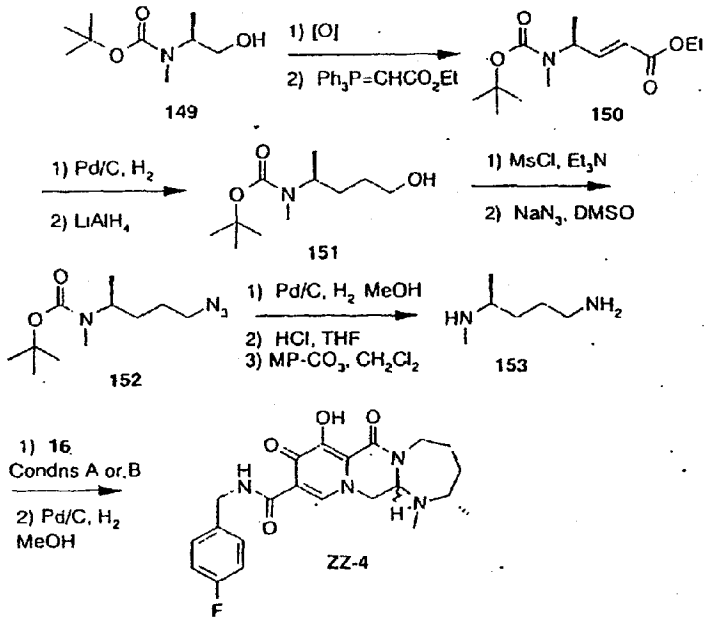

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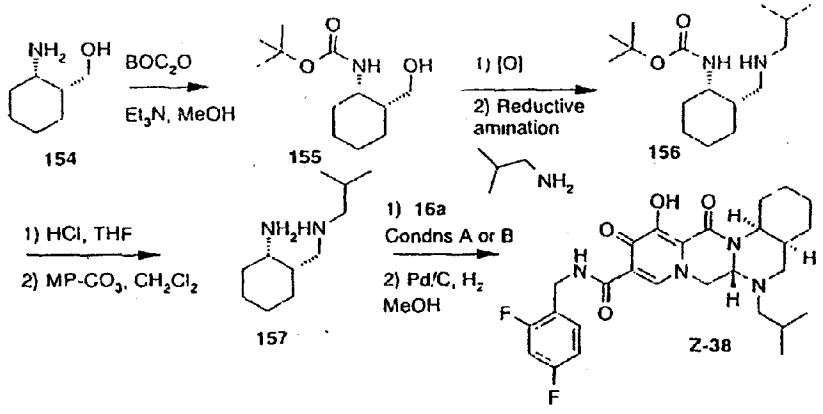

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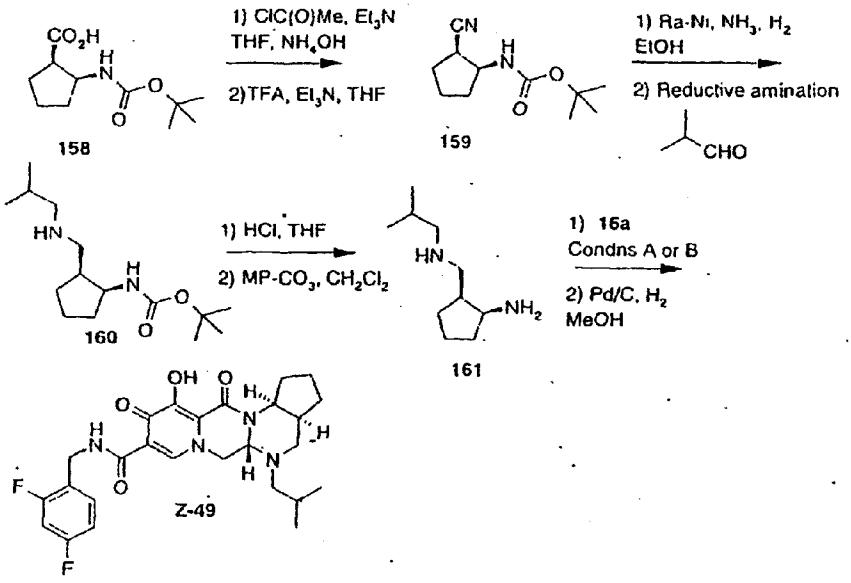

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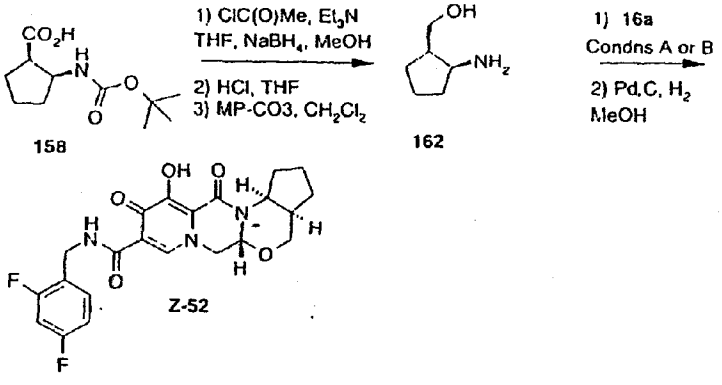
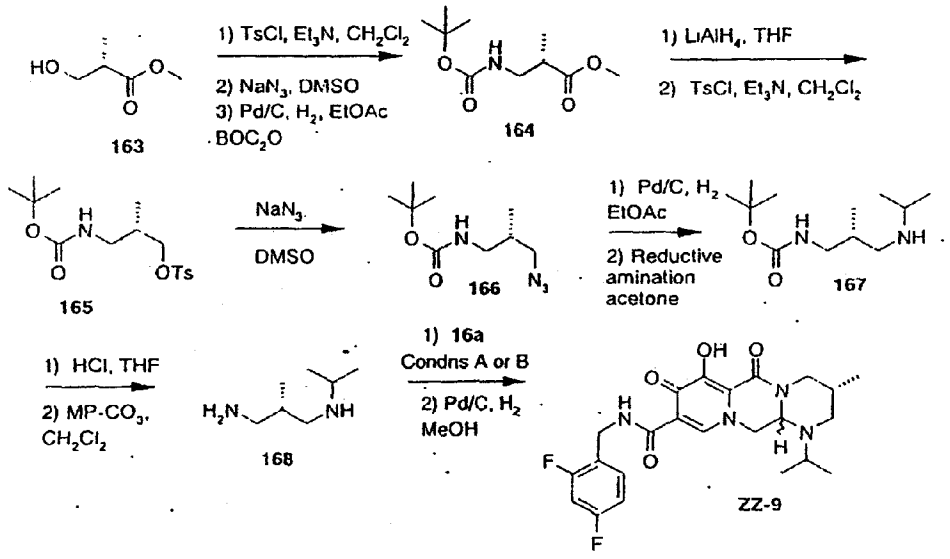
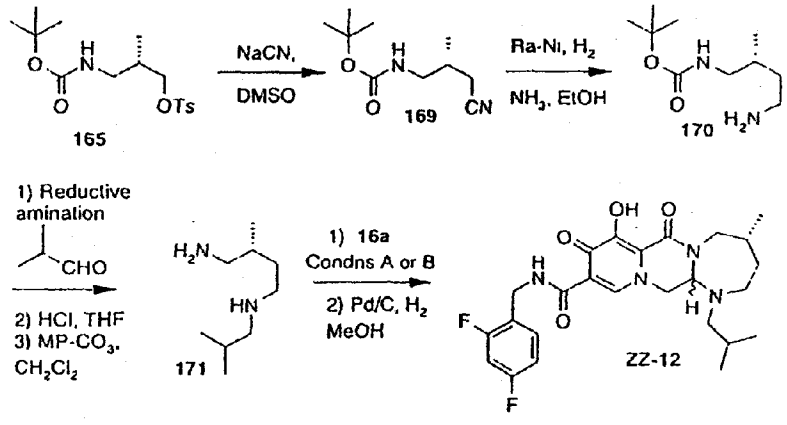


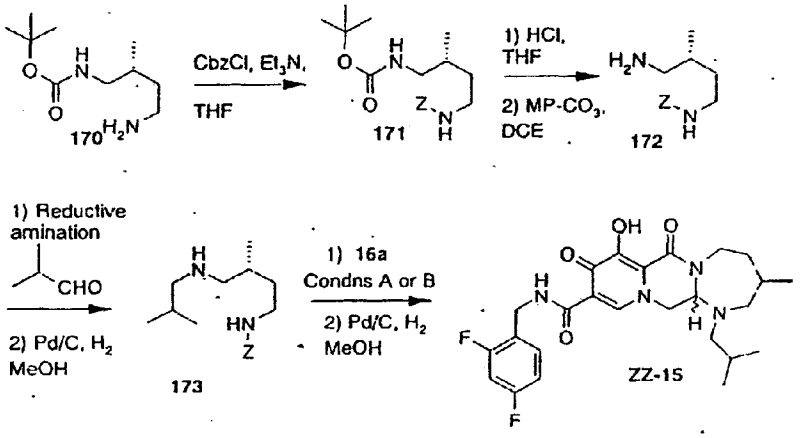
[Chemical formula 81]



[Chemical formula 82]

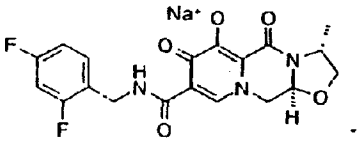


[Chemical formula 83]



Example Z-1

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide sodium salt



a)

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-3-methyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide. To a solution of 16a (409 mg, 0.87 mmol) in dichloroethane (20 mL) was added

(2*R*)-2-amino-1-propanol (0.14 mL, 1.71 mmol) and 10 drops of glacial acetic acid. The resultant solution was heated at reflux for 2 h. Upon cooling, Celite was added to the mixture and the solvents removed *in vacuo* and the material was purified via silica gel chromatography (2% CH_3OH/CH_2Cl_2 gradient elution) to give (3*R*,11a*S*) *N*-[(2,4-difluorophenyl)methyl]-3-methyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (396 mg, 92%) as a glass. ^{1}H NMR ($CDCl_3$) δ 10.38 (m, 1 H), 8.42 (s, 1 H), 7.54-7.53 (m, 2 H), 7.37-7.24 (m, 4 H), 6.83-6.76 (m, 2 H), 5.40 (d, *J* = 10.0 Hz, 1 H), 5.22 (d, *J* = 10.0 Hz, 1 H), 5.16 (dd, *J* = 9.6, 6.0 Hz, 1 H), 4.62 (m, 2 H), 4.41 (m, 1 H), 4.33-4.30 (m, 2 H), 3.84 (dd, *J* = 12.0, 10.0 Hz, 1 H), 3.63 (dd, *J* = 8.4, 7.2 Hz, 1 H), 1.37 (d, *J* = 6.0 Hz, 3 H); ESI$^+$ MS: 496 (M+1).

