RAJESHWARI & ASSOCIATES
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March 23, 2021

The Controller of Patent
The Patent Office
Boudhik Sampada Bhawan, Plot No. 32
Sector 14, Dwarka, New Delhi-110078

Re: **REPRESENTATION u/s 25(1) of the Patent act – By SANKALP REHABILITATION TRUST against Indian Patent Application No. 201817004931 filed on 09/02/2018**
Applicant: **THE GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT INC.**

Respected Sir,

We submit herewith Pre-Grant Opposition under Section 25(1) of the Patent Act, 2005 along with evidence and Form 7A.

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.

We crave the 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.

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

Thanking you,

Yours faithfully,

RAJESHWARI H. IN/PA - 0358
AGENT FOR THE OPPONENT
OF RAJESHWARI AND ASSOCIATES

Encl: As stated

C.C: K & S PARTNERS
515-B, Platinum Tower, 5th Floor, Sohna Road, Sector 47,
Gurgaon - 122002, National Capital Region, India
Email.: gurgaon@knspartners.com;

BEFORE THE CONTROLLER OF PATENTS, NEW DELHI

IN THE MATTER OF:

The Patents Act, 1970 as amended by the Patents (Amendment) Act 2005, and The Patents Rules, 2003, as amended by The Patents (Amendment) Rules, 2006
AND
IN THE MATTER of Pre-grant opposition under Section 25(1)
AND
IN THE MATTER of Indian Patent Application No. 201817004931

IN THE MATTER OF:

SANKALP REHABILITATION TRUST .....OPPONENT

VS.

THE GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT INC. .....APPLICANT

PRE-GRANT OPPOSITION BY SANKALP REHABILITATION TRUST

INDEX

Dated this day 23rd of March, 2021

RAJESHWARI H. IN/PA – 0358
AGENT FOR THE OPPONENT
OF RAJESHWARI AND ASSOCIATES

To,
The Controller of Patents
The Patent Office, New Delhi

FORM 7A
THE PATENTS ACT,
1970 (39 OF 1970)
AND
THE PATENTS RULES, 2003
REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT
[See Rule 55]

We, **SANKALP REHABILITATION TRUST**, having its registered office at SS Bengali Municipal School, First Floor, Thakurdwar Road, Charni Road East, Mumbai – 400002, hereby give Notice of opposition to the grant of patent in respect of Indian Patent Application No. 201817004931 filed on 09/02/2018 made by THE GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT INC. on the grounds.

(a) Section 25(1)(b): Lack of novelty
(b) Section 25(1)(e): Lack of inventive step
(c) Section 25(1)(f): Invention is not patentable under section 3 (d)
(d) 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.
(e) Section 25(1)(h): Failed to disclose to the Controller the information required by section 8.

(Detailed grounds are set out in the Opposition)

Our address for service in India is:

RAJESHWARI H.
RAJESHWARI & ASSOCIATES
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SHIVALIK ENCLAVE
MALVIYA NAGAR
NEW DELHI – 110017
INDIA
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Fax: +91-11-43851067
Mobile No. 9910206718
Email: rajeshwari@ralegal.co.in;

Dated this 23rd day of March, 2021

RAJESHWARI H. IN/PA – 0358
AGENT FOR THE OPPONENT
OF RAJESHWARI AND ASSOCIATES

To
The Controller of Patents
Patent Office, New Delhi

BEFORE THE CONTROLER OF PATENTS, THE PATENT OFFICE, NEW DELHI

In the matter of Section 25(1) of The Patents Act,1970 as amended by The Patents (Amendment) Act 2005;

AND

In the matter of Rule 55 of The Patents Rules 2003 as amended by thePatent (Amendment) Rules, 2006

AND

IN THE MATTER of Indian Patent Application 201817004931 filed on 09/02/2018 in the name of THE GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT INC.

REPRESENTATION BY:

SANKALP REHABILITATION TRUST .....OPPONENT

VS.

THE GLOBAL ALLIANCE FOR
TB DRUG DEVELOPMENT INC. .....APPLICANT

REPRESENTATION BY WAY OF PRE-GRANT OPPOSITION UNDER SECTION 25(1) OF THE PATENTS ACT, 1970

We, **SANKALP REHABILITATION TRUST,** an Indian citizen, hereby submit my representation by way of oppostion to the grant of patent in respect of Indian Patent Application 201817004931 filed on 09/02/2018 in the name of THE GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT INC. entitled "SUBSTITUTED PHENYLOXAZOLIDINONES FOR ANTIMICROBIAL THERAPY".

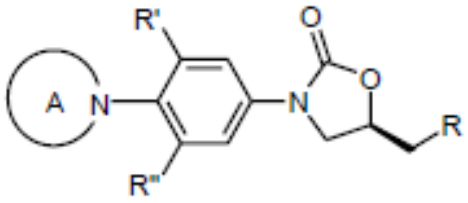
STATEMENT OF CASE OF OPPONENT

1. The Opponent has learnt that the Applicant has filed an Indian Patent Application No. 201817004931 (hereinafter "the Impugned Application") on 19/02/2018. The Impugned application was published in the Official Journal of the patent office on 11/05/2018, which is currently pending before the Patent Office.

2. The Impugned application is entitled "SUBSTITUTED PHENYLOXAZOLIDINONES FOR ANTIMICROBIAL THERAPY".

3. The opponent by way of this present pre-grant opposition submits that the claims currently pending on record are not patentable under the provisions provided in this Act. The claims as filed and currently on record are annexed herewith as **Annexure-1** and reproduced herein below for ready reference:

1. A compound of Formula I, or a pharmaceutically acceptable salt, hydrate, or solvate of:



(I)

wherein:

R is independently OR_1, $OC(O)R_2$, $OC(O)NHR_2$, $OS(O_2)R_2$, $NHS(O)_2R_2$, NR_3R_4, $NHC(O)R_5$;

R' and R'' are independently H, F, Cl or OMe;

each R_1 is independently H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, wherein said alkyl, cycloalkyl are optionally substituted with 1 to 4 groups selected from halo, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkyloxy;

each R_2 is independently C_1-C_6 alkyl, C_3-C_8 cycloalkyl, heterocyclyl, heteroaryl or aryl, wherein said alkyl, cycloalkyl, heterocyclyl, heteroaryl, or aryl are optionally substituted with 1 to 4 groups selected from halo, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 acyloxy, CF_3, NO_2, CN and NH_2;

each R_3 and R_4 is independently H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, heterocyclyl heteroaryl, aryl; or R_3 and R_4 taken together with the nitrogen to which they are attached, form a 4- to 8-membered heterocyclyl or heteroaryl with 1 to 3 additional heteroatoms selected from O, S, or N, wherein said alkyl, cycloalkyl, heterocyclyl, heteroaryl, or aryl are optionally substituted with 1 to 4 groups selected from halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, NO_2, CN;

each R_5 is independently C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, heteroaryl, aryl, wherein said alkyl, cycloalkyl, heterocyclyl, heteroaryl, or aryl are optionally substituted with 1 to 4 groups selected from halo, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 acyloxy, CF_3, NO_2, CN and NH_2;

Ring A is selected from:

wherein,

each R_6 and R_7 is independently H, F, CH_3, CH_2CH_3, CF_3, phenyl;

X = O, S, SO, SO_2;

Y = O, S, SO, SO_2, and NR_8;

m is 2;

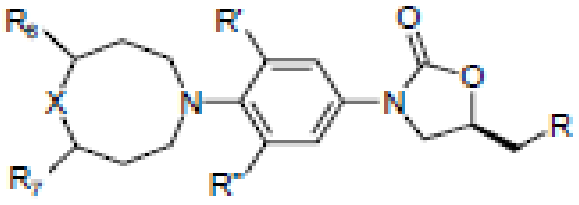
n is 1, or 2;

p is 1, or 2;

q is 1, or 2;

R_8 in independently H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $COCH_3$, and p-toluenesulfonyl, wherein said alkyl, cycloalkyl are optionally substituted with 1 to 4 groups selected from halo, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 acyloxy, CF_3, NO_2, CN and NH_2.

The compound as claimed in claim 1, wherein the compound is represented by Formula III:



III

wherein,

R is independently OR_1, $OC(O)R_2$, NR_3R_4, $NHS(O)_2R_2$, $NHC(O)R_5$;

R' and R'' are independently H, or F;

R_1 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl;

R_2 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl;

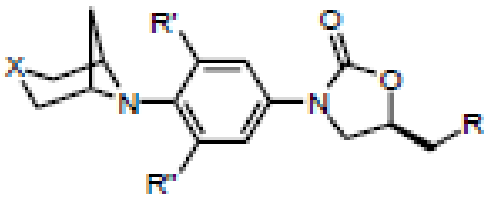
R_3 and R_4 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or phenyl; or R_3 and R_4 taken together with the nitrogen to which they are attached to form morpholine, thiamorpholine, piperazine and triazole;

R_5 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, 5- or 6-membered heteroaryl or phenyl;

R_6 and R_7 is independently H, F, CH_3, CH_2CH_3, CF_3; and

X = O, S, SO, SO_2.

3. The compound as claimed in claim 1, wherein the compound is represented by Formula IV:



IV

wherein,

R is independently OR_1, $OC(O)R_2$, NR_3R_4, $NHS(O)_2R_2$, $NHC(O)R_5$;

R' and R'' are independently H, or F;

R_1 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl;

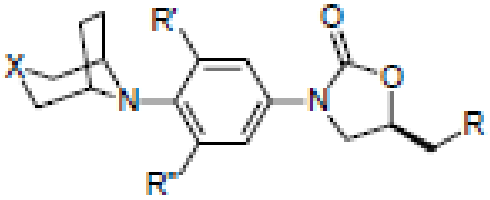
R_2 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl;

R_3 and R_4 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 5- or 6-membered heteroaryl or phenyl; or R_3 and R_4 taken together with the nitrogen to which they are attached, to form morpholine, thiamorpholine, piperazine and triazole;

R_5 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, 5- or 6-membered heteroaryl or phenyl; and

X = O, S, SO, SO_2.

4. The compound as claimed in claim 1, wherein the compound is represented by Formula V:



V

wherein,

R is independently OR_1, $OC(O)R_2$, NR_3R_4, $NHS(O)_2R_2$, $NHC(O)R_5$;

R' and R'' are independently H, or F;

R_1 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl;

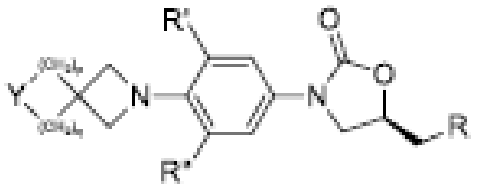
R_2 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl;

R_3 and R_4 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 5- or 6-membered heteroaryl or phenyl; or R_3 and R_4 taken together with the nitrogen to which they are attached, to form morpholine, thiamorpholine, piperazine and triazole;

R_6 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, 5- or 6-membered heteroaryl or phenyl; and

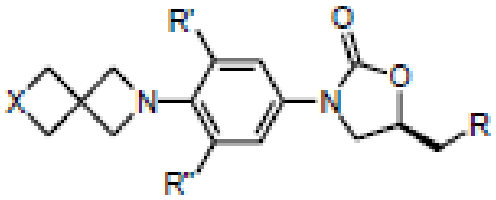
X = O, S, SO, SO_2.

5. The compound as claimed in claim 1, wherein the compound is represented by Formula VI:

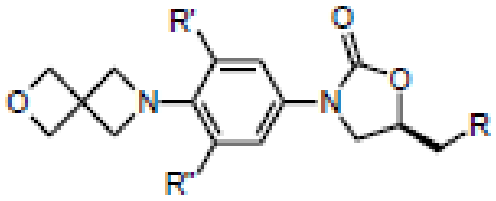


VI.

6. The compound as claimed in claim 5, wherein the compound is represented by Formula VII, Formula VIII, or Formula IX:



VII



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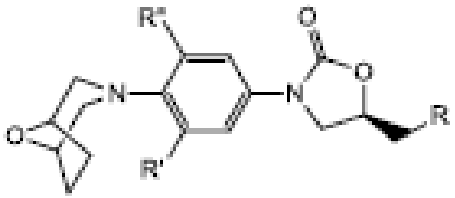


IX

wherein,

R is independently OR_1, $OC(O)R_2$, NR_3R_4, $NHS(O)_2R_2$, $NHC(O)R_5$;

R' and R'' are independently H, or F;

R_1 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl;

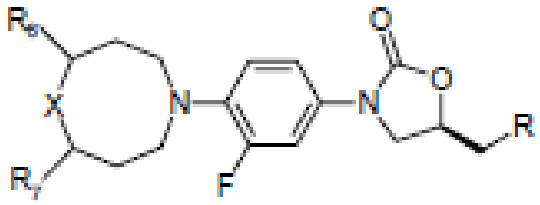
R_2 is independently C_1-C_6 alkyl, C_3-C_8 cycloalkyl;

R_3 and R_4 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 5- or 6-membered heteroaryl or phenyl; or R_3 and R_4 taken together with the nitrogen to which they are attached, to form morpholine, thiamorpholine, piperazine and triazole;

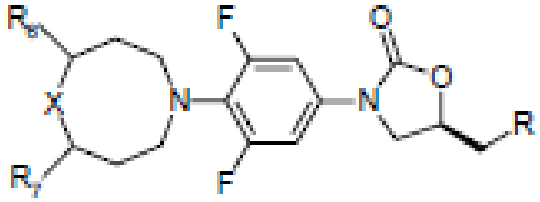
R_5 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, 5- or 6-membered heteroaryl or phenyl; and

X = O, S, SO, SO_2.

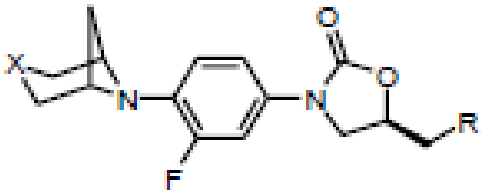
7. The compound as claimed in claim 1, wherein the compound is represented by Formula IIIa, IIIb, IVa, IVb, Va, Vb, VIIa, VIIb, VIIIa, VIIIb, IXa, or IXb:



IIIa



IIIb



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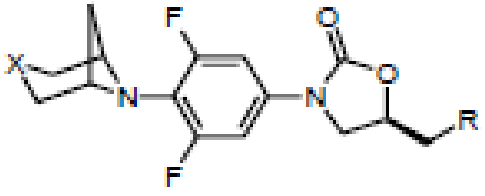

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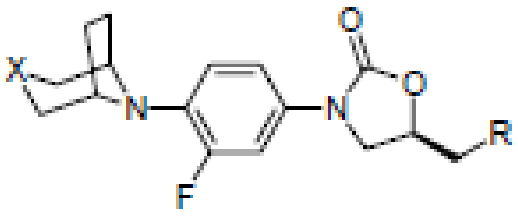
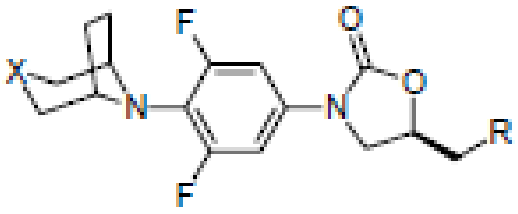


Va



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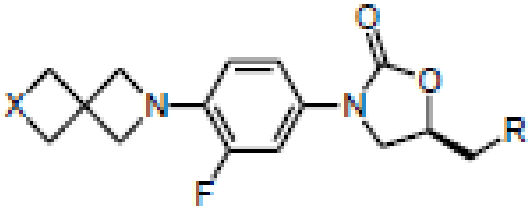
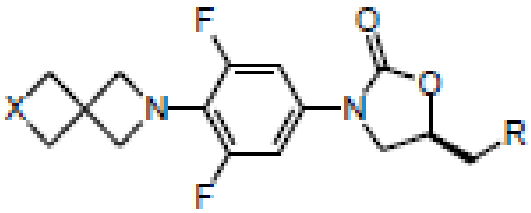


VIIa



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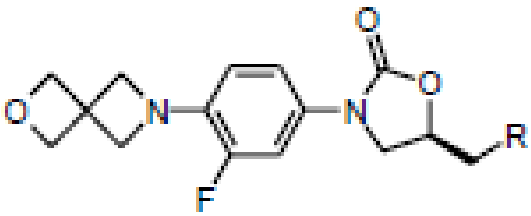
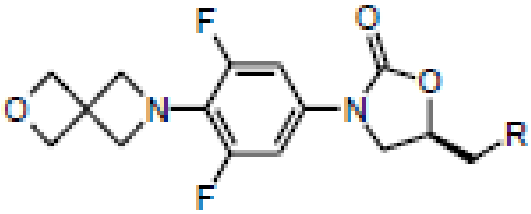
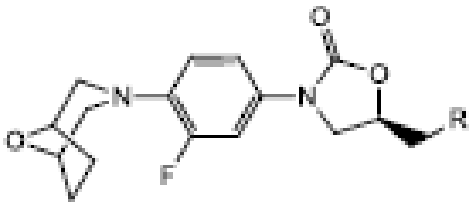


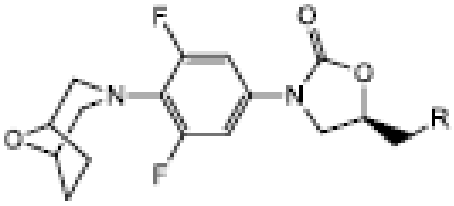
VIIIa



VIIIb



IXa



IXb

wherein,

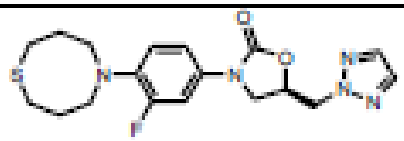
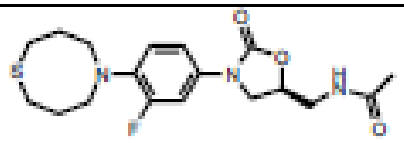
R is independently OH, OCH_3, OCH_2CH_3, $OC(O)CH_3$, NH_2, $NHCH_3$, NHC_6H_5, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, $NHS(O)_2R_5$, $NHC(O)R_5$;

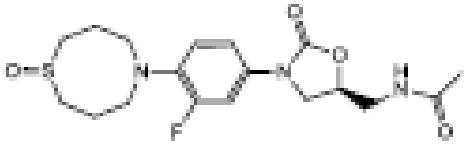
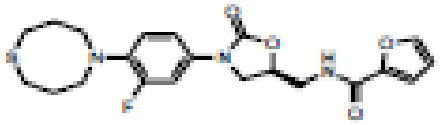
R_5 is independently C_1-C_6 alkyl;

R_6 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, furan, thiophene or phenyl; in Formula IIa, R_6 can not be CH_3; and

X = O, S, SO, SO_2.

8. The compounds of Formula I as claimed in claim 1, wherein the compound is:

OTB-110	
OTB-113	
OTB-114	

OTB124	
OTB-117	
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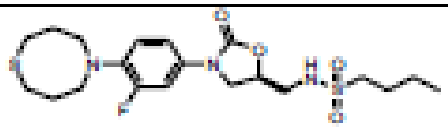
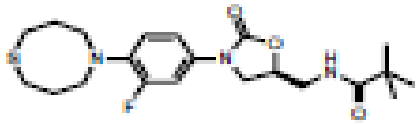
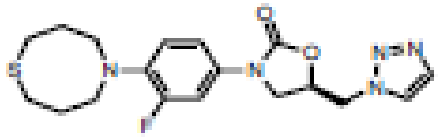
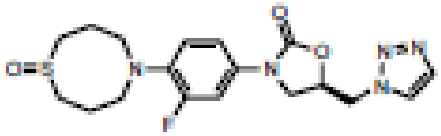
OTB-120	
OTB-121	
OBD-001	
OBD-002	
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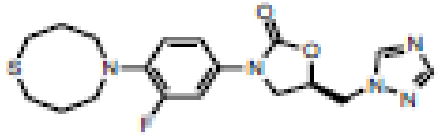
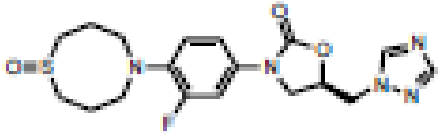
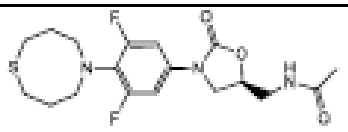
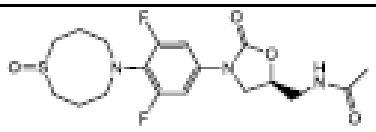
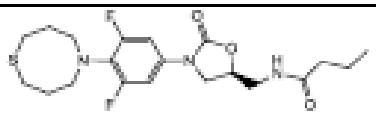
OBD-004	
OBD-008	
OBD-009	

OBD-027	
OBD-240	
OBD-026	
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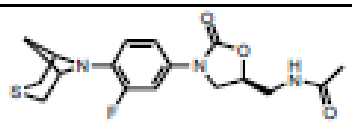
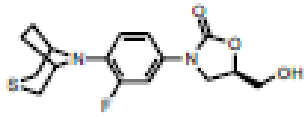
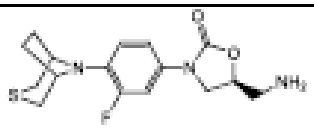
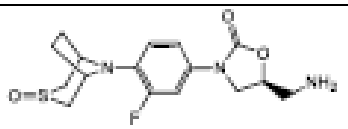
OTB-227	
OTB-501	
OBD-081	
OBD-085	
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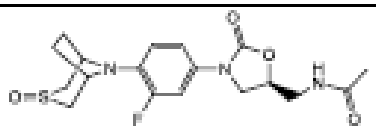
OTB-503	
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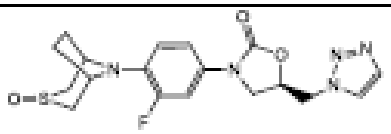
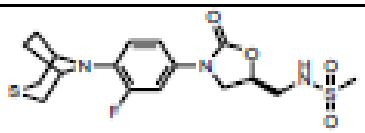
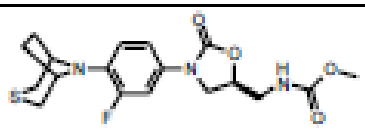
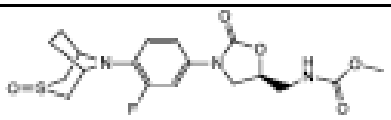
OTB-505	
OTB-236	
OTB-237	
OTB-518	
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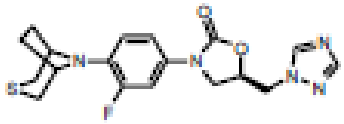
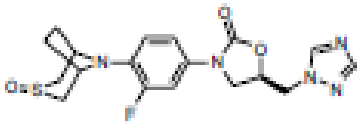
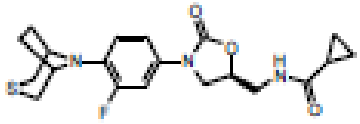
OBD-017	
OBD-021	
OBD-018	
OTB-506	
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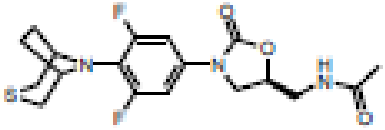
OTB-510	
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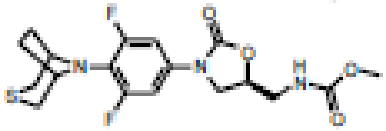
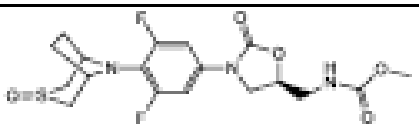
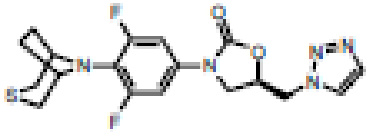
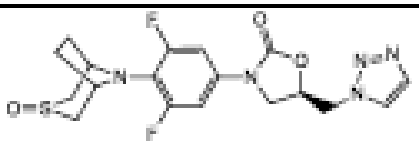
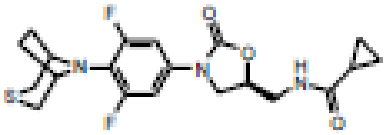
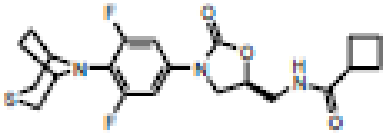
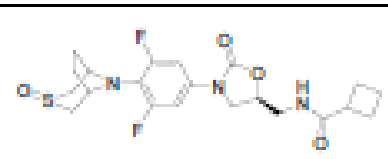
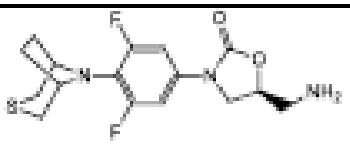
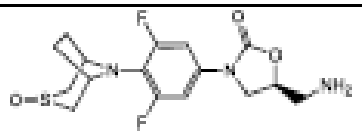
OTB-512	
OTB-519	
OTB-511	
OTB-517	
OTB-508	
OTB-509	
OTB-513	
OBD-083	

OBD-087	
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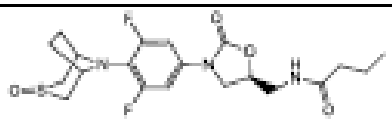
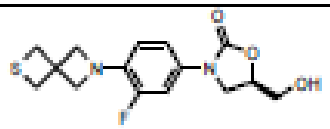
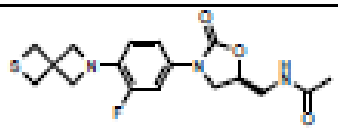
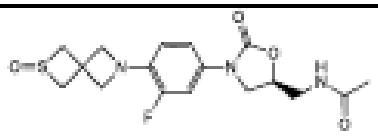
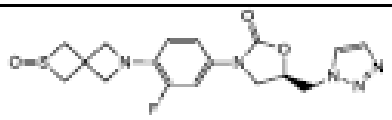
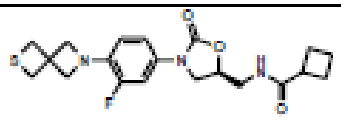
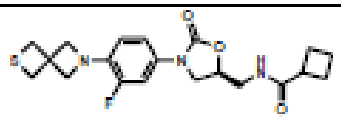
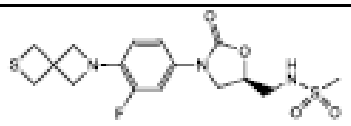
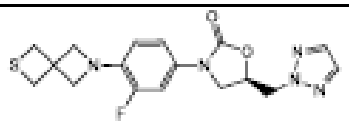
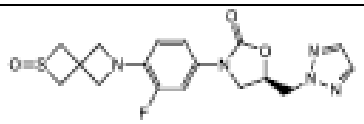
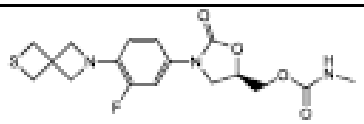
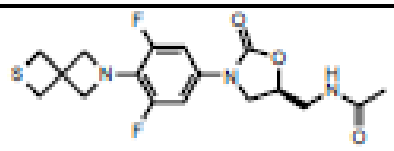
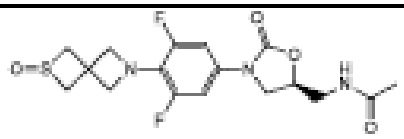
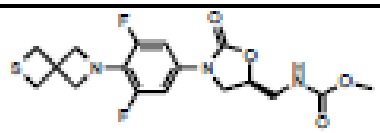
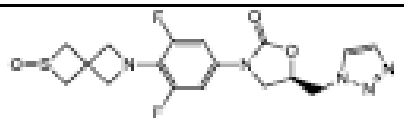
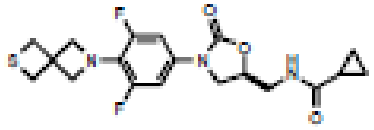
OBD-242	
OTB-260	
OTB-261	
OTB523	
OTB-515	
OTB-256	
OTB-241	
OTB-247	

OTB-249	
OTB-255	
OTB-250	
OTB-254	
OTB-260-2A	
OTB-260-2B	
OTB-260-5A	
OTB-260-5B	
OTB-260-4A	
OTB-260-4B	
OTB-516	

OTB-515	
OTB-520	
OTB-242	
OTB-253	
OTB-245	
OTB-522	
OTB-243	
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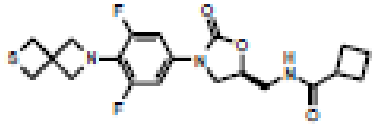
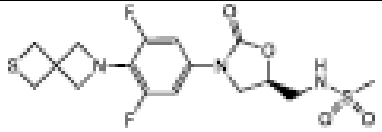
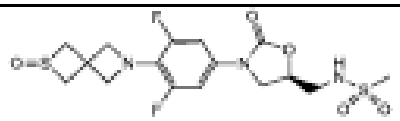
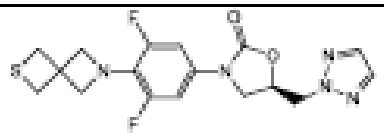
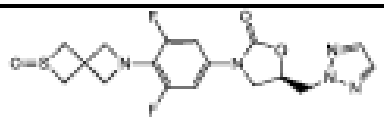
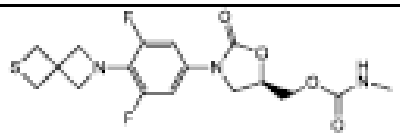
OTB-244	
OTB-251	
OTB-516-2A	

OTB-516-2B	
OTB-516-6A	
OTB-516-6B	
OTB-516-4A	
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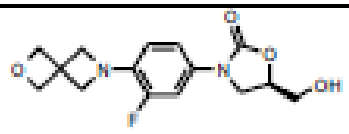
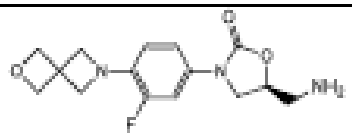
OTB-201	
OBD-057	
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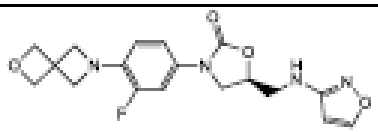
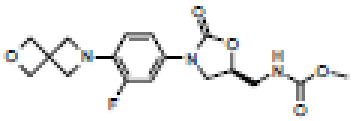
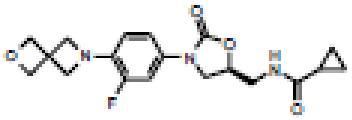
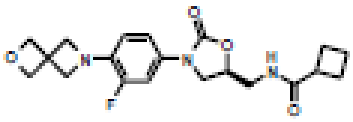
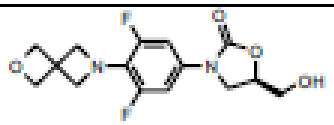
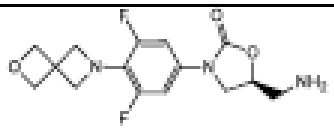
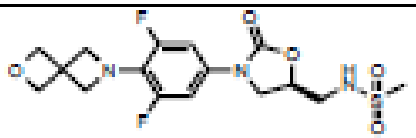
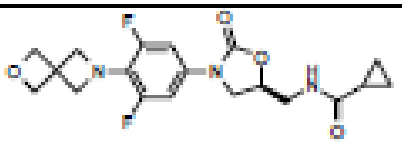
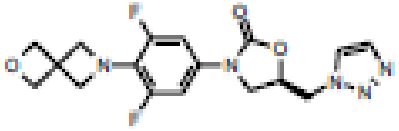
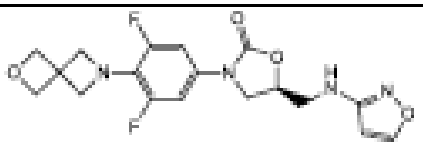
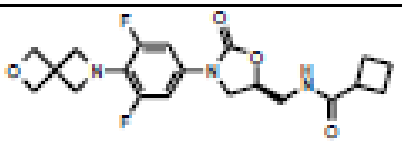
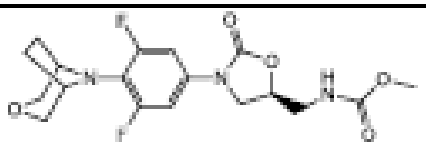
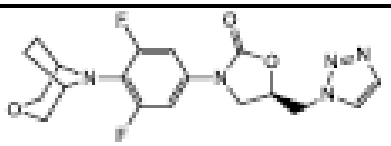
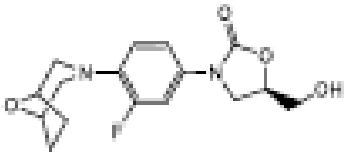
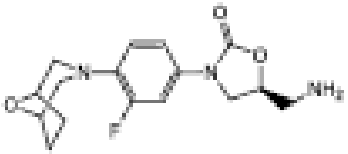
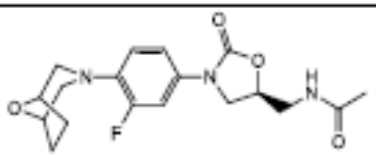
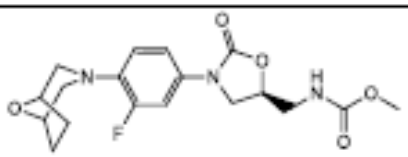
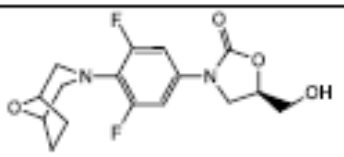
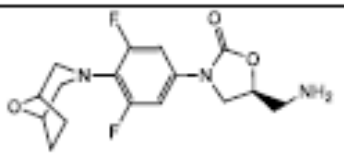
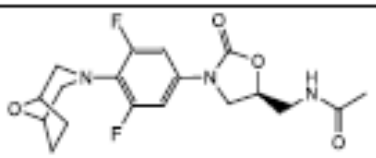
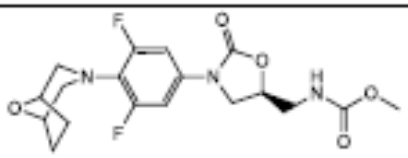
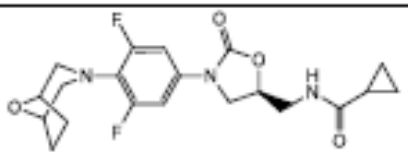
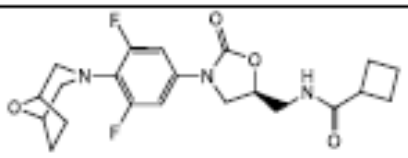
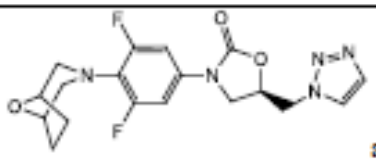
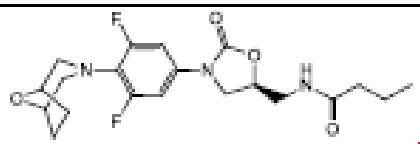
OTB-203	
OTB-204	
OTB-205	