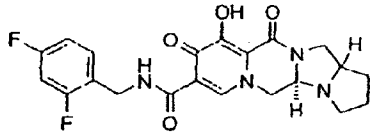
b)

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide sodium salt. To a solution of (3*R*,11a*S*)-*N*-[(2,4-difluorophenyl)methyl]-3-methyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (396 mg, 0.80 mmol) in methanol (30 mL) was added 10% Pd/C (25 mg). Hydrogen was bubbled through the reaction mixture via a balloon for 2 h. The resultant mixture was filtered through Celite with methanol and dichloromethane. The filtrate was concentrated *in vacuo* to give (3*R*,11a*S*)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-

hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide as a pink tinted white solid (278 mg, 86%) ^{1}H NMR ($CDCl_3$) δ 11.47 (m, 1 H), 10.29 (m, 1 H), 8.32 (s, 1 H), 7.36 (m, 1 H), 6.82 (m, 2 H), 5.31 (dd, *J* = 9.6, 3.6 Hz, 1 H), 4.65 (m, 2 H), 4.47-4.38 (m, 3 H), 3.93 (dd, *J* = 12.0, 10.0 Hz, 1 H), 3.75 (m, 1 H), 1.49 (d, *J* = 5.6 Hz, 3 H); ES$^+$ MS: 406 (M+1). The above material (278 mg, 0.66 mmol) was taken up in ethanol (10 mL) and treated with 1 *N* sodium hydroxide (aq) (0.66 mL, 0.66 mmol). The resulting suspension was stirred at room temperature for 30 min. Ether was added and the liquids were collected to provide the sodium salt of the title compound as a white powder (291 mg, 99%). ^{1}H NMR (DMSO-d_6) δ 10.68 (m, 1 H), 7.90 (s, 1 H), 7.35 (m, 1 H), 7.20 (m, 1 H), 7.01 (m, 1 H), 5.20 (m, 1 H), 4.58 (m, 1 H), 4.49 (m, 2 H), 4.22 (m, 2 H), 3.74 (dd, *J* = 11.2, 10.4 Hz, 1 H), 3.58 (m, 1 H), 1.25 (d, *J* = 4.4 Hz, 3 H)

Example 2-2:

(4a*R*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide.



a)

(4a*R*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-9,11-dioxo-10-[(phenylmethyl)oxy]-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide. A solution of 16a (24 mg, 0.05 mmol), [(2*S*)-2-pyrrolidinylmethyl]amine (0.1 mL) and 2 drops of glacial acetic acid were heated under microwave conditions at 140

°C for 10 min. Upon cooling, Celite was added to the mixture and the solvents removed *in vacuo* and the material was purified via silica gel chromatography (2% CH_3OH/CH_2Cl_2 gradient elution) to give (4a*R*,13a*S*)-*N*-[(2,4-difluorophenyl)methyl]-9,11-dioxo-10-[(phenylmethyl)oxy]-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide (19 mg, 71%) as a white solid. ^{1}H-NMR ($CDCl_3$) δ 10.41 (m, 1 H), 8.38 (s, 1 H), 7.56 (m, 2 H), 7.38-7.24 (m, 4 H), 6.80 (m, 2 H), 5.38 (d, *J* = 9.6 Hz, 1 H), 5.10 (d, *J* = 10.0 Hz, 1 H), 4.62 (m, 2 H), 4.40 (m, 1 H), 4.25 (dd, *J* = 12.0, 6.8 Hz, 1 H), 4.10 (d, *J* = 12.8 Hz, 1 H), 3.83 (m, 1 H), 3.71 (m, 1 H), 3.14-3.04 (m, 2 H), 2.78 (m, 1 H), 2.11-1.58 (m, 4 H); ES$^+$ MS: 521 (M+1).

b)

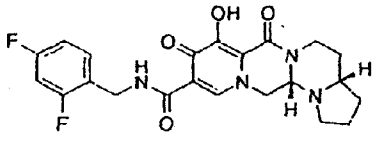
(4a*R*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide

To a solution of (4a*R*,13a*S*)-*N*-[(2,4-difluorophenyl)methyl]-9,11-dioxo-10-[(phenylmethyl)oxy]-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide (19 mg, 0.04 mmol) in methanol (8 mL) was added 10% Pd/C (10 mg). Hydrogen was bubbled through the reaction mixture via a balloon for 2 h. The resultant mixture was filtered through Celite with methanol and dichloromethane. The filtrate was concentrated *in vacuo* to give the title compound (6 mg, 38%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.73 (m, 1 H), 10.36 (m, 1 H), 8.31 (s, 1 H), 7.33 (m, 1 H), 6.78 (m, 2 H), 4.62 (m, 2 H), 4.50 (m, 1 H), 4.27-4.19 (m, 2 H), 3.87-3.77 (m, 2 H),

3.16-3.08 (m, 2 H), 2.83 (m, 1 H), 2.11-1.65 (m, 4 H); ES+ MS: 431 (M+1)

Example Z-3:

(3a*S*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carboxamide.



a) *N*-BOC-(2*S*)-2-(Hydroxymethyl)-1-pyrrolidine. To a solution of *N*-BOC-L-proline (4.17 g, 19.4 mmol) in THF (40 mL) at 0 °C was added BH_3-THF (21.4 mL, 1 M in THF, 21.4 mmol) dropwise. The bath was removed and the resultant solution stirred at room temperature for 2 h. Methanol was added to quench the mixture and the solvents were removed *in vacuo*. The residue was taken up in ethyl acetate and washed with sodium bicarbonate and brine. The aqueous layers were extracted twice with ethyl acetate. The combined organics were dried over Na_2SO_4, filtered and concentrated to give *N*-BOC-(2*S*)-2-(hydroxymethyl)-1-pyrrolidine (3.82 g, 98%) as a clear oil. This material was used without further purification. ^{1}H NMR ($CDCl_3$) δ 3.94 (m, 1 H), 3.62 (dd, *J* = 11.2, 3.2 Hz, 1 H), 3.56 (dd, *J* = 10.8, 7.2 Hz, 1 H), 3.44 (m, 1 H), 3.29 (m, 1 H), 2.62 (br, 1 H), 1.98 (m, 1 H), 1.85-1.72 (m, 2 H), 1.58 (m, 1 H).

b) *N*-BOC-(2*S*)-2-({[(4-Methylphenyl)sulfonyl]oxy}methyl)-1-pyrrolidine. To a cold (0 °C) solution of *N*-BOC-(2*S*)-2-(hydroxymethyl)-1-pyrrolidine (350 mg, 1.74 mmol) in dichloromethane (20 mL) was added triethylamine (0.29 mL, 2.08 mmol), and

toluenesulfonyl chloride (398 mg, 2.08 mmol) *N,N*-dimethylaminopyridine (70 mg) was added and the resultant solution was allowed to warm to rt as the bath warmed and stirred for 4 h. Water was added and the layers separated The aqueous layer was washed with sodium bicarbonate and then with brine The combined organics were dried over Na_2SO_4, filtered and concentrated followed by flash chromatography purification to give *N*-BOC-(2*S*)-2-({[(4-methylphenyl)sulfonyl]oxy}methyl)-1-pyrrolidine (460 mg, 75%) as a clear oil. ^{1}H NMR exists as rotomers (CDCl$_3$) δ 7.77 (d, 2 H), 7 33 (m, 2 H), 4 08 (m, 1 H), 3.97-3.88 (m, 1 H), 3 35-3 25 (m, 2 H), 2.43 (s, 3 H), 1.95-1.79 (m, 1 H), 1.40 and 1.35 (s, 9 H rotomeric BOC *t*-butyl).

c) *N*-BOC-(2*S*)-2-Cyano-1-pyrrolidine. A mixture of *N*-BOC-(2*S*)-2-({[(4-methylphenyl)sulfonyl]oxy}methyl)-1-pyrrolidine (460 mg, 1 29 mmol) and KCN (256 mg, 3.88 mmol) were heated at 90 °C in DMSO (10 mL) for 6.5 h The mixture was cooled to room temperature and EtOAc and water were added The organics were washed with water twice and then with brine. The aqueous layers were extracted with EtOAc and the combined organics dried over Na_2SO_4, filtered and concentrated followed by flash chromatography purification to give *N*-BOC-(2*S*)-2 cyano 1 pyrrolidine (179 mg, 66%) as an oil ^{1}H NMR exists as rotomers (CDCl$_3$) δ 3.99 (m, 1 H), 3.43-3.37 (m, 2 H), 2.83-2.51 (m, 2 H), 2.17-1.83 (m, 4 H), 1.46 and 1.44 (s, 9 H rotomeric BOC *t*-butyl).

d) *N*-BOC-(2*S*)-2-(2 Aminoethyl)-1-pyrrolidine A solution of *N*-BOC-

(2*S*)-2-cyano 1 pyrrolidine (179 mg, 0 85 mmol) in ethanol saturated with anhydrous ammonia was treated with Raney-Ni (1 mL of 50% aq Suspension) and 50 psi of H_2 overnight. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (10% CH_3OH/CH_2Cl_2 with 1% NH_4OH gradient elution) through a short plug of silica gel to give *N*-BOC-(2*S*)-2-(2-aminoethyl)-1-pyrrolidine (90 mg, 50%) as a clear oil. ^{1}H NMR exists as rotomers ($CDCl_3$) δ 3.88-3.77 (m, 1 H), 3.33-3.24 (m, 2 H), 2 66 (m, 2 H), 1.89-1.54 (m, 6 H), 1 40 (s, 9 H).