OTB-206	
OBD-056	
OTB-222	
OTB-223	
OTB-238	
OTB-239	
OTB-229	
OBD-062	
OTB-230	
OTB-231	

OTB-232	
OTB-233	
OTB-234	
OBD-061	
OTB-240	
OBD-051	
OBD-052	
OBD-055	
OBD-112	
OBD-113	

OBD-110	
OBD-111	
OBD-114	
OBD-115	
OBD-048	
OBD-049	
OBD-252	
OBD-253	
OBD-054	 and

OBD-254	

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

9. A pharmaceutical composition, comprising one or more compound of Formula I as claimed in claim 1, or a salt, hydrate, or solvate thereof, and one or more pharmaceutically acceptable carriers and/or additives.

10. The pharmaceutical , composition as claimed in claim 09 optionally comprising one or more additional anti-infective treatments.

4. Impugned Patent Application: The present pre-grant opposition is against Indian Patent Application 201817004931, entitled "SUBSTITUTED PHENYLOXAZOLIDINONES FOR ANTIMICROBIALTHERAPY"and is drawn towards the compounds having with antibacterial activity and,more specifically, with anti-tuberculosis properties.

5. Disclosure in the impugned patent application: As per the Applicant, the present invention relates generally to compounds with antibacterial activity and,more specifically, with anti-tuberculosis properties. In particular, it relates tosubstituted phenyloxazolidinone compounds useful for the treatment of tuberculosisin patients in need thereof.

6. PRIOR ARTS: The opponent wishes to rely on the following prior arts as evidence in support of the grounds of opposition.

i. **D1**-WO 1996015130 (WO'130)

ii. **D2**-Neha Pandit et al; Current Updates on Oxazolidinone and Its Significance; International Journal of Medicinal Chemistry; Volume 2012, Article ID 159285, 24 pages.

iii. **D3-**WO 2004/033451 (WO'451)

iv. **D4**-US2010/0069449 (US 449)

7. It is submitted that all claims of the impugned patent application are liable to be refusedon following grounds as below:

(a) Section 25(1)(b): Lack of novelty

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

(c) Section 25(1)(f): Invention is not patentable under section 3 (d)

(d) 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.

(e) Section 25(1)(h): Failed to disclose to the Controller the information required by section 8.

(a) <u>GROUND 1: LACK OF NOVELTY</u>

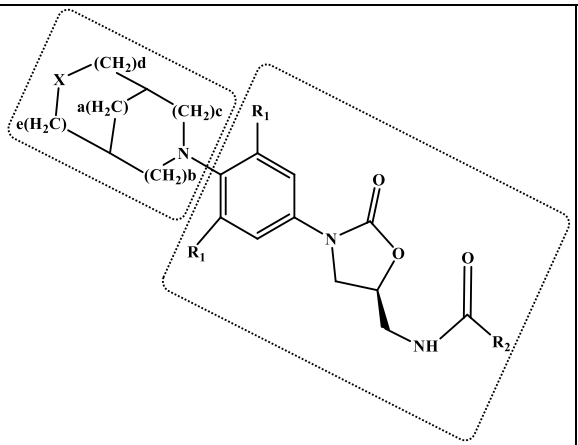
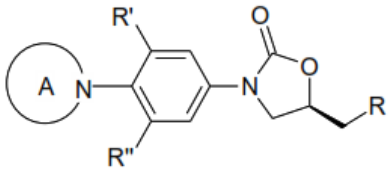
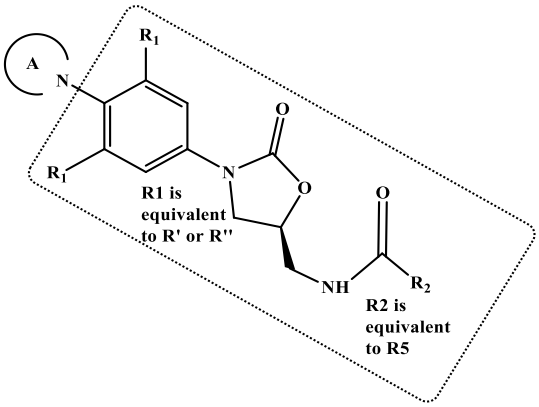
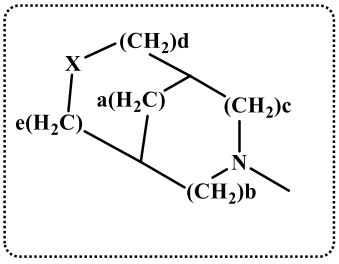
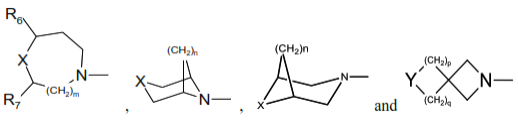
8. CLAIMS 1 TO 10 ARE NOT NOVEL, AND THEREFORE HAVE TO BE REJECTED UNDER SECTION 25(1)(b) OF THE PATENTS ACT.

9. The impugned patent application lacks novelty in view of WO1996015130 (WO'130).This document was published on 23 May 1996 which is prior to priority date of impugned patent application i.e. 17/07/2015. The impugned patent application claims compounds which are already covered in WO'130 patent. The justification given below sets out the manner in which the claims of impugned patentapplication are anticipated by WO'130.

10. A similarity table is given below which clearly discloses that impugned patent application lacks novelty.

Table 1:

S. No	Prior art (WO 1996015130) (WO'130)	Impugned patent application (201817004931)

1	 **Formula I**	 (I) R1'= R2'=H or F; R= NHC(O)R5 where R_5C1-C6 alkyl, therefore R_5 is equivalent to R_2 Now reach to prior art Formula (I)  R1 is equivalent to R' or R'' R2 is equivalent to R5
2		A is equivalent to side arm part of prior art which is given on the left side. 

11. From the above mentioned table, it is clear that not only the structure of formula (I) of the prior art but its different substituents also present in the impugned patent application. Therefore, the present impugned patent application lacks novelty over WO' 130. Therefore, the impugned patent application ought to be rejected on this ground alone.

(b) GROUND 2: LACK OF INVENTIVE STEP:

12. It is submitted that the invention as claimed is obvious and does not involve any inventive step in view of whatever was known and published in India or elsewhere prior to the priority date of impugned patent application i.e. prior to 17/07/2015the earliest claimed priority.

13. It is submitted that all the claims of the impugned patent application are not inventive and are obvious in view of common general knowledge in art and combined with teachings of above mentioned prior arts.

14. The claimed compound of formula I can be divided in two sections and all these sections were known in the art before the priority of this impugned patent application. Applicant has only assembled these two sections in one box. These sections are (A) Aryl ring containing oxazolidinone group and (B) Substituted amine group. A figure has been given below to understand it.

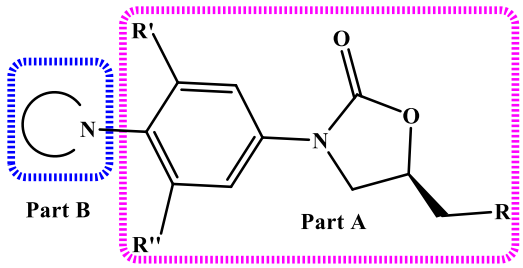


Figure 1: Markush structure of Impugned patent application

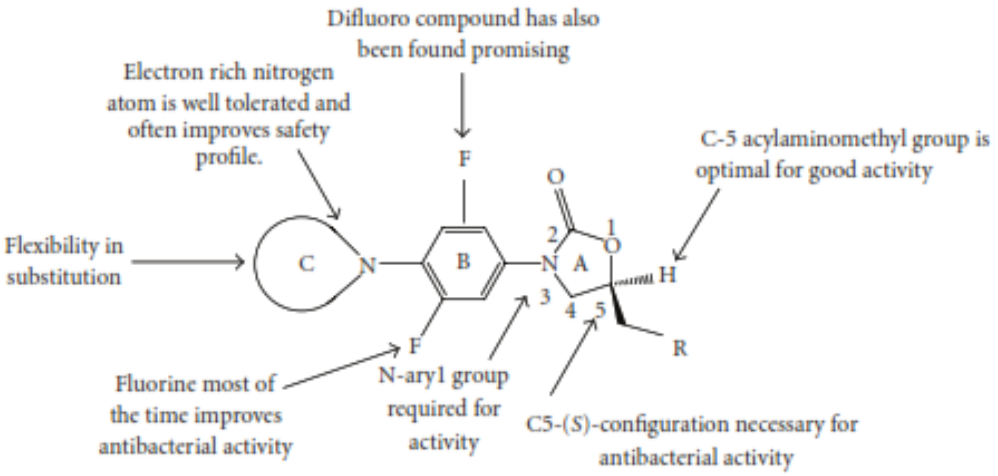
15. **Neha Pandit et al; 2012:**

Neha Pandit et al; published an article that discloses Current Updates on Oxazolidinone and Its Significance. It discloses "*The oxazolidinones are a new class of antimicrobial agents which have a unique structure and good activity against gram-positive pathogenic bacteria. Oxazolidinones are a class of compounds containing 2-oxazolidine in the structure. Oxazolidinones represent a new class of synthetic*

antibacterial agents active against multiple-resistant grampositive pathogens, including methicillin-resistant Staphylococcus aureus (MRSA), penicillin-resistant streptococci, and vancomycin-resistant enterococci."

16. It further discloses the Structure Activity Relationship(SAR)to find better molecules that have significant antibacterial activities.It discloses "*To find out the most potent and comparatively less toxic compounds, we need to to do exhaustive study of SAR. This paper cites the modifications directed for the different parts of the oxazolidinone template as shown in Figure 20. The "A" part manifests oxazolidinone ring, which bears aryl system on the 3rd position of the oxazolidinonering termed as B region and the 4th position of the aryl group is extended by amine functionality that has been termed as C region. Oxazolidinone ring exclusively possess C5 side chain in the (S)-configuration, which has been optimized for the better efficacy.*"

17. The relevant figure is given below-



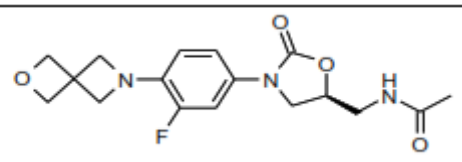
18. The above figure teaches following points-

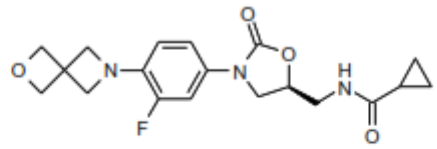
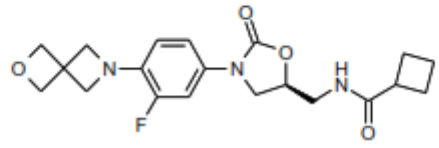
- Presence of oxazolidinone ring is required
- Presence of aryl group at the 3rd position of oxazolidinone ring required for activity.
- S- Configuration is necessary for anti-bacterial activity.
- Presence of R group can be modified to get better activity.

- ❖ Presence of fluorine on phenyl ring improves antibacterial activity.
- ❖ Furthermore, presence of di-fluoro compounds has also been found promising. It means presence of single fluoro atom on phenyl group provides significant activity.
- ❖ The ring C is flexible where a person skilled in the art can make some modification. However, it also discloses that electron rich nitrogen atom is well tolerated and often improves safety profile.

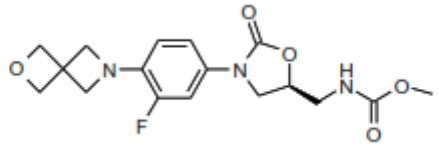
19. The combined teaching of above figure reflects that if a person skilled in the art wants to synthesize some molecules that possess anti-bacterial activity then he/she can make some modification in ring "C" and "R" group. Furthermore, it further narrowed down the selection of various groups for "C" by teaching "electron rich nitrogen atom is well tolerated and often improves safety profile".

20. It also discloses that most of the compounds possess methyl with –NHCO- group at C-5 position of oxazolidinone ring. It clearly teaches that an alkyl group is optimal to provided significant activity. The impugned patent application has claimed several compounds like OTB-202,OTB-238 and OTB-239 that contain cyclopropyl and cyclobutyl group by following the same teaching as mentioned by Neha Pandit et al.

OTB-202	

OTB-238	
OTB-239	

21. Moreover, it further discloses that thio-carbamate at C5 side chain have shown antibacterial activity in the range of 0.25–1 µg/mL against resistant and sensitive gram-positive strains. Therefore, a person skilled in the art can also use oxygen in place of Sulphur to get some molecules that possess promising activity and active against resistant and sensitive gram-positive strains. The impugned patent application further follows the same teaching and prepared a compound OTB-223.

OTB-223	

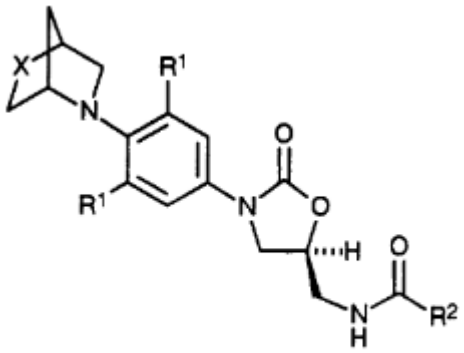
22. It further discloses that oxazolidinone group containing compounds also possess anti-tubercular activity. A relevant snapshot is reproduced here for ready reference.

> (3) *Antitubercular Activity*. During the course of investigation in the oxazolidinones antibacterial agent area was identified a subclass with especially potent in vitro activity against mycobacteria [69]. The salient structural feature of these oxazolidinone analogues, U-100480, U-101603, and U-101244, is their appended thiomorpholine. Potent activity against a screening strain of *M. tuberculosis* was determined by U-100480 and U-101603 (MIC = 0.125 mg/mL).

23. The above mentioned paragraphs clearly disclose the part A of impugned Markush as mentioned in figure 1. Therefore, part A clearly shows obviousfrom the document D2.

WO 1996015130(WO'130):

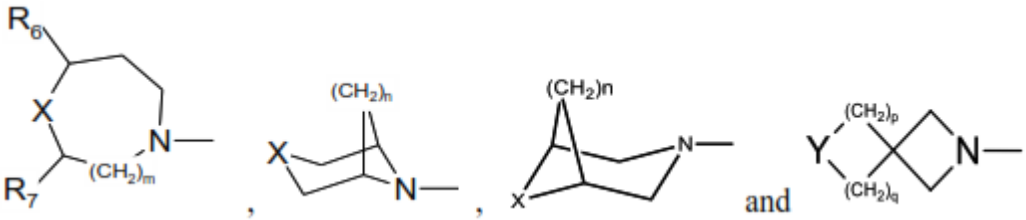
24. WO' 130 discloses a Markush formula which is given below-



Formula II

25. The above mentioned figure not only discloses the Part A of the Markush structure of impugned patent application but it also discloses the Part B after some substitutions.In the formula II the X could be O, S, SO and SO_2.

26. The impugned application represents A which could be-



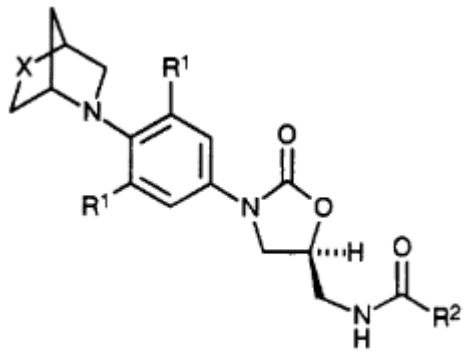
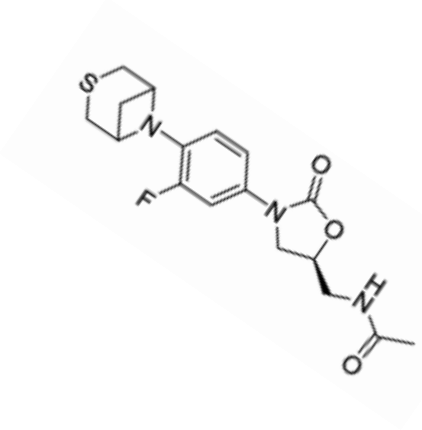
27. The X and Y in impugned patent application are equivalent to X of prior art WO'130. The X and Y in impugned patent are given below-

X = O, S, SO, SO_2;

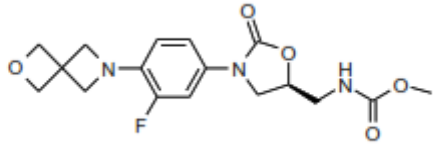
Y = O, S, SO, SO_2, and NR_8;

28. An example given in impugned patent is looks like Formula II of WO'130.

WO' 130	Impugned Application

 Formula II	 OTB 227

29. Although, the bridge position of CH_2 is different but a person skilled in the art would try make all possible variables as claimed by impugned patent application. Following the teaching of above, a person skilled in the art would also make some spiro compound as claimed in claim 8. An example is given below.

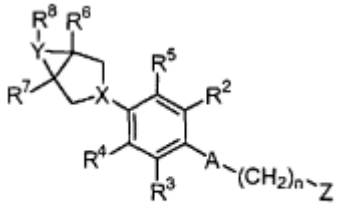
OTB-223	

30. Therefore, the above paragraphs disclose not only part 'A' but also Part 'B' of impugned Markush structure.

WO 2004/033451 (WO'451):

31. This document was published on 22.04.2004 much prior of priority date of impugned patent application. This document discloses that oxazolidinone ring containing compounds possess antimicrobial and anti-tubercular activities.

32. This document discloses a Markush formula which is given below-



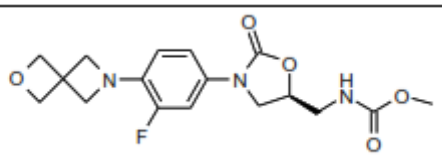
I

33. The above mentioned Markush is also equivalent to present impugned invention. The A is oxazolidinone ring and z is a group that present in impugned patent application like –NHC(=O)R^1 where R^1 could be alkyl or alkoxy group.

34. Furthermore, R2 and R3 is H;R4 and R5 could be hydrogen or F then the phenyl ring and its substitution will be same as mentioned in impugned patent Application.

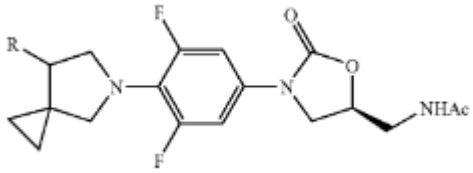
35. Moreover, the terminal ring where X could be N and Y could be O; It will be equivalent to impugned application.

36. Although, there is no CH_2 group between R6 and R7 but a person skilled in the art would try make all possible variables as claimed by impugned patent application. Following the teaching of above, a person skilled in the art would also make some spiro compound as claimed in claim 8. An example is given below.

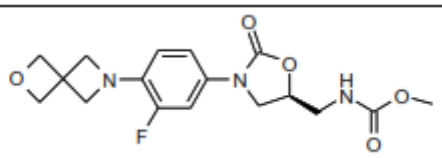
OTB-223	

US2010/0069449 (US 449):

37. This document was published on 18 March 2010 prior to priority date of impugned patent application. The document discloses a Markush Structure which is given below-



38. Just like above mentioned various prior arts, this is also suggest that bicyclic ring attached with nitrogen play significant role to show some antibacterial activity. Therefore, a person skilled in the art would try making all possible variables as claimed by impugned patent application. Following the teaching of above, a person skilled in the art would also make some spiro compound as claimed in claim 8. An example is given below.

OTB-223	

39. In light of above, the present impugned patent application lack inventive steps and therefore, this application should be rejected on this ground alone.

(c) <u>GROUND 3: CLAIMS NOT PATENTABLE UNDER SECTION 25(1)(F)</u>

40. It is submitted that the impugned patent application should not be allowed under Section 3(d) which states that"*the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.*

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

41. The Opponent states that the compounds claimed in impugned patent application are a derivative of known compound as disclosed in prior arts. The opponent submits that the applicant has failed to demonstrate any enhancement in the therapeutic efficacy with respect to known efficacy. The Opponent states that the Applicant miserably failed to provide data demonstrating enhanced 'therapeutic' efficacy as there is no comparative data disclosed in the impugned patent application showing improved efficacy of substance of impugned patent application over known substance.

42. Therefore, the claimed compounds does not show any enhancement of known efficacy and thus not patentable under section 3 (d). Thus, the subject matter of impugned patent application squarely falls within the purview of Section 3(d) of the Act. Hence the impugned patent application should be rejected under section 3(d) of the act.

(d) GROUND 4: INSUFFICIENCY OF DISCLOSURE

43. The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

44. The Applicant has not shown any standard compound data in table 1 that discloses the standard IC_{50} value. There are various antibacterial compounds available that possess significant antibacterial activity. Applicant has mentioned only IC_{50} data of some synthesized compounds in table 1.

45. Furthermore, the Applicant failed to provide the procedure to carry out the antibacterial activity. Applicant has provides only MPS inhibition of some compounds. Furthermore, Applicant has not given any *in vivo* data regarding these compounds.

46. The impugned patent application does not provide adequate teaching to a person skilled in the art to practice the invention. In light of above, it is clear that impugned patent application does not

sufficiently and clearly describe the invention. Therefore, the impugned patent application should be refused on this ground alone.

(e) GROUND 5 -SECTION 25(1)(H)

47. The Applicant has failed to disclose to the Controller the information required under Section 8.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. It is observed that applicant has not updated the status of corresponding application in the Form-3 which information has not been provided to the learned Controller.

48. 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. It is submitted that the Applicant has failed to disclose the details of corresponding foreign applications and impugned patent application to be refused.

CONCLUSION

In view of the above, the claims are not inventive, not patentable and insufficient. The pre-grant opposition as filed may be allowed and the subject patent application may be refused.

P R A Y E R

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

i. that the Indian Patent application number 201817004931 made by The Global Alliance For TB Drug Development Inc., be refused under Section 25(1) of the Patents (Amendment) Act, 2005;

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

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

Dated this day 23rd of March, 2021

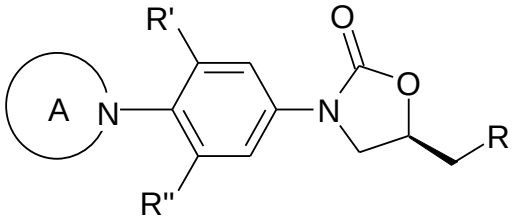
RAJESHWARI H. IN/PA – 0358
AGENT FOR THE OPPONENT
OF RAJESHWARI AND ASSOCIATES

To,
The Controller of Patents
The Patent Office, New Delhi

Annexure -1

We Claim::

1. A compound of Formula I, or a pharmaceutically acceptable salt, hydrate, or solvate of:



(I)

wherein:

R is independently OR_1, $OC(O)R_2$, $OC(O)NHR_2$, $OS(O_2)R_2$, $NHS(O)_2R_2$, NR_3R_4, $NHC(O)R_5$;

R' and R'' are independently H, F, Cl or OMe;

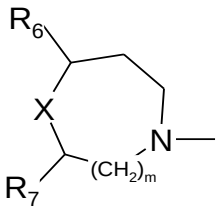
each R_1 is independently H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, wherein said alkyl, cycloalkyl are optionally substituted with 1 to 4 groups selected from halo, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkyloxy;

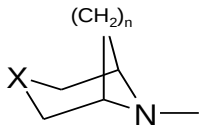
each R_2 is independently C_1-C_6 alkyl, C_3-C_8 cycloalkyl, heterocyclyl, heteroaryl or aryl, wherein said alkyl, cycloalkyl, heterocyclyl, heteroaryl, or aryl are optionally substituted with 1 to 4 groups selected from halo, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 acyloxy, CF_3, NO_2, CN and NH_2;

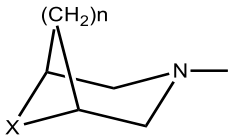
each R_3 and R_4 is independently H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, heterocyclyl heteroaryl, aryl; or R_3 and R_4 taken together with the nitrogen to which they are attached, form a 4- to 8-membered heterocyclyl or heteroaryl with 1 to 3 additional heteroatoms selected from O, S, or N, wherein said alkyl, cycloalkyl, heterocyclyl, heteroaryl, or aryl are optionally substituted with 1 to 4 groups selected from halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3, NO_2, CN;

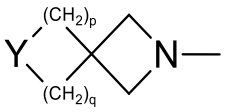
each R_5 is independently C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, heteroaryl, aryl, wherein said alkyl, cycloalkyl, heterocyclyl, heteroaryl, or aryl are optionally substituted with 1 to 4 groups selected from halo, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 acyloxy, CF_3, NO_2, CN and NH_2;

Ring A is selected from:



,


,


and


wherein,

each R_6 and R_7 is independently H, F, CH_3, CH_2CH_3, CF_3, phenyl;

X = O, S, SO, SO_2;

Y = O, S, SO, SO_2, and NR_8;

m is 2;

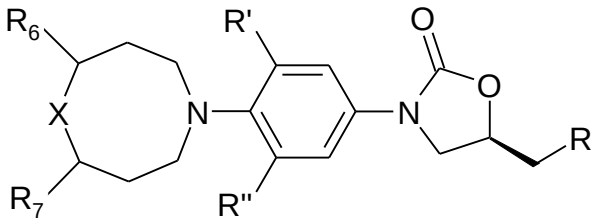
n is 1, or 2;

p is 1, or 2;

q is 1, or 2;

R_8 in independently H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, $COCH_3$, and p-toluenesulfonyl, wherein said alkyl, cycloalkyl are optionally substituted with 1 to 4 groups selected from halo, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 acyloxy, CF_3, NO_2, CN and NH_2.

2. The compound as claimed in claim 1, wherein the compound is represented by Formula III:



III

wherein,

R is independently OR_1, $OC(O)R_2$, NR_3R_4, $NHS(O)_2R_2$, $NHC(O)R_5$;

R' and R'' are independently H, or F;

R_1 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl;

R_2 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl;

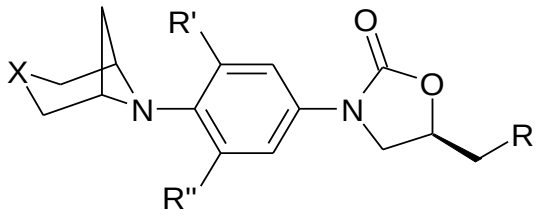
R_3 and R_4 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or phenyl; or R_3 and R_4 taken together with the nitrogen to which they are attached to form morpholine, thiamorpholine, piperazine and triazole;

R_5 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, 5- or 6-membered heteroaryl or phenyl;

R_6 and R_7 is independently H, F, CH_3, CH_2CH_3, CF_3; and

X = O, S, SO, SO_2.

3. The compound as claimed in claim 1, wherein the compound is represented by Formula IV:



IV

wherein,

R is independently OR_1, $OC(O)R_2$, NR_3R_4, $NHS(O)_2R_2$, $NHC(O)R_5$;

R' and R'' are independently H, or F;

R_1 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl;

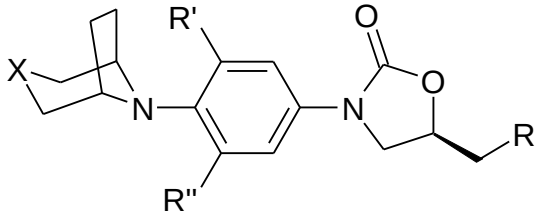
R_2 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl;

R_3 and R_4 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 5- or 6-membered heteroaryl or phenyl; or R_3 and R_4 taken together with the nitrogen to which they are attached, to form morpholine, thiamorpholine, piperazine and triazole;

R_5 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, 5- or 6-membered heteroaryl or phenyl; and

X = O, S, SO, SO_2.

4. The compound as claimed in claim 1, wherein the compound is represented by Formula V:



V

wherein,

R is independently OR_1, $OC(O)R_2$, NR_3R_4, $NHS(O)_2R_2$, $NHC(O)R_5$;

R' and R'' are independently H, or F;

R_1 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl;

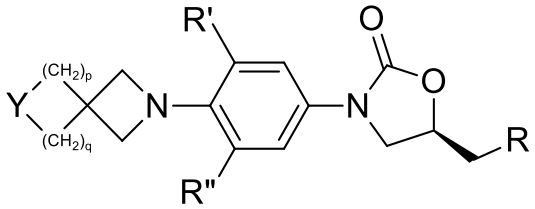
R_2 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl;

R_3 and R_4 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 5- or 6-membered heteroaryl or phenyl; or R_3 and R_4 taken together with the nitrogen to which they are attached, to form morpholine, thiamorpholine, piperazine and triazole;

R_5 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, 5- or 6-membered heteroaryl or phenyl; and

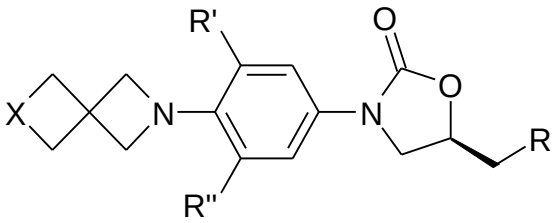
X = O, S, SO, SO_2.

5. The compound as claimed in claim 1, wherein the compound is represented by Formula VI:

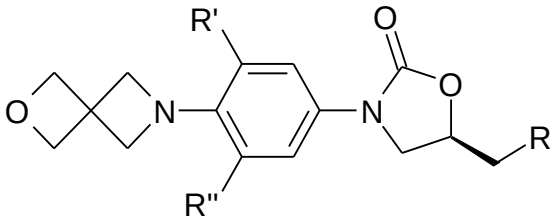


VI.