e) {2 [(2*S*)-2-Pyrrolidinyl]ethyl}amine A solution of *N*-BOC (2*S*)-2-(2-aminoethyl)-1-pyrrolidine (90 mg, 0.42 mmol) in THF (6 mL) was treated with 4 *N* HCl (aq) (2 mL) and stirred at room temperature for 3 h The mixture was concentrated *in vacuo* to give the title compound as its HCl salt A portion of this material (40 mg) was dissolved in methanol and treated with solid supported carbonate resin (MP-Carbonate, Argonaut Technologies) to freebase the amines. After 30 minutes, the solution was filtered through a fritted tube and the solvents removed carefully *in vacuo* to give {2-[(2*S*)-2-pyrrolidinyl]ethyl}amine (30 mg) as its free base ^{1}H NMR ($CDCl_3$) δ 3.06 (m, 1 H), 2 94 (m, 1 H), 2.83 (m, 1 H), 2.79-2.69 (m, 2 H), 1.90-1 56 (m, 6 H).

f)

(3a*S*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7,9-dioxo-8-[(phenylmethyl)oxy]-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2'-4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carb

oxamide. A solution of 16a (30 mg, 0.06 mmol), {2-[(2*S*)-2-pyrrolidinyl]ethyl}amine (30 mg, 0.26mmol) and 2 drops of glacial acetic acid were heated under microwave conditions at 140 °C for 10 min. Upon cooling, Celite was added to the mixture and the solvents removed *in vacuo* and the material was purified via silica gel chromatography (2% CH_3OH/CH_2Cl_2 gradient elution) to give (3a*S*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7,9-dioxo-8-[(phenylmethyl)oxy]-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carboxamide (25 mg, 74%) as a film. ^{1}H NMR ($CDCl_3$) δ 10.44 (m, 1 H), 8.32 (s, 1 H), 7.59 (m, 2 H), 7.38-7.24 (m, 4 H), 6.80 (m, 2 H), 5.28-5.22 (m, 2 H), 4.67 (dd, *J* = 13.6, 2.8 Hz, 1 H), 4.62 (m, 2 H), 4.26 (m, 1 H), 4.11-4.03 (m, 2 H), 2.91 (m, 1 H), 2.81 (m, 1 H), 2.37 (m, 1 H), 2.24 (m, 1 H), 1.92 (m, 1 H), 1.82-1.76 (m, 3 H), 1.52-1.38 (m, 2 H). ES$^+$ MS: 535 (M+1).

g)

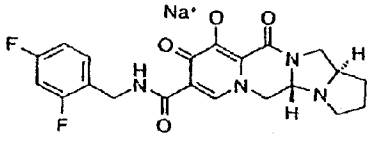
(3a*S*,13a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carboxamide.

To a solution of (3a*S*,13a*S*)-*N*-[(2,4-difluorophenyl)methyl]-7,9-dioxo-8-[(phenylmethyl)oxy]-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carboxamide (25 mg, 0.05 mmol) in methanol (8 mL) was added 10% Pd/C (10 mg). Hydrogen was bubbled through the reaction mixture via a balloon for 18 h. The resultant mixture was filtered through Celite with methanol and dichloromethane. The filtrate was concentrated *in vacuo* to give the title compound (14 mg, 67%) as a

white solid. ^{1}H NMR ($CDCl_3$) δ 12.53 (br, 1 H), 10.44 (s, 1 H), 8.29 (s, 1 H), 7.34 (m, 1 H), 6.78 (m, 2 H), 4.71-4.58 (m, 3 H), 4.29-4.14 (m, 3 H), 2.99 (m, 1 H), 2.88 (m, 1 H), 2.44 (m, 1 H), 2.30 (m, 1 H), 1.97-1.38 (m, 6 H); ES$^+$ MS: 445 (M+1).

Example Z-4:

(4a*S*,13a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2'-3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide sodium salt.



a) [(2*R*)-2-Pyrrolidinylmethyl]amine. To a solution of *N*-BOC-(2*R*)-2-(aminomethyl)-1-pyrrolidine (1.37 g, 6.85 mmol) in THF (20 mL) was added 4 *N* HCl (aq) (8 mL). The resultant solution was stirred at room temperature overnight. The solvents were removed *in vacuo* and the residue was treated with MP-carbonate resin in methanol and dichloromethane. After 1 h, the resin was removed via filtration through a fritted tube and the volatiles were removed carefully *in vacuo* to produce the free based amine (760 mg crude >100%) as a oil This material was used without further purification. ^{1}H NMR ($CDCl_3$) δ 3.13 (m, 1 H), 2.92 (m, 1 H), 2.82-2.62 (m, 5 H), 1.88-1.30 (m, 4 H)

b)

(4a*S*,13a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-9,11-dioxo-10-[(phenylmethyl)oxy]-2,3,4a,5

,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2'-3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide. In a similar manner as described in example Z-2 from 16a (435 mg, 0.93 mmol) and [(2*R*)-2-pyrrolidinylmethyl]amine (200 mg, 2.0 mmol) in 1,2-dichloroethane (20 mL) and 15 drops of glacial acetic acid was obtained (4a*S*,13a*R*)-*N*-[(2,4-difluorophenyl)methyl]-9,11-dioxo-10-[(phenylmethyl)oxy]-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2'-3,4]imidazo[1,2-*d*]pyrazine 8-carboxamide (321 mg, 67%) as a white solid ^{1}H NMR ($CDCl_3$) δ 10.41 (m, 1 H), 8.35 (s, 1 H), 7.56 (m, 2 H), 7.55-7.24 (m, 4 H), 6.80 (m, 2 H), 5.35 (d, *J* = 10.0 Hz, 1 H), 5.13 (d, *J* = 10.0 Hz, 1 H), 4.60 (m, 2 H), 4.38 (dd, *J* = 10.1, 3.2 Hz, 1 H), 4.21 (dd, *J* = 12.0, 6.8 Hz, 1 H), 4.04 (dd, *J* = 12.4, 2.8 Hz, 1 H), 3.77 (apparent t, *J* = 11.6 Hz, 1 H), 3.68 (m, 1 H), 3.11-3.00 (m, 2 H), 2.75 (m, 1 H), 2.08-1.84 (m, 3 H), 1.65 (m, 1 H); ESI MS: 521 (M+1)

c)

(4a*S*,13a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2'-3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide

In a similar manner as described in example Z-2 from (4a*S*,13a*R*)-*N*-[(2,4-difluorophenyl)methyl]-9,11-dioxo-10-[(phenylmethyl)oxy]-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2'-3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide (518 mg, 0.99 mmol) and 10% Pd/C (35 mg) in methanol (40 mL) was obtained (4a*S*,13a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2'-3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide (430 mg, 99%) as a white solid ^{1}H NMR ($CDCl_3$) δ 11.73 (m, 1 H), 10.36 (m, 1 H),

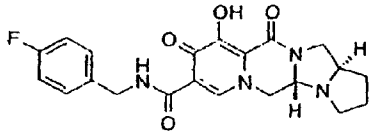
8.32 (s, 1 H), 7.35 (m, 1 H), 6 79 (m, 2 H), 4.64 (m, 2 H), 4.54 (dd, J = 10.8, 4.0 Hz, 1 H), 4.28-4.19 (m, 2 H), 3.90-3 79 (m, 2 H), 3.18-3.10 (m, 2 H), 2.84 (m, 1 H), 2.14-1.92 (m, 3 H), 1 72 (m, 1 H)

d)

(4a*S*,13a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2' 3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide sodium salt. In a similar manner as described in example Z-1 from (4a*S*,13a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide (430 mg, 1.0 mmol) and sodium hydroxide (1.0 mL, 1.0 M aq, 1.0 mmol) in 20 mL of ethanol was formed the corresponding sodium salt (425 mg, 94%) as a white solid ^{1}H NMR (D_2O) δ 7.85 (s, 1 H), 7 23 (m, 1 H), 6.82 (m, 2 H), 4.51-4.46 (m, 3 H), 4.28 (m, 1 H),3 95 (m, 1 H), 3.84 (m, 1 H), 3.62 (m, 1 H), 3.16 (m, 1 H), 2.89 (m, 1 H), 2 84 (m, 1H), 1.90 (m, 2 H), 1.73 (m, 1 H), 1 60 (m, 1 H). ES$^+$ MS: 431 (M+1).

Example Z-5:

(4a*S*,13a*R*)-*N*-[(4-Fluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2':3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide

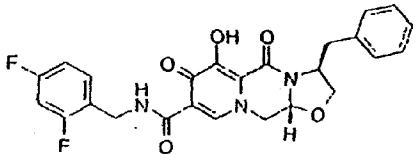


The title compound was made in two steps using a similar process to that described

in example Z-2 16 (60 mg, 0.13 mmol) and [(2*R*)-2-pyrrolidinylmethyl]amine (100 mg, 1.0 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4a*S*,13a*R*)-*N*-[(4-fluorophenyl)methyl]-9,11-dioxo-10-[(phenylmethyl)oxy]-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2'-3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide (60 mg, 91%). This material was hydrogenated in a second step as described in example Z-2 to give (4a*S*,13a*R*)-*N*-[(4-fluorophenyl)methyl]-10-hydroxy-9,11-dioxo-2,3,4a,5,9,11,13,13a-octahydro-1*H*-pyrido[1,2-*a*]pyrrolo[1',2'-3,4]imidazo[1,2-*d*]pyrazine-8-carboxamide (21 mg, 42%) as a white solid ^{1}H NMR ($CDCl_3$) δ 11.72 (m, 1 H), 1.37 (m, 1 H), 8.33 (s, 1 H), 7.29 (m, 2 H), 6.97 (m, 2 H), 4.57 (m, 2 H), 4.52 (m, 1 H), 4.24-4.19 (m, 2 H), 3.87-3.76 (m, 2 H), 3.14-3.07 (m, 2 H), 2.82 (m, 1 H), 2.11-1.89 (m, 3 H), 1.68 (m, 1 H); ES$^+$ MS: 413 (M+1).