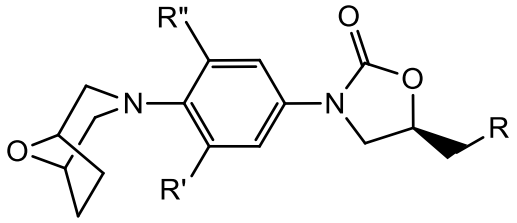
6. The compound as claimed in claim 5, wherein the compound is represented by Formula VII, Formula VIII, or Formula IX:



VII



VIII



IX

wherein,

R is independently OR_1, $OC(O)R_2$, NR_3R_4, $NHS(O)_2R_2$, $NHC(O)R_5$;

R’ and R’’ are independently H, or F;

R_1 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl;

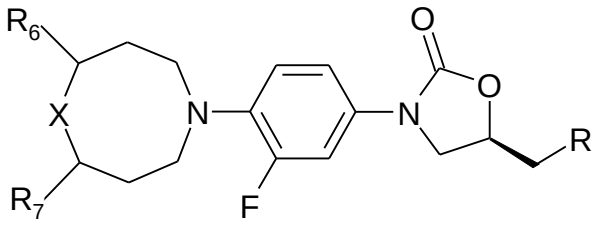
R_2 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl;

R_3 and R_4 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, 5- or 6-membered heteroaryl or phenyl; or R_3 and R_4 taken together with the nitrogen to which they are attached, to form morpholine, thiamorpholine, piperazine and triazole;

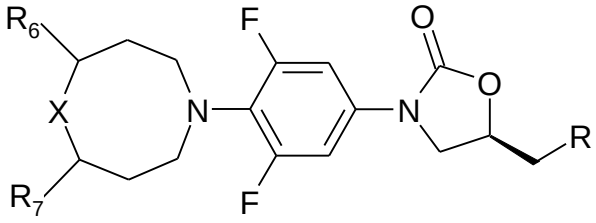
R_5 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, 5- or 6-membered heteroaryl or phenyl; and

X = O, S, SO, SO_2.

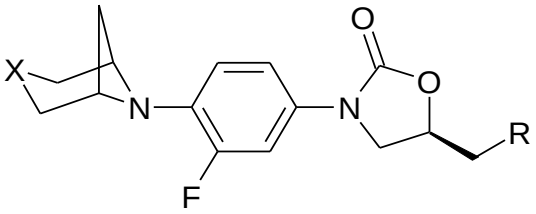
7. The compound as claimed in claim 1, wherein the compound is represented by Formula IIIa, IIIb, IVa, IVb, Va, Vb, VIIa, VIIb, VIIIa, VIIIb, IXa, or IXb:



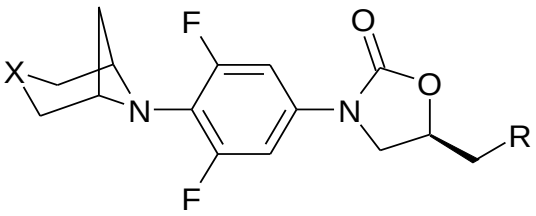
IIIa



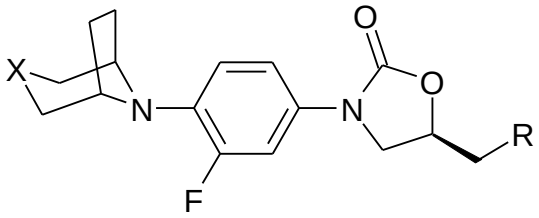
IIIb



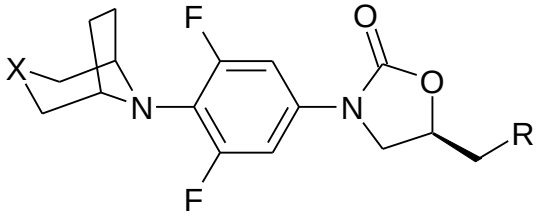
IVa



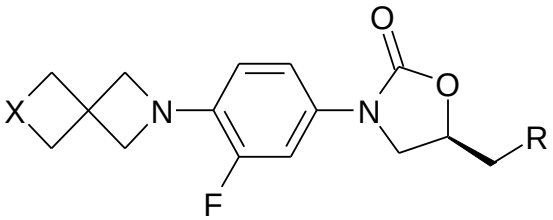
IVb



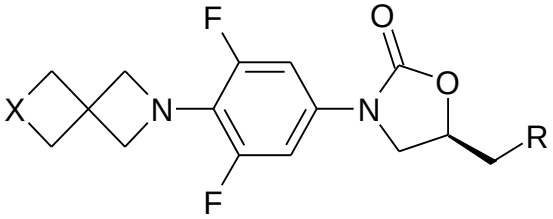
Va



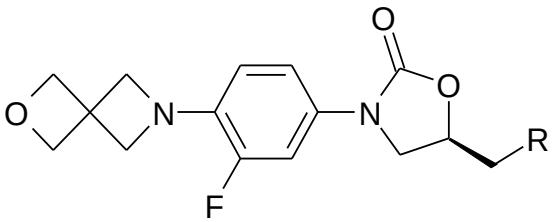
Vb



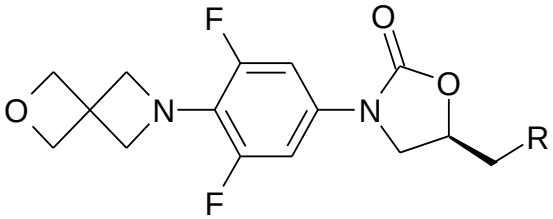
VIIa



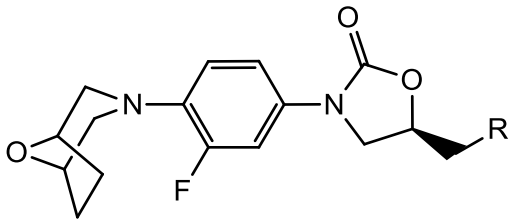
VIIb



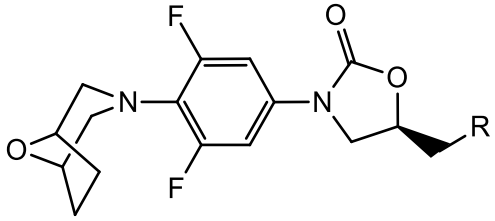
VIIIa



VIIIb



IXa



IXb

wherein,

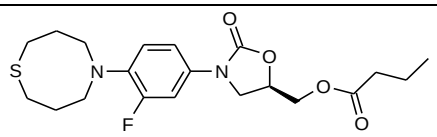
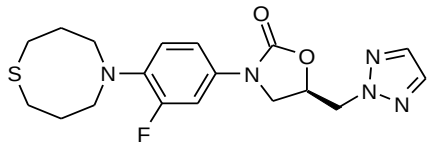
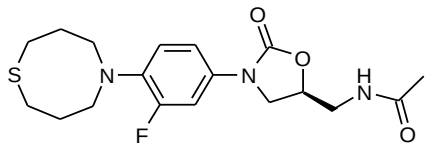
R is independently OH, OCH_3, OCH_2CH_3, $OC(O)CH_3$, NH_2, $NHCH_3$, NHC_6H_5, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, $NHS(O)_2R_2$, $NHC(O)R_5$;

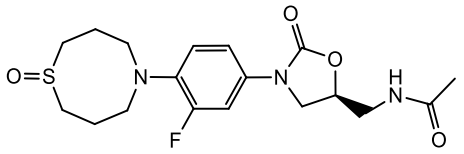
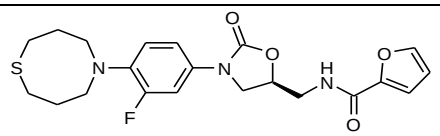
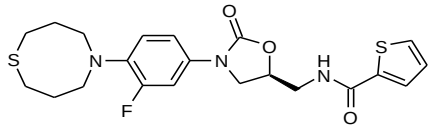
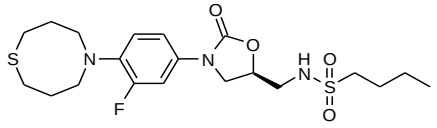
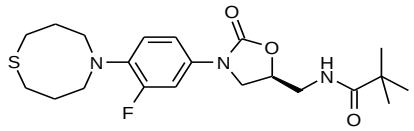
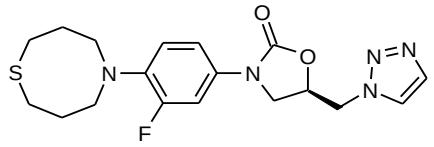
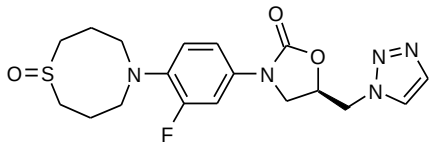
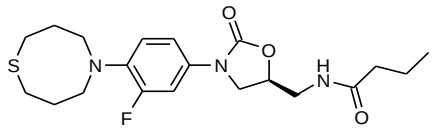
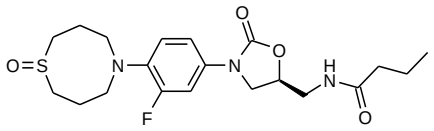
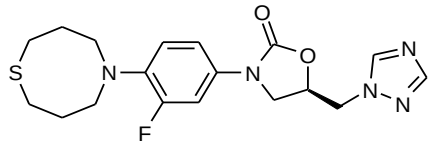
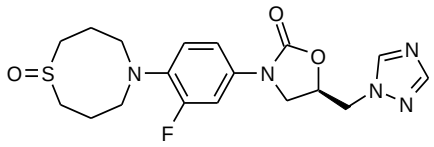
R_2 is independently C_1-C_6 alkyl;

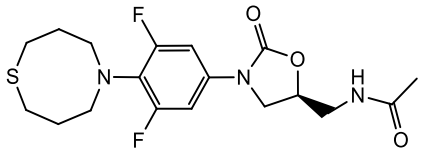
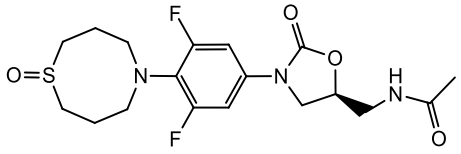
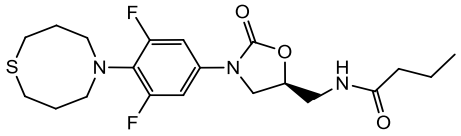
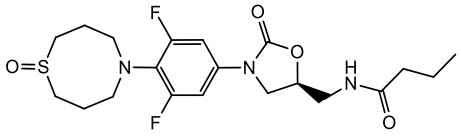
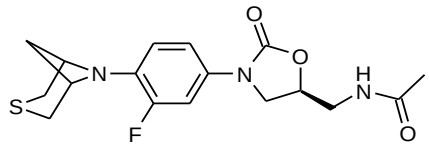
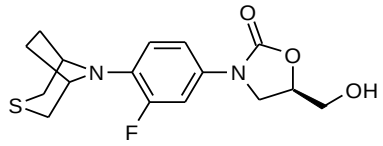
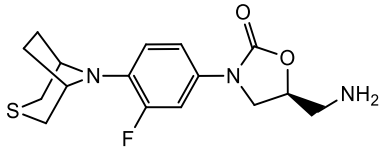
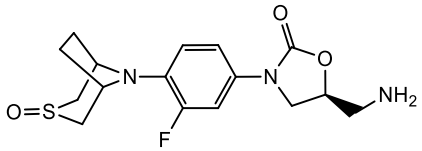
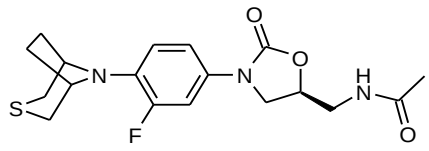
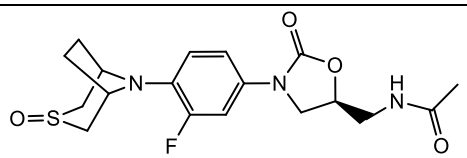
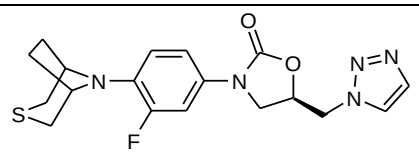
R_5 is independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, furan, thiophene or phenyl; in Formula IIa, R_5 can not be CH_3; and

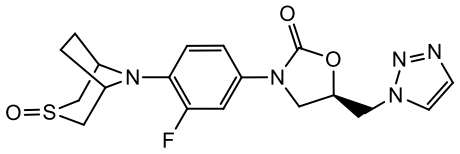
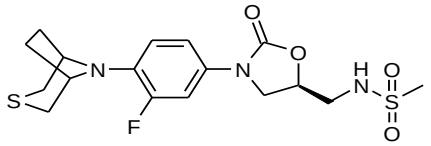
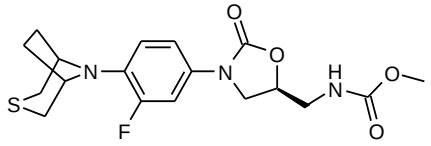
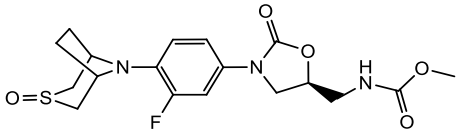
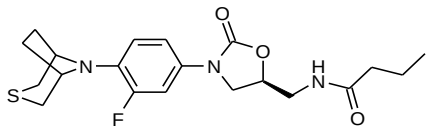
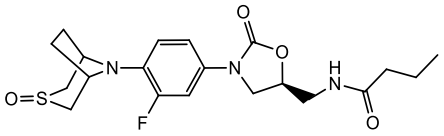
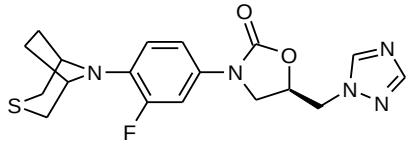
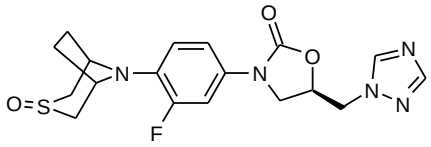
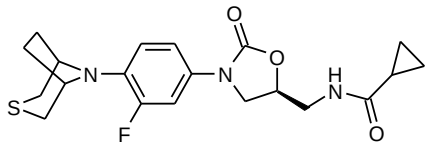
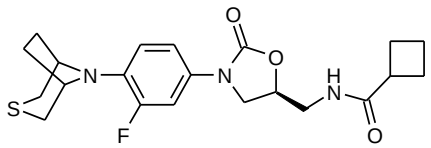
X = O, S, SO, SO_2.