Example Z-6

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide

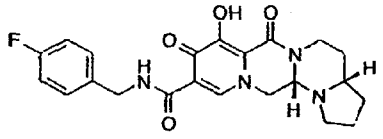


The title compound was made in two steps using a similar process to that described in example Z-2. 16a (37 mg, 0.08 mmol) and (2*S*)-2-amino-3-phenyl-1-propanol (35 mg, 0.24 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-5,7-dioxo-3-(phenylmethyl)-6-[(phenylmethy

l)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (41 mg, 91%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide. (25 mg, 75%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.47 (br, 1 H), 10.28 (m, 1 H), 8.35 (m, 1 H), 7.37-7.26 (m, 4 H), 7.18 (m, 2 H), 6.79 (m, 2 H), 5.03 (m, 1 H), 4.64-4.61 (m, 3 H), 4.40 (m, 1 H), 4.23 (apparent t, *J* = 7.2 Hz, 1 H), 3.96 (dd, *J* = 8.8, 6.4 Hz, 1 H), 3.88 (apparent t, *J* = 11.2 Hz, 1 H), 3.37 (dd, *J* = 13.6, 3.2 Hz, 1 H), 2.99 (dd, *J* = 13.2 8.8 Hz, 1 H); ES+ MS: 482 (M+1).

Example Z-7:

(3a*S*,13a*S*)-*N*-[(4-Fluorophenyl)methyl]-8-hydroxy-7,9-dioxo-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2'-4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*d*]pyrimidine-10-carboxamide

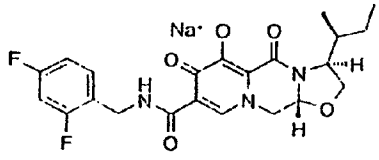


The title compound was made in two steps using a similar process to that described in example Z-2. 16 (84 mg, 0.13 mmol) and {2-[(2*S*)-2-Pyrrolidinyl]ethyl}amine (150 mg, 1.3 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3a*S*,13a*S*)-*N*-[(4-fluorophenyl)methyl]-7,9-dioxo-8-[(phenylmethyl)oxy]-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2'-4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*d*]pyrimidine-10-carboxamide (86 mg, 90%). This material was hydrogenated in a second step as described in

example Z-2 to give (3a*S*,13a*S*)-*N*-[(4-Fluorophenyl)methyl] 8-hydroxy-7,9-dioxo-1,2,3,3a,4,5,7,9,13,13a-decahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine-10-carboxamide. (63 mg, 88%) as a white solid. ^{1}H NMR ($CDCl_3/CD_3OD$) δ 10.45 (m, 1 H), 8.23 (s, 1 H), 7.35 (m, 2 H), 6.94 (t, *J* = 8.8 Hz, 2 H), 4.63 (m, 1 H), 4.58-4.48 (m, 2 H), 4.33 (dd, *J* = 13.6, 3.6 Hz, 1 H), 4.21 (m, 1 H), 4.11 (m, 1 H), 2.98 (m, 1 H), 2.85 (td, *J* = 13.2, 3.2 Hz, 1 H), 2.41 (m, 1 H), 2.29 (m, 1 H), 1.92 (m, 1 H), 1.83-1.75 (m, 3 H), 1.54-1.35 (m, 2 H); ES$^+$ MS: 427 (M+1).

Example Z-8:

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(1*S*)-1-methylpropyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide sodium salt

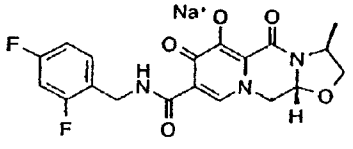


The title compound was made in two steps using a similar process to that described in example Z-1. 16a (417 mg, 0.89 mmol) and L-isoleucinol (259 mg, 2.21 mmol) were reacted in 1,2-dichloroethane (40 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-[(1*S*)-1-methylpropyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (426 mg, 90%). This material was hydrogenated in a second step as described in example Z-1 to give

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(1*S*)-1-methylpropyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (376 mg, 99%) as a coarse white solid. ^{1}H NMR ($CDCl_3$) δ 11.43 (br, 1 H), 10.27 (br, 1 H), 8.32 (s, 1 H), 7.33 (m, 1 H), 6.79 (m, 2 H), 5.26 (dd, *J* = 9.6, 4.0 Hz, 1 H), 4.62 (m, 2 H), 4.42-4.35 (m, 2 H), 4.19 (dd, *J* = 8.8, 7.2 Hz, 1 H), 4.01 (dd, *J* = 8.8, 5.6 Hz, 1 H), 3.86 (dd, *J* = 12.0, 10.0 Hz, 1 H), 2.27 (m, 1 H), 1.40 (m, 1 H), 1.15 (m, 1 H), 0.97 (t, *J* = 7.2 hz, 3 H), 0.91 (d, *J* = 6.8 Hz, 3 H). ES$^+$ MS 448 (M+1). This material (360 mg, 0.81 mmol) was treated with sodium hydroxide (0.81 mL, 1.0 M, 0.81 mmol) in ethanol (15 mL) as described in example Z-1 to provide its corresponding sodium salt (384 mg, 99%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.82 (m, 1 H), 7.80 (m, 1 H), 7.33 (m, 1 H), 7.18 (m, 1 H), 7.00 (m, 1 H), 5.14 (m, 1 H), 4.47 (d, *J* = 5.6 Hz, 2 H), 4.31 (m, 1 H), 4.18 (m, 1 H), 3.96 (m, 1 H), 3.84 (m, 1 H), 3.71 (m, 1 H), 3.40 (m, 1 H), 1.88 (m, 1 H), 1.36 (m, 1 H), 1.04 (m, 1 H), 0.85 (t, *J* = 7.2 Hz, 3 H), 0.80 (d, *J* = 6.8 Hz, 3 H); ES$^+$ MS 448 (M+1).

Example Z-9:

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide sodium salt.

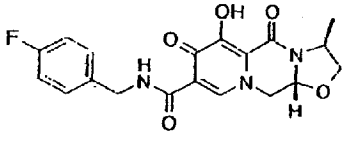


The title compound was made in two steps using a similar process to that described in example Z-1. 16a (510 mg, 1.08 mmol) and (2*S*)-2-amino-1-propanol (0.17 mL,

2.17 mmol) were reacted in 1,2-dichloroethane (20 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-methyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (500 mg, 93%). This material was hydrogenated in a second step as described in example Z-1 to give 3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (386 mg, 94%) as a tinted white solid. ^{1}H NMR ($CDCl_3$) δ 11.46 (m, 1 H), 10.28 (m, 1 H), 8.32 (s, 1 H), 7.35 (m, 1 H), 6.80 (m, 2 H), 5.30 (dd, *J* = 10.0, 4.0 Hz, 1 H), 4.63 (m, 2 H), 4.48-4.37 (m, 3 H), 3.91 (dd, *J* = 12.0, 10.0 Hz, 1 H), 3.73 (m, 1 H), 1.48 (d, *J* = 6.0 Hz, 3 H). ES$^+$ MS: 406 (M+1). This material (385 mg, 0.95 mmol) was treated with sodium hydroxide (0.95 mL, 1.0 M, 0.95 mmol) in ethanol (15 mL) as described in example Z-1 to provide its corresponding sodium salt (381 mg, 91%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.66 (m, 1 H), 7.93 (s, 1 H), 7.33 (m, 1 H), 7.20 (m, 1 H), 7.01 (m, 1 H), 5.19 (m, 1 H), 4.59 (m, 1 H), 4.48 (m, 2 H), 4.22 (m, 2 H), 3.75 (m, 1 H), 3.57 (m, 1 H), 1.24 (d, *J* = 5.6 Hz, 3 H)

Example Z-10:

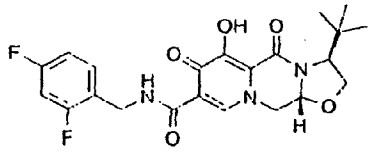
(3*S*,11a*R*)-*N*-[(4-Fluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.



The title compound was made in two steps using a similar process to that described in example Z-2. 16 (100 mg, 0.22 mmol) and (2*S*)-2-amino-1-propanol (0.10 mL, 1 28 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(4-fluorophenyl)methyl]-3-methyl-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (100 mg, 95%) This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11a*R*)-*N*-[(4-Fluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (80 mg, 99%) as a white solid ^{1}H NMR ($CDCl_3$) δ 11.43 (br, 1 H), 10.28 (br, 1 H), 8 35 (s, 1 H), 7 28 (m, 2 H), 6.97 (m, 2 H), 5.29 (m, 1 H), 4 55-4 38 (m, 5 H), 3.89 (apparent t, *J* = 10.8 Hz, 1 H), 3.70 (m, 1 H), 1.45 (d, *J* = 5 6 Hz, 3 H), ES MS 386 (M-1).

Example Z-11:

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-3-(1,1-dimethylethyl)-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide

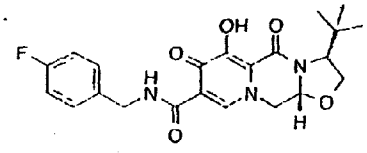


The title compound was made in two steps using a similar process to that described in example Z-2 16a (41 mg, 0.09 mmol) and freebased L-*tert*-leucinol (59 mg, 0.50 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11a*R*) *N*-[(2,4-difluorophenyl)methyl]-3-(1,1-dimethylethyl)-5,7-dioxo-6-[(phenylm

ethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (40 mg, 86%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl] 3-(1,1-dimethylethyl)-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (33 mg, 99%) as a tinted white solid ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1 H), 8.37 (s, 1 H), 7.34 (m, 1 H), 6.79 (m, 2 H), 5.43 (m, 1 H), 4.62 (m, 2 H), 4.36 (m, 2 H), 4.21 (m, 1 H), 3.99 (, 1 H), 3.81 (m, 1 H), 1.03 (s, 9 H); ES$^+$ MS: 448 (M+1).

Example Z-12:

(3*S*,11a*R*)-3-(1,1-Dimethylethyl)-*N*-[(4-fluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide

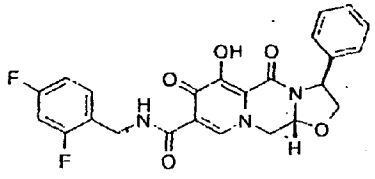


The title compound was made in two steps using a similar process to that described in example Z-2 16 (41 mg, 0.09 mmol) and freebased L-*tert*-leucinol (59 mg, 0.50 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11a*R*)-3-(1,1-dimethylethyl)-*N*-[(4-fluorophenyl)methyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (40 mg, 85%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11a*R*)-3-(1,1-Dimethylethyl)-*N*-[(4-fluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,

7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (32 mg, 97%) as a tinted white solid ^{1}H NMR ($CDCl_3$) δ 11.15 (br, 1 H), 10.32 (s, 1 H), 8.38 (s, 1 H), 7.29 (m, 2 H), 6.98 (m, 2 H), 5.43 (m, 1 H), 4.58 (m, 2 H), 4.36 (m, 2 H), 4.21 (m, 1 H), 3.99 (, 1 H), 3.79 (m, 1 H), 1.02 (s, 9 H); ES$^+$ MS 430 (M+1).

Example Z-13:

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide

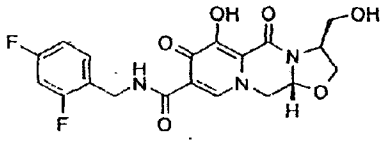


The title compound was made in two steps using a similar process to that described in example Z-2 16a (33 mg, 0.07 mmol) and L-phenylglycinol (19 mg, 0.14 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(4-fluorophenyl)methyl]-5,7-dioxo-3-phenyl-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (37 mg, 95%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (33 mg, 99%) as a tinted white solid ^{1}H NMR ($CDCl_3$) δ 11.23 (br, 1 H), 10.27 (s, 1 H), 8.39 (s, 1 H), 7.43-7.32 (m, 6 H), 6.80 (m, 2 H), 5.58 (d, J = 6.8 Hz, 1 H), 5.37 (apparent t, J = 6.8 Hz, 1 H), 4.67-4.62 (m, 3 H), 4.54 (d, J = 10.4 Hz, 1 H), 4.11 (m, 1 H), 4.01 (m, 1 H), ES$^+$

MS: 468 (M+1).

Example Z-14

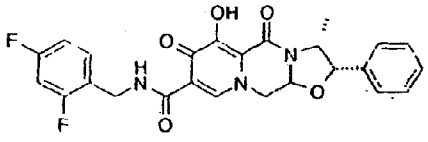
(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(hydroxymethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide



The title compound was made in two steps using a similar process to that described in example Z-2. 16a (50 mg, 0.10 mmol) and (2*R*)-2-amino-3-[(phenylmethyl)oxy]-1-propanol (0.1 mL) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-3-{[(phenylmethyl)oxy]methyl}-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (61 mg, 99%). This material was hydrogenated in a second step as described in example Z-2 to give (3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(hydroxymethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (37 mg, 87%) as a tinted white solid. ^{1}H NMR ($CDCl_3/CD_3OD$) δ 8.23 (s, 1 H), 7.32 (m, 1 H), 6.79 (m, 2 H), 5.31 (d, J = 7.6 Hz, 1 H), 4.56 (s, 2 H), 4.42-4.36 (m, 3 H), 4.17-4.11 (m, 2 H), 3.85 (m, 1 H), 3.62 (d, J = 11.2 Hz, 1 H).

Example Z-15.

(2*S*,3*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.

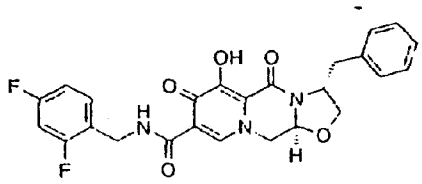


The title compound was made in two steps using a similar process to that described in example Z-2. 16a (25 mg, 0.05 mmol) and (1*S*,2*R*)-(+)-norephedrine (0.1 mL) were reacted in dichloromethane (2 mL) with acetic acid to give (2*S*,3*R*)-*N*-[(2,4 difluorophenyl)methyl]-3-methyl-5,7-dioxo-2-phenyl-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (30 mg, 99%). This material was hydrogenated in a second step as described in example Z-2 to give (2*S*,3*R*)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (25 mg, 91%) as a white solid. This material is a single diastereomer (>6:1 diastereomeric ratio but unconfirmed relative stereochemistry at the aminal center) ^{1}H NMR ($CDCl_3/CD_3OD$) δ 10.28 (m, 1 H), 8.38 (s, 1 H), 7.10-7.30 (m, 6 H), 6.78 (m, 2 H), 5.70 (d, *J* = 7.6 Hz, 1 H), 5.36 (d, *J* = 5.2 Hz, 1 H), 4.82 (m, 1 H), 4.61 (m, 2 H), 4.47 (d, *J* = 10.4 Hz, 1 H), 4.00 (apparent t, *J* = 10.4 Hz, 1 H), 0.94 (d, *J* = 6.4 Hz, 3 H); ES$^+$ MS: 482 (M+1)

Example Z-16.

(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-3-(phenylmethyl)-2,3,5,

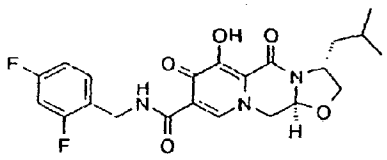
7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide



The title compound was made in two steps using a similar process to that described in example Z-2: .16a (34 mg, 0.07 mmol) and (2*R*)-2-amino-3-phenyl-1-propanol (D-phenylalaninol) (50 mg, 0.33 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*R*,11a*S*) *N*-[(2,4-difluorophenyl)methyl]-5,7-dioxo-3-(phenylmethyl)-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (29 mg, 70%). This material was hydrogenated in a second step as described in example Z-2 to give (3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl] 6-hydroxy 5,7 dioxo-3-(phenylmethyl)-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (24 mg, 98%) as a white solid ^{1}H NMR ($CDCl_3$) δ 11.46 (br, 1 H), 10.27 (m, 1 H), 8.33 (m, 1 H), 7.32-7.16 (m, 6 H), 6.78 (m, 2 H), 5.02 (m, 1 H), 4.61 (m, 3 H), 4.39 (m, 1 H), 4.22 (m, 1 H), 3.95 (m, 1 H), 3.87 (m, 1 H), 3.36 (m, 1 H), 2.97 (dd, J = 13.2 8.8 Hz, 1 H); ES$^+$ MS: 482 (M+1)

Example Z-17

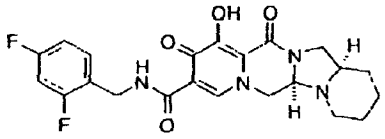
(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(2-methylpropyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide



The title compound was made in two steps using a similar process to that described in example Z-2. 16a (32 mg, 0.07 mmol) and (2*R*)-2-amino-4-methyl-1-pentanol (0.1 mL) were reacted in dichloromethane (2 mL) with acetic acid to give (3*R*,11a*S*)-*N*-[(2,4-difluorophenyl)methyl]-3-(2-methylpropyl)-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (43 mg, 99%). This material was hydrogenated in a second step as described in example Z-2 to give (3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(2-methylpropyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (32 mg, 90%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.47 (br, 1 H), 10.29 (m, 1 H), 8.35 (s, 1 H), 7.39 (m, 1 H), 6.80 (m, 2 H), 5.31 (m, 1 H), 4.62 (m, 2 H), 4.44 (m, 2 H), 4.37 (m, 1 H), 3.88 (m, 1 H), 3.84 (dd, *J* = 8.0, 5.6 Hz, 1 H), 2.04 (m, 1 H), 1.62 (m, 1 H), 1.41 (m, 1 H), 1.00 (d, *J* = 5.6 Hz, 3 H), 0.99 (d, *J* = 6.0 Hz, 3 H). ES$^+$ MS: 448 (M+1).

Example Z-18

(5a*R*,14a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-*a*]pyrido[1',2':3,4]imidazo[1,2-*d*]pyrazine-9-carboxamide



a) 1,1-Dimethylethyl (2*R*)-2-(aminocarbonyl)-1-piperidinecarboxylate. To a cold (0 °C) solution of (2*R*)-1-{[(1,1-dimethylethyl)oxy]carbonyl}-2-piperidinecarboxylic acid (1.0 g, 4.36 mmol) in THF (20 mL) was added triethylamine (0.60 mL, 4.36 mmol) followed by slow addition of methyl chloroformate (0.34 mL, 4.36 mmol). After a few minutes a suspension had formed. To this mixture was added concentrated NH_4OH (1.5 mL) and the solution was allowed to warm to rt as the bath warmed and stirred for a total of 4 h. The mixture was concentrated *in vacuo* and the residue was taken up in EtOAc. The organic layer was washed with citric acid, bicard and then brine, dried over Na_2SO_4. Filtration and concentration gave 1,1-dimethylethyl (2*R*)-2-(aminocarbonyl)-1-piperidinecarboxylate (1.0 g, 99%). ^{1}H NMR ($CDCl_3$) δ 6.03 (br, 1 H), 5.45 (br, 1 H), 4.77 (br, 1 H), 4.06 (br, 1 H), 2.82 (m, 1 H), 2.29 (m, 1 H), 1.67-1.43 (m, 13 H).