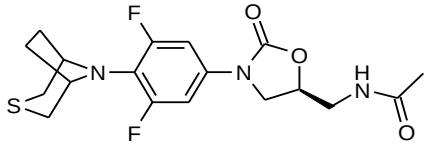
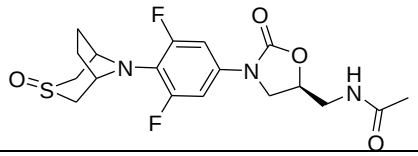
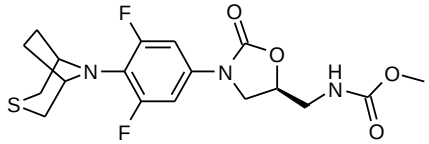
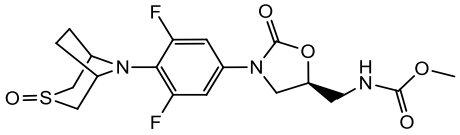
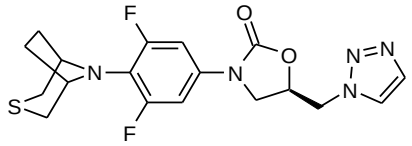
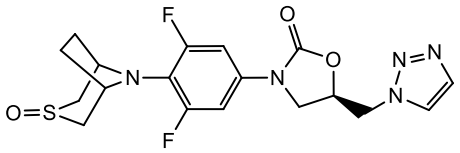
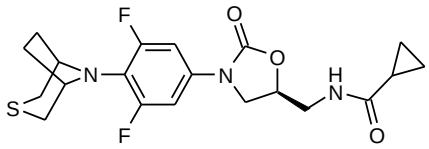
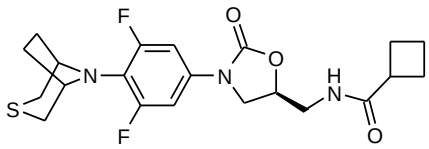
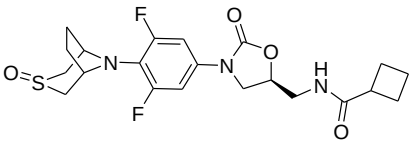
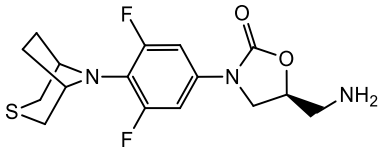
8. The compounds of Formula I as claimed in claim 1, wherein the compound is:

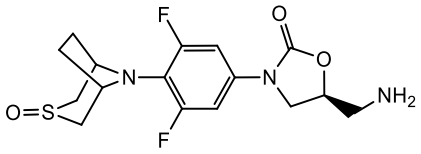
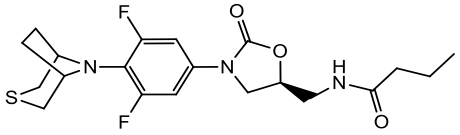
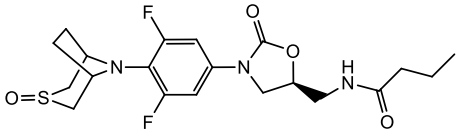
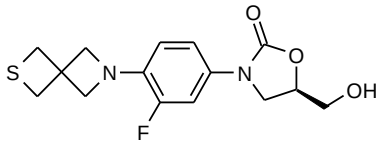
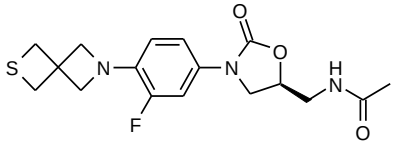
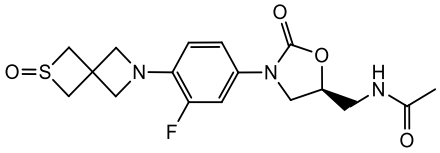
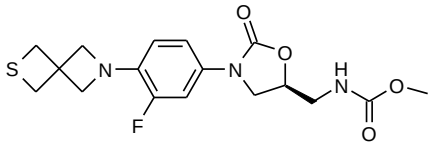
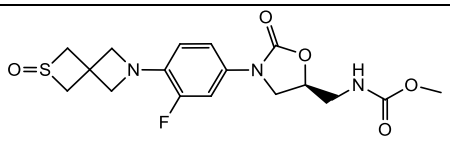
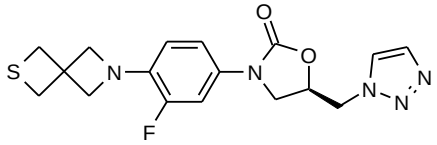
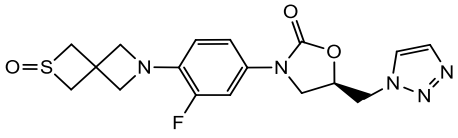
OTB-110	
OTB-113	
OTB-114	

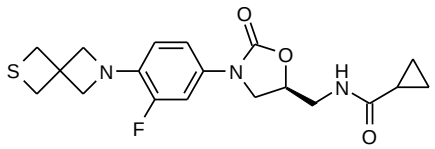
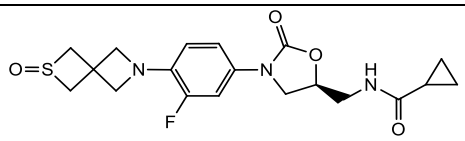
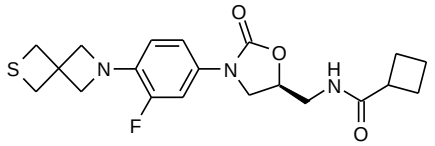
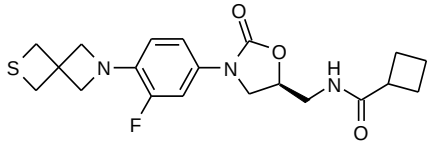
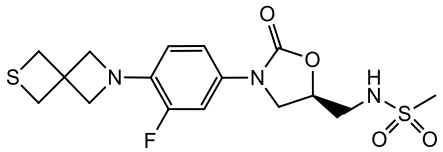
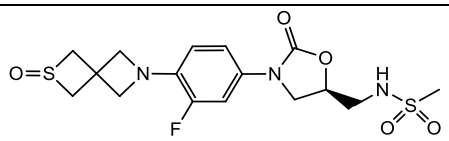
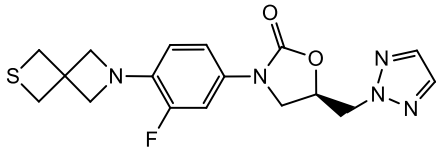
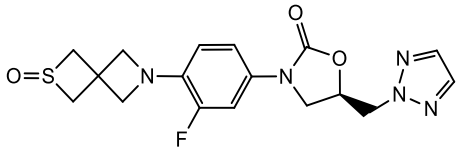
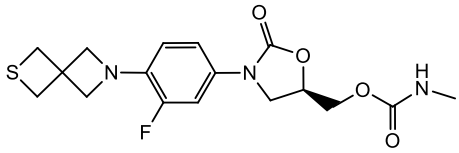
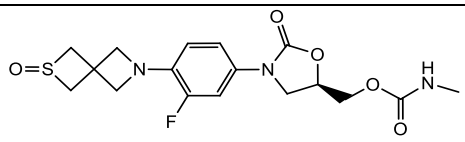
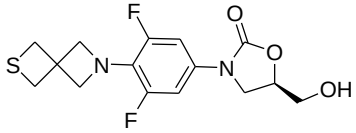
OTB124	
OTB-117	
OTB-118	
OTB-120	
OTB-121	
OBD-001	
OBD-002	
OBD-003	
OBD-004	
OBD-008	
OBD-009	

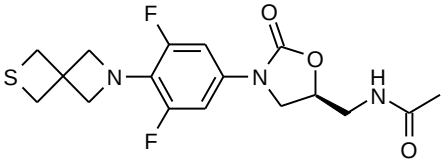
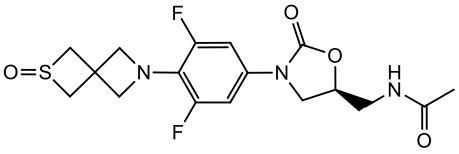
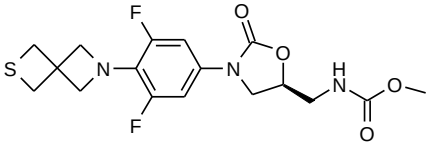
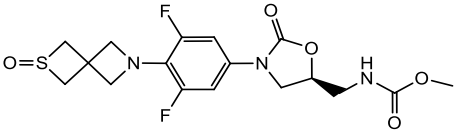
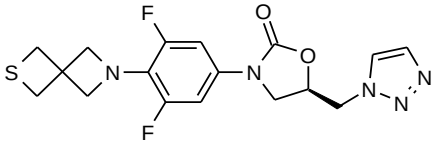
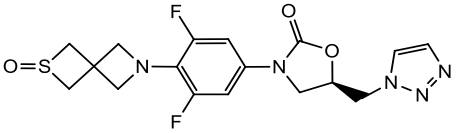
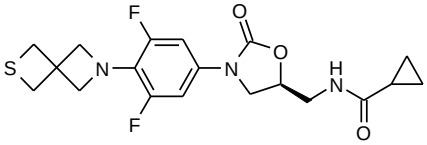
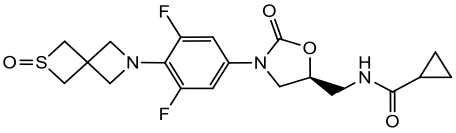
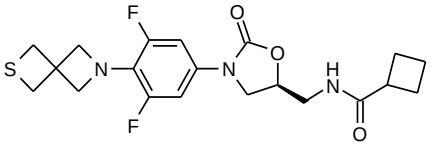
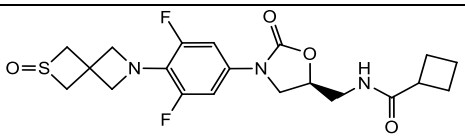
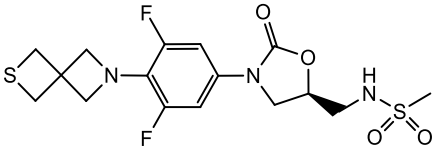
OBD-027	
OBD-240	
OBD-026	
OBD-241	
OTB-227	
OTB-501	
OBD-081	
OBD-085	
OTB-502	
OTB-503	
OTB-504	

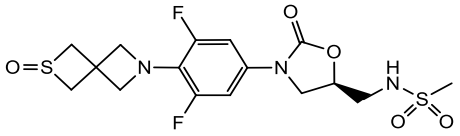
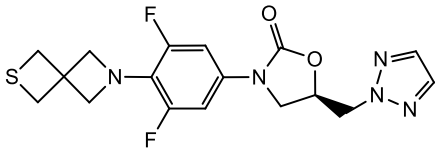
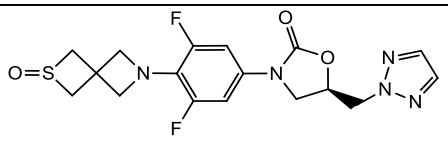
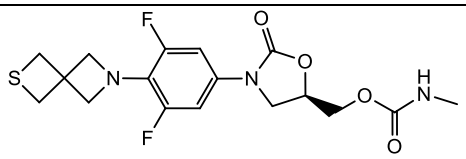
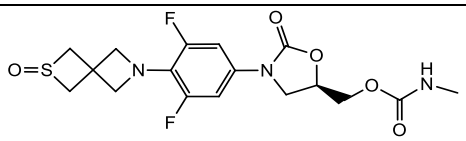
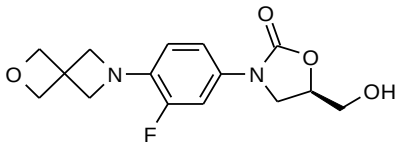
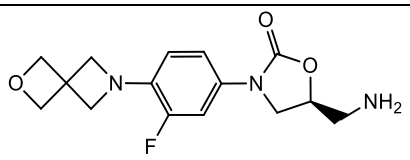
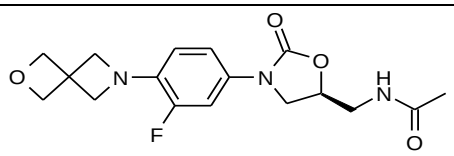
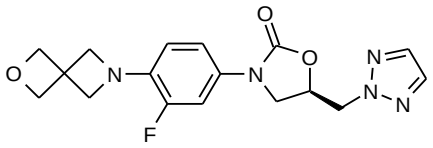
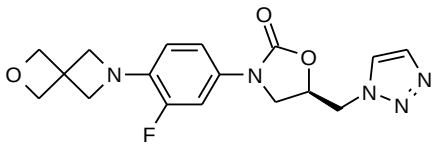
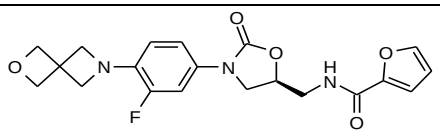
OTB-505	
OTB-236	
OTB-237	
OTB-518	
OBD-016	
OBD-017	
OBD-021	
OBD-018	
OTB-506	
OTB-507	

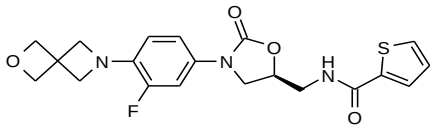
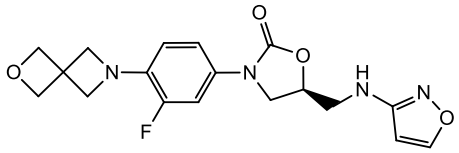
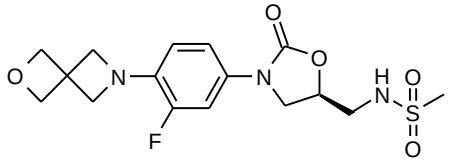
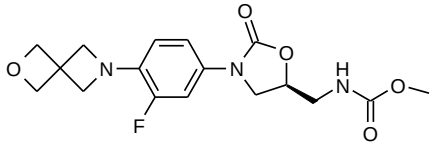
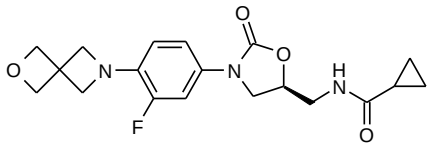
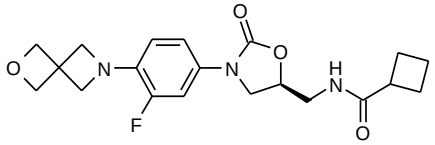
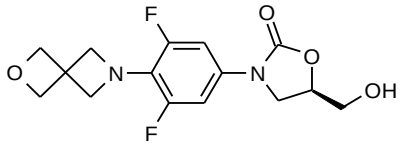
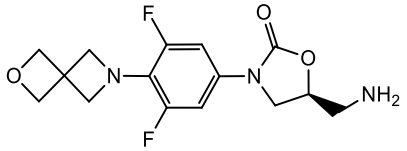
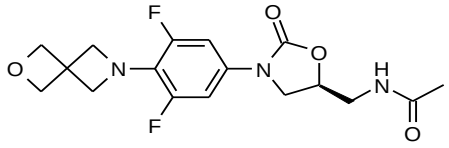
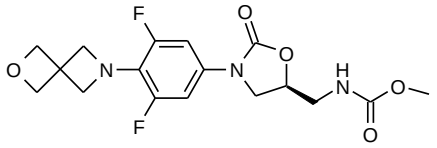
OTB-510	
OTB-514	
OTB-512	
OTB-519	
OTB-511	
OTB-517	
OTB-508	
OTB-509	
OTB-513	
OBD-083	

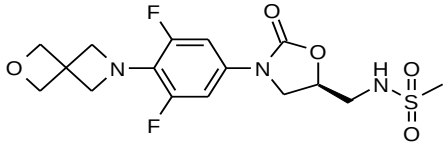
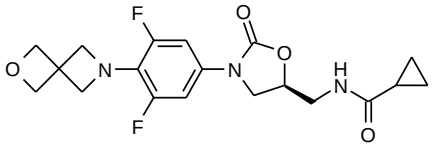
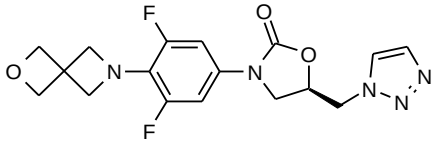
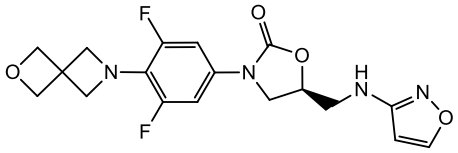
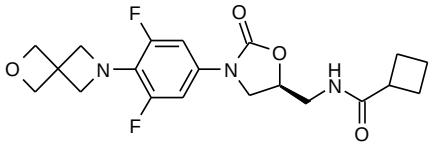
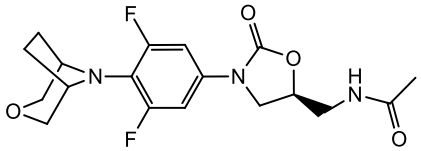
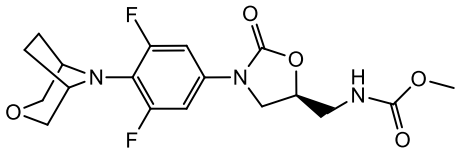
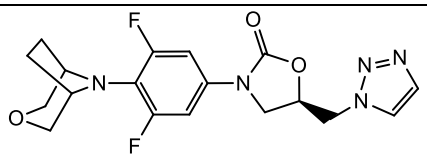
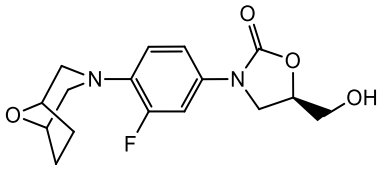
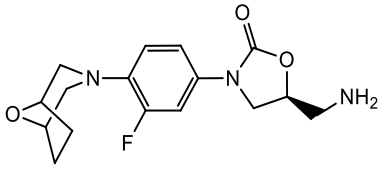
OBD-087	
OBD-029	
OBD-242	
OTB-260	
OTB-261	
OTB523	
OTB-515	
OTB-256	
OTB-241	
OTB-247	