b) 1,1-Dimethylethyl (2*R*)-2-cyano-1-piperidinecarboxylate. To a cold (0 °C) solution of 1,1-dimethylethyl (2*R*)-2-(aminocarbonyl)-1-piperidinecarboxylate (269 mg, 1.17 mmol) in THF (10 mL) was added triethylamine (0.33 mL, 2.34 mmol) and then trifluoroacetic anhydride (0.17 mL, 1.17 mmol). The mixture was stirred at 0 °C for 1 h and concentrated *in vacuo*. The residue was taken up in EtOAc and washed successively with sodium bicarbonate, 0.5 *N* HCl and brine. The organics were dried over Na_2SO_4, filtered and concentrated to give 1,1-dimethylethyl (2*R*)-2-cyano-1-piperidinecarboxylate (255 mg, 99%) as a crystalline solid upon standing. ^{1}H NMR ($CDCl_3$) δ 5.23 (br, 1 H), 4.05 (br, 1 H), 2.93 (br, 1 H), 1.93-1.39 (m, 6 H), 1.46 (s, 9 H).

c) 1,1-Dimethylethyl (2*R*)-2-(aminomethyl)-1-piperidinecarboxylate An ammonia saturated ethanol solution of 1,1-dimethylethyl (2*R*) 2-cyano-1-piperidinecarboxylate (255 mg, 1.19 mmol) was reduced with Raney-Ni in a similar manner to that described in example Z-3 to give after filtration through a short plug of silica, 1,1-dimethylethyl (2*R*)-2-(aminomethyl)-1-piperidinecarboxylate (236 mg, 91%), as an oil. ^{1}H NMR ($CDCl_3/CD_3OD$) δ 4.15 (br, 1 H), 3.97 (m, 1 h), 2.96 (m, 1 H), 2.75-2.69 (m, 2 H), 2.23-2.08 (m, 3 H), 1 59-1 55 (m, 3 H), 1.43 (s, 9 H).

d) [(2*R*)-2-Piperidinylmethyl]amine bis HCl salt. A solution of 1,1-dimethylethyl (2*R*)-2-(aminomethyl)-1-piperidinecarboxylate (236 mg, 1.08 mmol) in THF (10 mL) was treated with 4 *N* HCl (3 mL) as described in example Z-3 to give the bis HCl salt of[(2*R*) 2-Piperidinylmethyl]amine ^{1}H NMR (DMSO-d_6) δ 9.67 (br, 1 H), 9.48 (br, 1 H), 8 48 (br, 2 H), 3 70 (br, 2 H), 3.20 (m, 1 H), 3.04 (m, 1 H), 2.86 (m, 1 H), 1 89-1.41 (m, 6 H).

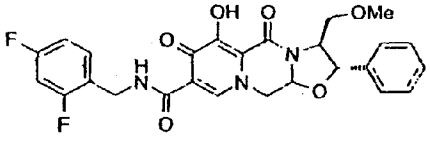
e)

(5a*R*,14a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-*a*]pyrido[1',2':3,4]imidazo[1,2-*d*]pyrazine-9-carboxamide The title compound was made in two steps using a similar process to that described in example Z-2. 16a (50 mg, 0 11 mmol) and [(2*R*) 2-Piperidinylmethyl]amine (150 mg, 1.31 mmol) (free based using carbonate resin as described in example Z-3) were reacted in dichloromethane (2 mL) with acetic acid to give

(5a*R*,14a*R*)-*N*-[(2,4-difluorophenyl)methyl]-10,12-dioxo-11-[(phenylmethyl)oxy]-1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-*a*]pyrido[1',2':3,4]imidazo[1,2-*d*]pyrazine-9-carboxamide (50 mg, 88%). This material was hydrogenated in a second step as described in example Z-2 to give (5a*R*,14a*R*)-*N*-[(2,4-difluorophenyl)methyl]-11-hydroxy-10,12-dioxo-1,2,3,4,5a,6,10,12,14,14a-decahydropyrido[1,2-*a*]pyrido[1',2':3,4]imidazo[1,2-*d*]pyrazine-9-carboxamide (11 mg, 44%) as a white solid. ^{1}H NMR ($CD_3OD/CDCl_3$) δ 10.46 (m, 1 H), 8.32 (s, 1 H), 7.31 (m, 1 H), 6.80 (m, 2 H), 4.64-4.52 (m, 3 H), 4.14 (dd, *J* = 10.4, 2.8 Hz, 1 H), 3.91-3.82 (m, 2 H), 3.19 (apparent t, *J* = 10.8 Hz, 1 H), 3.08 (d, *J* = 10.4 Hz, 1 H), 2.50 (m, 1 H), 2.27 (m, 1 H), 1.99-1.30 m, 6 H); ES$^+$ MS: 445 (M+1).

Example Z-19

(2*S*,3*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(methyloxy)methyl]-5,7-dioxo-2-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide

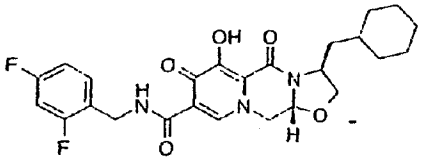


The title compound was made in two steps using a similar process to that described in example Z-2. 16a (36 mg, 0.07 mmol) and (2*R*)-2-amino-4-methyl-1-pentanol (0.1 mL) were reacted in dichloromethane (2 mL) with acetic acid to give 2*S*,3*S*)-*N*-[(2,4-difluorophenyl)methyl]-3-[(methyloxy)methyl]-5,7-dioxo-2-phenyl-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-c

arboxamide. This material was hydrogenated in a second step as described in example Z-2 to give (2*S*,3*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[(methyloxy)methyl]-5,7-dioxo-2-phenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (25 mg, 64% for 2 steps) as a white solid. This material is a single diastereomer (>6:1 diastereomeric ratio but unconfirmed relative stereochemistry at the aminal center) ^{1}H NMR ($CDCl_3$) δ 11.48 (br, 1 H), 10.30 (m, 1 H), 8.39 (s, 1 H), 7.39-7.24 (m, 6 H), 6.78 (m, 2 H), 5.46 (dd, *J* = 10.0, 3.6 Hz, 1 H), 5.33 (d, *J* = 7.2 Hz, 1 H), 4.63 (m, 2 H), 4.54 (dd, *J* = 12.4, 4.0 Hz, 1 H), 4.19 (m, 1 H), 4.12 (dd, *J* = 10.4, 3.2 Hz, 1 H), 4.06 (m, 1 H), 3.55 (dd, *J* = 10.4, 1.6 Hz, 1 H), 3.40 (s, 3 H). ES$^+$ MS: 512 (M+1)

Example Z-20.

(3*S*,11a*R*)-3-(Cyclohexylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide

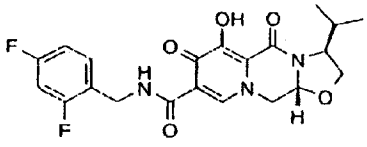


The title compound was made in two steps using a similar process to that described in example Z-2. 16a (36 mg, 0.08 mmol) and (2*S*)-2-amino-3-cyclohexyl-1-propanol (30 mg, 0.19 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (3*S*,11a*R*)-3-(cyclohexylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (27 mg, 61%). This material was hydrogenated in a second step as described in

example Z-2 to give (3*S*,11a*R*)-3-(cyclohexylmethyl)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (25 mg, 99%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.48 (br, 1 H), 10.28 (s, 1 H), 8.33 (s, 1 H), 7.33 (m, 1 H), 6.78 (m, 2 H), 5.29 (m, 1 H), 4.61 (m, 2 H), 4.47-4.33 (m, 3 H), 3.87-3.81 (m, 2 H), 2.05 (m, 1 H), 1.75-1.64 (m, 6 H), 1.39 (m, 1 H), 1.25-1.14 (m, 3 H), 1.02-0.97 (m, 2 H); ES$^+$ MS 488 (M+1)

Example Z-21

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1-methylethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.

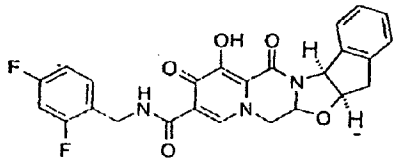


The title compound was made in two steps using a similar process to that described in example Z-1 16a (42 mg, 0.09 mmol) and (2*S*)-2-amino-3-methyl-1-butanol (0.1 mL) were reacted in 1,2-dichloroethane (8 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-(1-methylethyl)-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (40 mg, 86%). This material was hydrogenated in a second step as described in example Z-1 to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-(1-methylethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (34 mg,

99%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 10.29 (br, 1 H), 8.36 (s, 1 H), 7.33 (m, 1 H), 6.79 (m, 2 H), 5.29 (d, J = 6.4 Hz, 1 H), 4.61 (m, 2 H), 4.44 (d, J = 9.6 Hz, 1 H), 4.34 (m, 1 H), 4.17 (m, 1 H), 4.02 (dd, J = 8.4, 5.2 Hz, 1 H), 3.86 (m, 1 H), 2.37 (m, 1 H), 0.97 (m, 6 H); ES$^+$ MS: 434 (M+1)

Example Z-22.

(5a*R*,14a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-5a,6a,7,11,13,14a-hexahydro-5*H*-indeno[1',2':4,5][1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-10-carboxamide



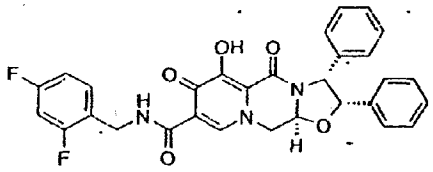
The title compound was made in two steps using a similar process to that described in example Z-1. 16a (42 mg, 0.09 mmol) and (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (100 mg, 0.67 mmol) were reacted in 1,2-dichloroethane (5 mL) with acetic acid to give (5a*R*,14a*S*)-*N*-[(2,4-difluorophenyl)methyl]-11,13-dioxo-12-[(phenylmethyl)oxy]-5a,6a,7,11,13,14a-hexahydro-5*H*-indeno[1',2':4,5][1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-10-carboxamide (55 mg, 99%). This material was hydrogenated in a second step as described in example Z-1 to give (5a*R*,14a*S*)-*N*-[(2,4-difluorophenyl)methyl]-12-hydroxy-11,13-dioxo-5a,6a,7,11,13,14a-hexahydro-5*H*-indeno[1',2':4,5][1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-10-carboxamide (45 mg, 97%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 10.28 (m, 1 H), 8.33 (s, 1 H),

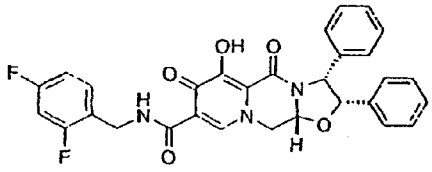
7.69 (d, J = 7.2 Hz, 1 H), 7.34-7.19 (m, 4 H), 6.78 (m, 2 H), 5.96 (d, J = 6.0 Hz, 1 H), 5.32 (m, 1 H), 5.22 (m, 1 H), 4.60 (m, 2 H), 4.45 (d, J = 9.2 Hz, 1 H), 3.96 (apparent t, J = 10.8 Hz, 1 H), 3.40 (dd, J = 18.0, 6.8 Hz, 1 H), 3.24 (d, J = 17.6 Hz, 1 H). ESI-MS: 480 (M+1).