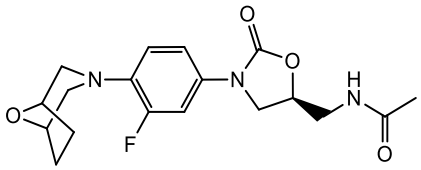
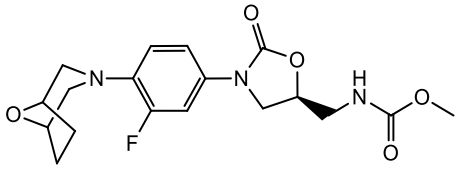
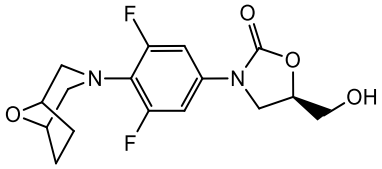
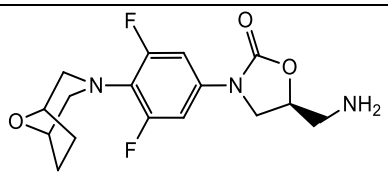
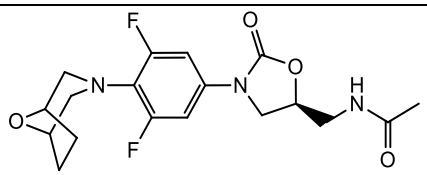
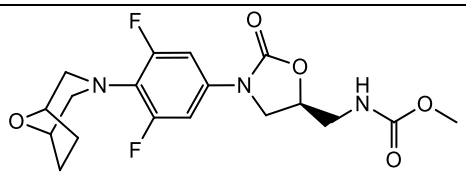
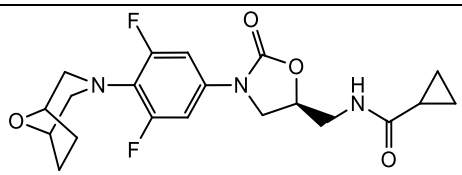
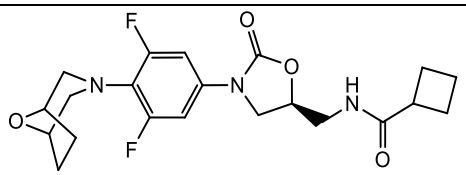
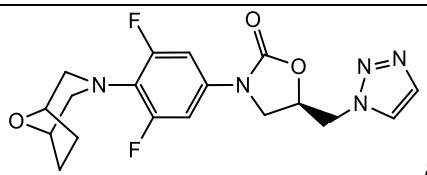
OTB-249	
OTB-255	
OTB-250	
OTB-254	
OTB-260-2A	
OTB-260-2B	
OTB-260-5A	
OTB-260-5B	
OTB-260-4A	
OTB-260-4B	
OTB-516	

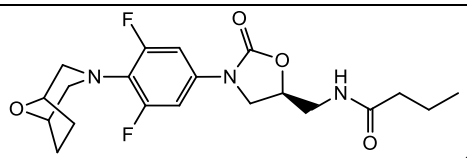
OTB-515	
OTB-520	
OTB-242	
OTB-253	
OTB-245	
OTB-522	
OTB-243	
OTB-252	
OTB-244	
OTB-251	
OTB-516-2A	

OTB-516-2B	
OTB-516-6A	
OTB-516-6B	
OTB-516-4A	
OTB-516-4B	
OTB-201	
OBD-057	
OTB-202	
OTB-203	
OTB-204	
OTB-205	

OTB-206	
OBD-056	
OTB-222	
OTB-223	
OTB-238	
OTB-239	
OTB-229	
OBD-062	
OTB-230	
OTB-231	

OTB-232	
OTB-233	
OTB-234	
OBD-061	
OTB-240	
OBD-051	
OBD-052	
OBD-055	
OBD-112	
OBD-113	

OBD-110	
OBD-111	
OBD-114	
OBD-115	
OBD-048	
OBD-049	
OBD-252	
OBD-253	
OBD-054	 and

OBD-254	

or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

9. A pharmaceutical composition, comprising one or more compound of Formula I as claimed in claim 1, or a salt, hydrate, or solvate thereof, and one or more pharmaceutically acceptable carriers and/or additives.

10. The pharmaceutical , composition as claimed in claim 09 optionally comprising one or more additional anti-infective treatments.

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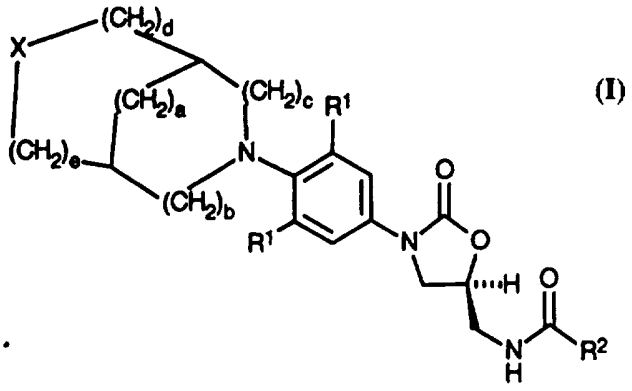
(54) Title: BICYCLIC OXAZINE AND THIAZINE OXAZOLIDINONE ANTIBACTERIALS

(57) Abstract

Phenyloxazolidinone compounds of formula (I) or a pharmaceutically acceptable salt thereof characterized by a bicyclic thiazine or oxazine substituent. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiply-resistant staphylococci, streptococci and enterococci as well as anaerobic organisms such as *Bacteroides spp.* and *Clostridia spp.* species, and acid-fast organisms such as *Mycobacterium tuberculosis*, *Mycobacterium avium* and *Mycobacterium spp.*



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BICYCLIC OXAZINE AND THIAZINE OXAZOLIDINONE ANTIBACTERIALS

Background of the Invention

The subject invention discloses new and useful phenyloxazolidinone compounds characterized by having either a bicyclic thiazine or oxazine substituent. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiply-resistant staphylococci, streptococci and enterococci as well as anaerobic organisms such as *Bacteroides spp.* and *Clostridia spp.* species, and acid-fast organisms such as *Mycobacterium tuberculosis*, *Mycobacterium avium* and *Mycobacterium spp.*

Information Disclosure

The present compounds are related by their phenyloxazolidinone ring structure to those disclosed in the publications below except that the subject compounds have either a bicyclic thiazine or oxazine phenyl substituent. The instant compounds have useful antibacterial activity.

PCT/US94/08904 application discloses oxazolidinone antibacterial compounds having either a morpholine or thiomorpholine substituent.

PCT/US93/03570 application discloses oxazolidinones containing a substituted diazine moiety and their uses as antimicrobials.

PCT/US92/08267 application discloses substituted aryl and heteroaryl-phenyl-oxazolidinones useful as antibacterial agents.

PCT/US89/03548 application discloses 5'indolinyl-5ß-amidomethyloxazolidinones, 3-(fused-ring substituted)phenyl-5ß-amidomethyloxazolidinones, and 3-(nitrogen substituted)phenyl-5ß-amidomethyloxazolidinones which are useful as antibacterial agents.

Other references disclosing various oxazolidinones include US Patent 4,801,600, 4,921,869, Gregory W. A., et al., J. Med. Chem., 32, 1673-81 (1989); Gregory W. A., et al., J. Med. Chem., 33, 2569-78 (1990); Wang C., et al., Tetrahedron, 45, 1323-26 (1989); and Brittelli, et al., J. Med. Chem., 35, 1156 (1992).

European Patent Publication 352,781 discloses phenyl and pyridyl substituted phenyl oxazolidinones.

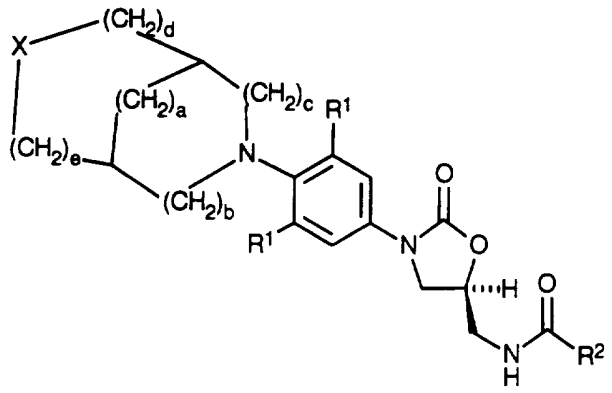
European Patent Publication 316,594 discloses 3-substituted styryl oxazolidinones.

European Patent Publication 312,000 discloses phenylmethyl and

pyridinylmethyl substituted phenyl oxazolidinones.

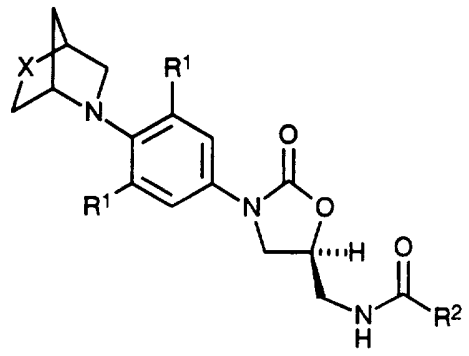
Summary of the Invention

In one aspect the subject invention is a compound of structural Formula I:



Formula I

More preferred compounds, a subset of those described by structural Formula I, are represented by structural Formula II:



Formula II

or pharmaceutically acceptable salts thereof wherein:

X is (a) O,

(b) S,

(c) SO,

(d) SO_2;

R^1 is independently H, F, Cl or OMe;

R^2 is (a) hydrogen,

(b) C_1-C_8 alkyl optionally substituted with one or more of the following: F, Cl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy,

(c) C_3-C_6 cycloalkyl,

(d) amino,

(e) C_1-C_8 alkylamino,

(f) C_1-C_8 dialkylamino,

(g) C_1-C_8 alkoxy;

a is 0 to 3;

b is 0 to 2;

c is 0 to 2 (provided b and c cannot both be 0);

d is 0 to 2; and

e is 0 to 2 (provided d and e cannot both be 0).

In another aspect, the subject invention is directed toward a method for treating microbial infections in humans or other warm-blooded animals by administering to a patient in need thereof an effective amount of a compound of Formula I or II as described above. The compound can be administered in a pharmaceutical composition either orally, parenterally or topically. Preferably the compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day, more preferably, from about 3.0 to about 50 mg/kg of body weight/day.

Detailed Description of the Invention

The present invention discloses novel substituted bicyclic oxazinyl- or thiazinylphenyloxazolidinones of structural Formula I and II as described above.

The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, particularly aerobic gram-positive bacteria, including multiply-resistant staphylococci and streptococci, as well as anaerobic organisms such as bacteroides and clostridia species, and acid-fast bacteria such as as *Mycobacterium tuberculosis* and other mycobacterial species.

"Alkyl" means carbon atom chains having the designated number of carbon atoms which can be either straight chained or branched.

"Alkoxy" means the designated number of carbon atoms attached to an oxygen forming such groups as methoxy (-OCH_3), ethyloxy, butyloxy, etc. and isomeric forms thereof.

"Acyloxy" means the designated number of carbon atoms to form an organic acid where the OH group has been deleted, such as acetyl, CH_3 CO-; benzoyl, C_6 H_5CO-.

Cycloalkyl" means the designated number of carbon atoms forming cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. and isomeric forms thereof.

"Amino" means an NH_2, "alkylamino" is where one of the hydrogen positions is replaced by an alkyl and "dialkylamino" is where both hydrogens are replaced by an alkyl group.

"Pharmaceutically acceptable salts" are acid addition salts which can be prepared by any of the art recognized means. Typical, acid addition salts include hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, malate, succinate, tartrate, cyclohexanesulfamates, methanesulfonates, ethanesulfonates, benxenesulfonates, toluenesulfonates, fumarates and other pharmaceutically acceptable couter ions for amines.

Preferably X is S.

The R^1 substituents are preferably both fluorine and, more preferably, fluorine and hydrogen.

The R^2 substituent is preferably hydrogen, methyl, dichloromethyl, hydroxymethyl or methoxy. More preferably R^2 is hydrogen, methoxy or methyl. It is most preferred that R^2 is methyl.

The preferred absolute configuration at C-5 of the oxazolidinone ring of compounds claimed in this invention is as represented in the structures of Formula I and II. This absolute configuration is called (*S*) under the Cahn-Ingold-Prelog nomenclature system. It is this (*S*)-enantiomer which is pharmacologically active. The racemic mixture is useful in the same way and for the same purpose as the pure (*S*)-enantiomer; the difference is that twice as much racemic material must be

used to produce the same antibacterial effect. It will be apparent to one skilled in the art that when an additional chiral center(s) is present in the bicyclic oxazine or thiazine fragment of compounds of structural Formula I and II, then diastereomers are possible. These diastereomers, in racemic and enantiomerically enriched forms, are also within the scope of the compounds of Formula I and II of the invention.

Preferred compounds of Formula I are

(*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 1);

(*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 2);

(*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-2,2-dioxo-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 3);

(*S*)-*N*-[[3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-*c*]pyrrol-5(3*H*)-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 4)

(*S*)-*N*-[[3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-*c*]pyrrol-5(3*H*)-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, S-oxide (Example 5)

(*S*)-*N*-[[3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-*c*]pyrrol-5(3*H*)-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, S,S-dioxide (Example 6)

cis-(S)-N-[[3-[3-fluoro-4-[3-oxa-7azabicyclo[3.3.0]octane-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Exmaple 7)

(*S*)-N-[[3-[3-fluoro-4-[(1*R*,4*R*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(2-thia-6-azabicyclo[3.2.0]heptan-6-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(3-thia-6-azabicyclo[3.2.0]heptan-6-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(3-thia-7-azabicyclo[3.3.1]nonan-7-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(3-thia-9-azabicyclo[3.3.1]nonan-9-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(2-thia-6-azabicyclo[3.2.1]octan-6-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(2-thia-6-azabicyclo[3.3.1]nonan-6-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(7-thia-3-azabicyclo[4.2.1]nonan-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(9-thia-3-azabicyclo[3.3.1]nonan-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(3-oxa-6-azabicyclo[3.2.0]heptan-6-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(3-oxa-7-azabicyclo[3.3.1]nonan-7-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(3-oxa-9-azabicyclo[3.3.1]nonan-9-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(9-oxa-3-azabicyclo[3.3.1]nonan-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(2-oxa-5-azabicyclo[2.2.2]octan-5-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(2-oxa-6-azabicyclo[3.2.1]octan-6-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(3-oxa-7-azabicyclo[4.2.0]octan-7-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(6-oxa-2-azabicyclo[3.2.1]octan-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(*S*)-N-[[3-[3-fluoro-4-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; and

(*S*)-N-[[3-[3-fluoro-4-[(1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

The most preferred compound is (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 2).

(*S*)-*N*-[[3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-*c*]pyrrol-5(3*H*)-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Example 4)

(*S*)-*N*-[[3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-*c*]pyrrol-5(3*H*)-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, S,S-dioxide (Example 6)

The pharmaceutical compositions of this invention may be prepared by combining the compounds of Formula I or II of this invention with a solid or liquid pharmaceutically acceptable carrier and, optionally, with pharmaceutically

acceptable adjuvants and excipients employing standard and conventional techniques. Solid form compositions include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be at least one substance which may also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Inert solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, cellulosic materials, low melting wax, cocoa butter, and the like. Liquid form compositions include solutions, suspensions and emulsions. For example, there may be provided solutions of the compounds of this invention dissolved in water and water-propylene glycol and water-polyethylene glycol systems, optionally containing suitable conventional coloring agents, flavoring agents, stabilizers and thickening agents.

Preferably, the pharmaceutical composition is provided employing conventional techniques in unit dosage form containing effective or appropriate amounts of the active component, that is, the compound of Formula I according to this invention.