Example Z-23 & Z-24.

(2*S*,3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide &

(2*S*,3*R*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide



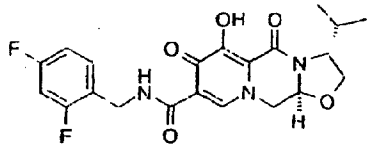


The title compounds were made in two steps using a similar process to that described in example Z-1. **16a** (40 mg, 0.09 mmol) and (1*S*,2*R*)-2-amino-1,2-diphenylethanol (50 mg, 0.23 mmol) were reacted in 1,2-dichloroethane (5 mL) with acetic acid to give (2*S*,3*R*,11a*S*)-*N*-[(2,4-difluorophenyl)methyl]-5,7-dioxo-2,3-diphenyl-6-[(phenylmethyl)

oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (34 mg, 63%) and (2*S*,3*R*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-5,7-dioxo-2,3-diphenyl-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (13 mg, 24%). These materials were hydrogenated in a second step as described in example Z-1 to give (2*S*,3*R*,11a*S*) *N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (example Z-23, 29 mg, 99%), as a white solid and (2*S*,3*R*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-5,7-dioxo-2,3-diphenyl-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (example Z-24, 10 mg, 89%) as a white solid respectively. For example Z-23: ^{1}H NMR (DMSO-d_6) δ 10.29 (t, J = 5.6 Hz, 1 H), 8.55 (s, 1 H), 7.38 (m, 1 H), 7.22 (m, 1 H), 7.11-6.95 (m, 11 H), 6.16 (dd, J = 10.4, 3.6 Hz, 1 H), 5.71 (m, 2 H), 4.90 (m, 1 H), 4.54 (m, 2 H), 4.38 (t, J = 11.2 Hz, 1 H). ES$^+$ MS 544 (M+1). For example Z-24: ^{1}H NMR ($CDCl_3$) δ 11.64 (br, 1 H), 10.30 (s, 1 H), 8.45 (s, 1 H), 7.31 (m, 1 H), 7.01-6.90 (m, 10 H), 6.80 (m, 2 H), 5.56 (m, 2 H), 5.42 (d, J = 6.4 Hz, 1 H), 4.73 (m, 1 H), 4.63 (m, 2 H), 4.49 (m, 1 H); ES$^+$ MS: 544 (M+1)

<u>Example Z-25:</u>

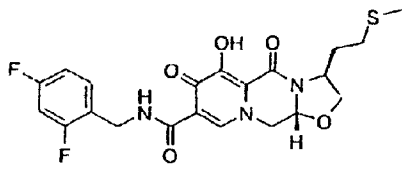
<u>(3*R*,11a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1-methylethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide.</u>



The title compound was made in two steps using a similar process to that described in example Z-1. 16a (40 mg, 0.09 mmol) and (2*R*)-2-amino-3-methyl-1-butanol (0.1 mL) were reacted in 1,2-dichloroethane (8 mL) with acetic acid to give (3*R*,11a*S*)-*N*[(2,4-difluorophenyl)methyl]-3-(1-methylethyl)-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (41 mg, 92%). This material was hydrogenated in a second step as described in example Z-1 to give (3*R*,11a*S*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1-methylethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (32 mg, 91%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.42 (br, 1 H), 10.27 (br, 1 H), 8.34 (s, 1 H), 7.31 (m, 1 H), 6.78 (m, 2 H), 5.28 (d, *J* = 6.0 Hz, 1 H), 4.60 (m, 2 H), 4.42 (m, 1 H), 4.33 (m, 1 H), 4.16 (m, 1 H), 4.01 (dd, *J* = 8.8, 5.2 Hz, 1 H), 3.85 (m, 1 H), 2.37 (m, 1 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 0.95 (d, *J* = 6.4 Hz, 3 H). ES$^+$ MS 434 (M+1)

Example Z-26

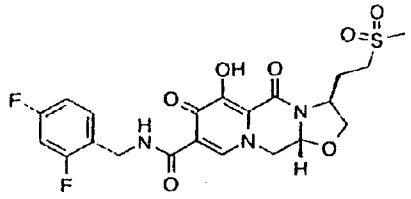
(3*S*,11a*R*)-*N*[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylthio)ethyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide



The title compound was made in two steps using a similar process to that described in example Z-1. 16a (43 mg, 0.09 mmol) and (2*S*)-2-amino-4-(methylthio)-1 butanol (0.1 mL) were reacted in 1,2-dichloroethane (5 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-[2-(methylthio)ethyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (41 mg, 81%). This material (20 mg, 0.04 mmol) was treated with trifluoroacetic acid (1 mL) in dichloromethane (3 mL) at 0 °C to rt over 6 h. The mixture was concentrated *in vacuo* and subjected to reverse phase preparative HPLC purification to provide (3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylthio)ethyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (12 mg, 72%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.35 (br, 1 H), 10.25 (s, 1 H), 8.34 (s, 1 H), 7.33 (m, 1 H), 6.79 (m, 2 H), 5.32 (m, 1 H), 4.62-4.53 (m, 3 H), 1.43-1.39 (m, 2 H), 3.91-3.87 (m, 2 H), 2.63-2.53 (m, 2 H), 2.39 (m, 1 H), 2.12 (s, 3 H), 1.89 (m, 1 H). ESI MS: 466 (M+1).

Example Z-27

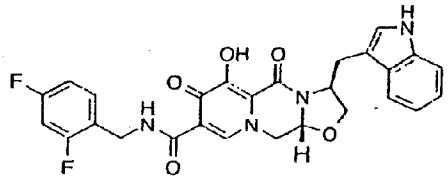
(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylsulfonyl)ethyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide



To a solution of (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-[2-(methylthio)ethyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (20 mg, 0.04 mmol) in dichloromethane (5 mL) at 0 °C was added *m*-CPBA (20 mg, 70%, 0.082 mmol). The resultant solution was allowed to warm as the bath warmed and stirred a total of 3 h. The reaction was quenched by the addition of $Na_2S_2O_3$ (aq) and sodium bicarbonate. The layers were separated and the organic layer washed with brine. The aqueous layer was extracted with dichloromethane and the combined organics dried over Na_2SO_4. Filtration and concentration provided (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-[2-(methylsulfonyl)ethyl]-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (26 mg, 99%) as a white solid. This material was hydrogenated in a second step as described in example Z-1 to give (3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-[2-(methylsulfonyl)ethyl]-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (22 mg, 99%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 11.00 (br, 1 H), 10.16 (s, 1 H), 8.33 (s, 1 H), 7.36 (m, 1 H), 6.81 (m, 2 H), 5.42 (m, 1 H), 4.62 (m, 3 H), 4.41 (m,2 H), 3.93 (m, 2 H), 3.31 (m, 2 H), 2.98 (s, 3 H), 2.40 (m, 1 H), 2.28 (m, 1 H); ES+ MS: 498 (M+1).

Example Z-28

(3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1*H*-indol-3-ylmethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide



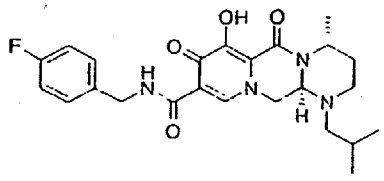
The title compound was made in two steps using a similar process to that described in example Z-1 16a (43 mg, 0.09 mmol) and (2*S*)-2-amino-3-(1*H*-indol-3-yl)-1-propanol (100 mg, 0.52 mmol) were reacted in 1,2-dichloroethane (5 mL) with acetic acid to give (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-(1*H*-indol-3-ylmethyl)-5,7-dioxo-6-[(phenylmethyl)oxy]-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (36 mg, 64%). This material was hydrogenated in a second step as described in example Z-1 to give (3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-(1*H*-indol-3-ylmethyl)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (29 mg, 95%) as a white solid ^{1}H NMR ($CDCl_3/CD_3OD$) δ 10.34 (m, 1 H), 8.98 (br, 1 H), 8.24 (s, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.32 (m, 2 H), 7.15-7.01 (m, 3 H), 6.78 (m, 2 H), 4.94 (d, J = 6.8 Hz, 1 H), 4.71 (d, J = 5.6 Hz, 1 H), 4.59 (m, 2 H), 4.35 (d, J = 10.1 Hz, 1 H), 4.22 (m, 1 H), 3.99 (m, 1 H), 3.81 (m, 1 H), 3.40 (dd, J = 13.6, 11.6 Hz, 1 H), 3.18 (dd, J = 14.0, 8.4 Hz, 1 H); ES$^+$ MS 521 (M+1).

Example Z-29:

(1*R*,12a*R*)-*N*-[(1-fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-diox

o-1,2,3,4,6,8,12,12a-octahydropyrido[1',2',4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamid

e.



a) (2*R*)-2-({[(1,1-Dimethylethyl)oxy]carbonyl}amino)propyl methanesulfonate. To a stirred solution of 1,1-dimethylethyl [(1*R*)-2-hydroxy-1-methylethyl]carbamate (5.00 g, 28.5 mmol) and triethylamine (5.92 mL, 42.9 mmol) in CH_2Cl_2 (30 mL) cooled to 0 °C and under a nitrogen atmosphere was added dropwise a solution of methanesulfonyl chloride (2.43 mL, 31.5 mmol) in CH_2Cl_2 (25 mL). Stirring was continued for 20 minutes at 0 °C, after which time the reaction was judged complete by TLC analysis (1:1 hexanes/EtOAc). The solution was poured into water and the layers were separated. The organic phase was washed with 0.1 N HCl and then with 5% $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated to give (2*R*)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)propyl methanesulfonate (7.08 g, 98%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, *J* = 6.8 Hz, 3H), 1.44 (s, 9H), 3.03 (s, 3H), 3.97 (m, 1H), 4.15 (dd, *J* = 4.2, 9.8 Hz, 1H), 4.21 (m, 1H), 4.61 (br s, 1H).

b) 1,1-Dimethylethyl [(1*R*)-2-cyano-1-methylethyl]carbamate. To a stirred solution of (2*R*)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)propyl methanesulfonate (7.08 g, 27.9 mmol) in DMSO (50 mL) was added NaCN (3.78 g, 84.0 mmol). The solution was stirred at 70 °C for 2 hours, over which time the formation of a precipitate was

observed After cooling at room temperature, water was added and the mixture was extracted with Et_2O. The ethereal layers were washed with a brine solution, dried over Na_2SO_4, filtered and concentrated to give 1,1-dimethylethyl [(1*R*)-2-cyano-1-methylethyl]carbamate (3.81 g, 73%) as a pale yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, *J* = 6.8 Hz, 3H), 1.42 (s, 9H), 2.51 (dd, *J* = 3.8, 16.6 Hz, 1H), 2.73 (m, 1H), 3.93 (m, 1H), 4.63 (br s, 1H).

c) 1,1-Dimethylethyl [(1*R*)-3-amino-1-methylpropyl]carbamate. A solution of 1,1-dimethylethyl [(1*R*)-2-cyano-1-methylethyl]carbamate (1.30 g, 7.1 mmol) in ethanol saturated with anhydrous ammonia was treated with Raney-Ni (1.5 mL of 50% aq. Suspension) and 55 psi of H_2 overnight. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (80:19:1 CH_2Cl_2/MeOH/NH_4OH (37%) gradient elution) through a short plug of silica gel to give 1,1-dimethylethyl [(1*R*)-3 amino-1-methylpropyl]carbamate (1.37 g, 100%) as a clear oil that solidified ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, *J* = 6.8 Hz, 3H), 1.43-1.62 (m, 13H), 2.76 (m, 2H), 3.77 (m, 1H), 4.57 (m, 1H).

d) 1,1-Dimethylethyl [(1*R*)-1-methyl-3-[(2-methylpropyl)amino]propyl]carbamate. 1,1 dimethylethyl [(1*R*)-3-amino-1-methylpropyl]carbamate (0.320 g, 1.70 mmol), isobutyraldehyde (150 µL, 1.62 mmol), and sodium triacetoxyborohydride (0.512 g, 2.42 mmol) were stirred in anhydrous dichloroethane (10 mL) at ambient temperature overnight The reaction was quenched by the addition of saturated $NaHCO_3$ and

then extracted with dichloromethane. The combined extracts were washed with water, dried over Na_2SO_4, filtered and concentrated The residue was purified by flash chromatography (80:19 1 CH_2Cl_2/MeOH/NH_4OH (37%) gradient elution) through a short plug of silica gel to afford 1,1-dimethylethyl {(1*R*)-1-methyl-3-[(2-methylpropyl)amino]propyl}carbamate (0.158 g, 40%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, *J* = 6.4 Hz, 6H), 1.13 (d, *J* = 6.4 Hz, 3H), 1.42-1.51 (m, 11H), 1.67-1.75 (m, 2H), 2.33-2 42 (m, 2H), 2.58-2.72 (m, 2H), 3.72 (m, 1H), 5.20 (m, 1H)

e) [(3*R*)-3-Aminobutyl](2-methylpropyl)amine. An ice cold solution of 1,1-dimethylethyl {(1*R*)-1-methyl-3-[(2-methylpropyl)amino]propyl}carbamate (0 158 g, 0.65 mmol) in THF (8 mL) was treated with 4 *N* HCl (aq) (2 mL) and then stirred at room temperature for 2 h. The mixture was concentrated *in vacuo* to give [(3*R*)-3-aminobutyl](2-methylpropyl)amine dihydrochloride The HCl salt was then dissolved in dichloromethane and a minimal amount of methanol and treated with solid supported carbonate resin (MP-Carbonate, Argonaut Technologies) After 30 minutes, the solution was filtered through a fritted tube and the solvents removed carefully *in vacuo* to give [(3*R*)-3-aminobutyl](2-methylpropyl)amine (65 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0 88 (d, *J* = 6 0 Hz, 6H), 1.06 (d, *J* = 5 6 Hz, 3H), 1.23-1 53 (m, 5H), 1 71-1.74 (m, 1H), 2 39 (m, 2H), 2.65 (m, 2H), 2.97 (m, 1H).

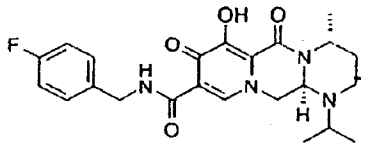
f)

(4*R*,12a*R*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1 (2-methylpropyl) 6,8-dio

xo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide. The title compound was made in two steps using a similar process to that described in example Z-2. 16 (40 mg, 0.09 mmol) and [(3*R*)-3-aminobutyl](2-methylpropyl)amine (65 mg, 0.45 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*R*,12a*R*)-*N*-[(4-fluorophenyl)methyl]-4-methyl-1-(2-methylpropyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (29 mg, 60%). This material was hydrogenated in a second step as described in example Z-2 to give (4*R*,12a*R*)-*N*-[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (18 mg, 75%) as a tan solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H), 1.32 (d, *J* = 7.2 Hz), 1.45-1.49 (m, 1H), 1.57-1.67 (m, 1H), 2.03-2.12 (m, 2H), 2.21-2.27 (m, 1H), 2.73-2.79 (m, 1H), 2.87-2.92 (m, 1H), 4.16-4.24 (m, 2H), 4.45 (s, 1H), 4.54-4.64 (m, 2H), 4.96-4.99 (m, 1H), 6.96-7.00 (m, 2H), 7.29-7.32 (m, 2H), 8.27 (s, 1H), 10.46 (s, 1H), 12.55 (s, 1H). ES$^+$ MS: 456 (M+1).

Example Z-30

(4*R*,12a*R*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide



a) [(3*R*)-3-Aminobutyl](1-methylethyl)amine The free diamine was prepared in a similar manner as described in example Z-29. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (d, *J* = 6.4 Hz, 6H), 1.06 (d, *J* = 6.4 Hz, 3H), 1.41-1.58 (m, 5H), 2.62-2.66 (m, 2H), 2.74-2.80 (m, 1H), 2.92-3.00 (m, 1H).

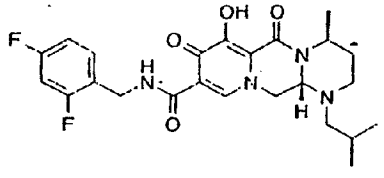
b)

(4*R*,12a*R*)-*N*-[(4-Fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide The title compound was made in two steps using a similar process to that described in example Z-2. 16 (40 mg, 0.088 mmol) and [(3*R*)-3-aminobutyl](1-methylethyl)amine (78 mg, 0.60 mmol) were reacted in dichloromethane (2 mL) with acetic acid to give (4*R*,12a*R*)-*N*-[(4-fluorophenyl)methyl]-4-methyl-1-(1-methylethyl)-6,8-dioxo-7-[(phenylmethyl)oxy]-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (26 mg, 56%). This material was hydrogenated in a second step as described in example Z-2 to give (4*R*,12a*R*)-*N*-[(4-fluorophenyl)methyl]-7-hydroxy-4-methyl-1-(1-methylethyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide (21 mg, 90%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, *J* = 5.6 Hz, 3H), 1.06 (d, *J* = 6.0 Hz, 3H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.57 (m, 1H), 1.98 (m, 1H),

2.70-2.82 (m, 2H), 3.15 (m, 1H), 4.15-4.19 (m, 1H), 4.30 (m, 1H), 4.48 (s, 1H), 4.54-4.59 (m, 2H), 4.97 (m, 1H), 6.98 (m, 2H), 7.29-7.32 (m, 2H), 8.27 (s, 1H), 10.49 (s, 1H), 12.52 (s, 1H).

Example Z-31

(4*S*,12a*S*)-*N*-[(2,4-Difluorophenyl)methyl]-7-hydroxy-4-methyl-1-(2-methylpropyl)-6,8-dioxo-1,2,3,4,6,8,12,12a-octahydropyrido[1',2':4,5]pyrazino[1,2-*a*]pyrimidine-9-carboxamide



a) 1,1-Dimethylethyl [(1*S*)-2-cyano-1-methylethyl]carbamate The nitrile was prepared in two steps using a modified procedure as described in example Z-29 To a stirred solution of (2*S*)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)propyl methanesulfonate (8.40 g, 35.2 mmol) in DMSO (50 mL) and KCN (6.51 g, 100.0 mmol) cooled to 0 °C was added 18-crown-6 (9.05 g, 34.3 mmol). The solution was allowed to warm to room temperature and then heated to 70 °C for 1 hour. After cooling at room temperature, water was added and the mixture was extracted with Et_2O. The ethereal layers were washed with a brine solution, dried over Na_2SO_4, filtered and concentrated to give 1,1-dimethylethyl [(1*S*)-2-cyano-1-methylethyl]carbamate (5.37 g, 88%) as a pale yellow solid ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, *J* = 6.8 Hz, 3H), 1.44 (s, 9H), 2.52 (dd, *J* = 4.0, 16.4 Hz, 1H), 2.74 (m, 1H), 3.95 (m, 1H), 4.65 (br s, 1H)