The quantity of active component, that is the compound of Formula I or II according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the potency of the particular compound, the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

In therapeutic use for treating, or combatting, bacterial infections in warm-blooded animals, the compounds or pharmaceutical compositions thereof will be administered orally and/or parenterally at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which will be antibacterially effective. Generally, such antibacterially effective amount of dosage of active component will be in the range of about 0.1 to about 100, more preferably about 3.0 to about 50 mg/kg of body weight/day. It is to be understood that the dosages may vary depending upon the requirements of the patient, the severity of the bacterial infection being treated, and the particular compound being used. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also

be divided into multiple doses for administration, e.g., two to four times per day.

The compounds of Formula I or II according to this invention are administered parenterally, i.e., by injection, for example, by intravenous injection or by other parenteral routes of administration. Pharmaceutical compositions for parenteral administration will generally contain a pharmaceutically acceptable amount of the compound according to Formula I or II as a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as, for example, water-for-injection and a buffer to provide a suitably buffered isotonic solution, for example, having a pH of about 3-7. Suitable buffering agents include, for example, trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine to name but a few representative buffering agents. The compound according to Formula I generally will be dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 mg/ml to about 400 mg/ml of solution. The resulting liquid pharmaceutical composition will be administered so as to obtain the above-mentioned antibacterially effective amount of dosage.

The preferred method of preparation of oxazolidinones of Formula I and II in enantiomerically pure form is depicted in Charts I-IV..

As shown in Chart I, bicyclic oxazines and thiazines (commercially available or known in the literature), such as (1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptane (X = O) and (1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptane (X = S) of structure **1**, are reacted with a functionalized nitrobenzene **2** (Y = halogen or trifluoromethanesulfonate) in the presence of a suitable base such as *N,N*-diisopropylethylamine and in a suitable solvent such as acetonitrile, tetrahydrofuran (THF) or ethyl acetate at ambient to reflux temperature to provide the adducts **3**. When X = O, the nitro group of **3** is then reduced by catalytic hydrogenation in the presence of a suitable catalyst such as 10% palladium on carbon or W-2 Raney nickel, and in a suitable solvent such as ethyl acetate, tetrahydrofuran, aqueous tetrahydrofuran, methanol and mixtures thereof, to furnish the anilines **4**. In the case where X = S, the nitro group of **3** can be reduced by the action of sodium hydrosulfite in aqueous tetrahydrofuran at ambient temperature to 55 °C to give the anilines **4**. Alternatively, reduction of the nitro group of **3** (X = S) can be accomplished by catalytic hydrogenation in the presence of a suitable catalyst, such as platinum on sulfide carbon or W-2 Raney nickel, and in an appropriate solvent system, for example aqueous tetrahydrofuran. The latter conditions are especially useful in that the reaction mixture is simply filtered through Celite® or the like to remove the catalyst and the filtrate containing

the aniline **4** is directly used in the next step. To this end, the anilines **4** are converted to their benzyl ($R^3 = CH_2Ph$) or methyl ($R^3 = CH_3$) carbamate derivatives **5**, employing standard Schotten-Baumann conditions or other variations known to one skilled in the art. The urethanes **5** are then deprotonated with a suitable base such as *n*-butyllithium, lithium diisopropylamide, or lithium bis(trimethylsilyl)amide in a suitable solvent such as tetrahydrofuran or N,N-dimethylformamide and at a suitable temperature such as -78 to -60°C to give a lithiated intermediate which is then treated with commercially available (-)-(*R*)-glycidyl butyrate. Warming to ambient temperature then directly affords the 5-(hydroxymethyl)oxazolidinones **6** in enantiomerically enriched form. Compound **6** is then converted to the corresponding mesylate **7** (R^4 = methanesulfonyl) or aryl sulfonate **7** ($R^4 = ArSO_2$, for example *p*-toluenesulfonyl) by the action of, for example, methanesulfonyl chloride/pyridine or methanesulfonyl chloride/triethylamine/dichloromethane or *p*-toluenesufonyl chloride/pyridine.

As illustrated in Chart II, the resultant sulfonate derivative **7** is then reacted with an azide source such as sodium or potassium azide in an aprotic solvent such as *N,N*-dimethylformamide (DMF) or 1-methyl-2-pyrrolidinone, optionally in the presence of a catalyst such as 18-crown-6, at a temperature of 50-90 °C to afford the azide **8**. The azide is then reduced by hydrogenation with palladium on carbon or a platinum catalyst in an appropriate solvent such as ethyl acetate or methanol to give the corresponding amine **9**. Alternatively, and preferably in the case where X = S, the azide can be reduced by treatment with a trivalent phosphorus compound such as triphenylphosphine in a suitable solvent such as tetrahydrofuran followed by the addition of water. Alternatively, the mesylate or aryl sulfonate group of compounds **7** can be displaced with potassium phthalimide in acetonitrile at reflux temperature to give the intermediate phthalimide **10**. The phthalimide **10** is then deprotected by treatment with aqueous methyl amine in refluxing ethanol to afford the amine **9**. In yet another alternative, the mesylate **7** is reacted with ammonium hydroxide in hot isopropanol or isopropanol/tetrahydrofuran, preferably in a sealed reaction vessel, to directly give the amine **9**. The amine **9** is then acylated by reactions known to those skilled in the art to give oxazolidinones of structure **11**. For example, the amine can be reacted with an acid chloride or anhydride in a basic solvent such as pyridine at a temperature ranging from -30 to 30 °C to provide the acylated compound **11** (R^2 = optionally substituted alkyl). It will be apparent to one skilled in the art that other acyl groups within the scope of this invention can be

readily appended to the amine **9** by standard acylation techniques, for example those highlighted in March, J. "Advanced Organic Chemistry", 4th ed.; John Wiley & Sons: New York, 1992; pp 417-425, to give additional examples of **11**. The compounds of structure **11** represent examples of bicyclic oxazine- and thiazine-substituted oxazolidinone antibacterial agents of Formula II, which are the subject of this invention.

As shown in Chart III, the oxazolidinones **11**, themselves examples of antibacterial agents of Formula II, can be further elaborated to additional compounds of Formula II. Specifically, **11** (X = S) can be oxidized to the corresponding sulfoxide(s) **12** (X = SO) with sodium metaperiodate in a mixture of water and methanol. It will be apparent to one skilled in the art that both *endo-* and *exo-* sulfoxides are possible, and both isomeric forms, as well as mixtures thereof, are within the scope of this invention. In addition, compounds **11** or **12** can be oxidized to the corresponding sulfones **13** (X = SO_2) by treatment with 4-methylmorpholine *N*-oxide and catalytic osmium tetroxide in aqueous acetone. It will be apparent to those skilled in the art that alternative conditions for oxidizing **11** (X = S) to **12** or **13** are known, for example those highlighted in March, J. "Advanced Organic Chemistry", 4th ed.; John Wiley & Sons: New York, 1992; pp 1201-1202.

As shown in Chart IV synthesis of compounds which incorporate a thienopyrrolidine begins with reduction of the diester **14** to the diol **15** using lithium aluminum hydride as the reducing agent. Compound **15** is then converted to the bis-mesylate **16** by reaction with methanesulfonyl chloride and a trialkylamine base. Cyclization of **16** to the thienopyrrolidine **17** is carried out by reaction with sodium sulfide, and compound **17** is debenzylated to the thienopyrrole **18** by reaction with hydrogen in the presence of a suitable catalyst such as palladium on carbon. The compound of example 4 is then prepared from **18** by following the procedures outlined in Charts I and II (but substituting **18** for **1**). The compounds of Examples 5 and 6 are prepared by oxidation of the compound of Example 4, using the same procedures as shown in Chart III.

Antimicrobial activity was tested *in vivo* using a Murine Assay procedure. Groups of female mice were injected intraperitoneally with bacteria which were thawed just prior to use and suspended in brain heart infusion with 4% Brewer's yeast UC9213 (*Staphylococcus aureus*) or brain hear infusion (*Streptococcus species*). Antibiotic treatment a six dose levels per drug was administered on hour and five

hours after infection by either oral or subcutaneous routes. Survival was observed daily for six days. ED50 values based on mortality ratios were calculated using probit analysis. The subject compounds were compared against a well-known antimicrobial (Vancomycin) as a control. The data is shown in Table 1.

Table 1

***In Vivo* Activity Against *S. aureus* UC®9213**

Example No.	ED_{50} (mg/kg)	
	Example, PO	Vancomycin, SC
1	7.7	11.2
2	4.2	4.0
4	4.3	-
5	10.0	-
6	3.5	-

It will be apparent to those skilled in the art that the described synthetic procedures are merely representative in nature and that the use of alternative bicyclic oxazines and thiazines known in the patent and open literature allows for the preparation of additional examples of structural Formula I.

EXAMPLE 1: (*S*)-N-[[3-[4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1: 4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluoronitrobenzene

A mixture of commercially available (1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride (0.200 g, 1.47 mmol), dipotassium hydrogen phosphate (1.030 g, 5.90 mmol) and 3,4-difluoronitrobenzene (0.195 mL, 1.77 mmol) in dimethyl sulfoxide (6 mL) was stirred at ambient temperature under a N_2 atmosphere. TLC analysis (5% MeOH/$CHCl_3$) after 3 h revealed the starting nitrobenzene was consumed. The reaction mixture was diluted with H_2O and (60 mL) and extracted with $CHCl_3$. The combined organic extracts were washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to a yellow solid. Chromatography over silica gel (60 g), eluting with a gradient of 0-2% MeOH/$CHCl_3$, afforded, after concentration of appropriate fractions, 0.314 g (90%) of the title compound as a yellow solid with mp 106.5-108 °C and MS(EI) 238 (M^+).

Step 2: N-(carbobenzyloxy)-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluoroaniline

A solution of 4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluoronitrobenzene (0.160 g, 0.672 mmol) in 3:1 THF/H_2O (4 mL) was treated with acetic acid (0.115 mL) and then 10% palladium/carbon (0.020 g) under a N_2 stream. The atmosphere was replaced with H_2 (balloon) by repeated evacuation and filling and the mixture stirred at ambient temperature. After 2 h, TLC analysis (6% $CH_3CN/CHCl_3$) revealed the reduction to be complete. The reaction mixture was filtered through Celite® and the filtrate immediately placed under an atmosphere of N_2 and treated with K_2CO_3 (0.464 g, 3.36 mmol) followed by benzyl chloroformate (0.117 mL, 0.864 mmol). TLC analysis (6% $CH_3CN/CHCl_3$) after 0.5 h revealed the reaction to be complete. The reaction mixture was concentrated under reduced pressure and chromatographed over silica gel (20 g), eluting with a gradient of 1-5% $CH_3CN/CHCl_3$. Concentration of appropriate fractions afforded 0.226 g (98 %) of the title compound as a white solid with mp 120-121 °C and MS(EI) 342 (M^+).

Step 3: (*R*)-[3-[4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methanol

A solution of N-(carbobenzyloxy)-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluoroaniline (0.169 g, 0.494 mmol) in dry THF (2 mL) was cooled to -78 °C under a N_2 atmosphere and then treated with *n*-butyllithium (0.312 mL of a 1.6 M

solution in hexane, 0.499 mmol). After stirring 10 min at -78 °C, the reaction mixture was treated with (*R*)-glycidyl butyrate (0.070 mL, 0.499 mmol). When the addition was completed, the cooling bath was removed and the mixture allowed to stir at ambient temperature overnight, during which time an off-white precipitate appeared. TLC analysis (5% MeOH/$CHCL_3$) revealed the reaction to be complete. The reaction mixture was treated with ca. 5 drops of saturated aqueous NH_4Cl, which made the reaction mixture a homogeneous solution. The reaction mixture was concentrated under reduced pressure to an off-white solid. Chromatography over silica gel, eluting with a gradient of 1-5% MeOH/$CHCl_3$, afforded, after concentration of appropriate fractions, 0.116 g (84%) of the title compound as a white solid with mp 138-140 °C and MS(EI) 308 (M^+). In addition, 0.018 g (10%) of a second component, identified as the butyrate ester of the title compound by ^1H NMR analysis, was obtained as an amber oil.

Step 4: (*R*)-[[3-[4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]methanesulfonate

A solution of (*R*)-[3-[4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methanol (0.765 g, 2.48 mmol) in dry CH_2Cl_2 (30 mL) was cooled to 0 °C under a N_2 atmosphere and treated with Et_3N (0.518 mL, 3.73 mmol) followed by methanesulfonyl chloride (0.202 mL, 2.61 mmol). TLC analysis (5% MeOH/$CHCl_3$) after 0.5 h revealed the reaction to be complete. The reaction mixture was washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give 0.992 g (ca. 100%) of the title compound as a tan solid. An analytical sample was prepared by recrystallization from 5% CH_2Cl_2/*i*-PrOH. This sample had mp 124.5-126 °C and MS(EI) 386 (M^+).

Step 5: (*R*)-[[3-[4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyllazide

A solution of (*R*)-[[3-[4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]methanesulfonate (0.869 g, 2.25 mmol) in dry DMF (10 mL) was tretaed with solid NaN_3 (0.732 g, 11.3 mmol) at ambient temperature under N_2. The mixture was then heated to 65 °C and reaction progress monitored by TLC. After 7.5 h at this temperature, TLC analysis (5% MeOH/$CHCl_3$) revealed the reaction to complete. The reaction mixture was diluted with EtOAc (100 mL), washed with H_2O (3 x 15 mL) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 0.692 g (92%) of the title

compound as a tan solid. An analytical sample was prepared by recrystallization from 1:1 EtOAc/hexane as an off-white solid with mp 101-102.5 °C and MS(EI) 333 (M^+).

Step 6: (*S*)-N-[[3-[4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A solution of (*R*)-[[3-[4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]azide (0.652 g, 1.96 mmol) in MeOH (20 mL) and CH_2Cl_2 (10 mL) was treated with 10% palladium/carbon (0.095 g) under a N_2 stream. The atmosphere was then replaced with H_2 (balloon) by repeated evacuation and filling and the mixture stirred at ambient temperature under H_2. After 3 h, TLC analysis (5% MeOH/$CHCl_3$) revealed the reduction to be complete. The reaction mixture was filtered through Celite® and the filtrate concentrated under reduced pressure. The crude 5-(aminomethyl)oxazolidinone was dissolved in CH_2Cl_2 (20 mL) and treated with pyridine (0.190 mL, 2.35 mmol) and then acetic anhydride (0.222 mL, 2.35 mmol). After 0.5 h, TLC analysis (5% MeOH/$CHCl_3$) indicated the acetylation to be complete. The reaction mixture was washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give an off-white solid. Chromatography over silica gel (70 g), eluting with a gradient of 1-3% MeOH/$CHCl_3$, afforded, after concentration of appropriate fractions, 0.517 g (76%) of the title oxazolidinone antibacterial agent as a white solid with mp 60-65 °C and MS(EI) 349 (M^+).

EXAMPLE 2: (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1: 4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluoronitrobenzene

A mixture of commercially available (1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptane (0.500 g, 3.30 mmol), diisopropylethylamine (1.434 mL, 8.24 mmol) and 3,4-difluoronitrobenzene (0.437 mL, 3.96 mmol) in dry acetonitrile (15 mL) was heated to reflux temperature under a N_2 atmosphere for 1 h and then cooled to ambient temperature overnight. The reaction mixture was concentrated under reduced pressure to give a yellow syrup. Chromatography over silica gel (50 g), eluting with chloroform, afforded, after concentration of appropriate fractions, 0.700 g (84%) of the title compound as a yellow solid with mp 97-98 °C and MS(EI) 254 (M^+).

Step 2: N-(carbobenzyloxy)-4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluoroaniline

A solution of 4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluoronitrobenzene (1.64 g, 6.46 mmol) in 20% H_2O/THF (50 mL) was treated with platinum on sulfide carbon (0.200 g) under a N_2 stream. The atmosphere was replaced with H_2 (balloon) by repeated evacuation and filling. After 12 h TLC analysis revealed a significant amount of starting material still remained. The reaction mixture was transferred to a Parr apparatus and shaken under 45 psi H_2. TLC analysis after 2 h indicated some starting material still remained. The reaction mixture was filtered through Celite® and the filtrate, containing a mixture of the desired aniline intermediate and starting nitrobenzene derivative, was cooled to 0 °C and treated with $NaHCO_3$ (2.170 g, 25.8 mmol) and benzyl chloroformate (1.02 mL, 7.10 mmol). After 0.5 h the reaction mixture was concentrated under reduced pressure to a yellow/green syrup. This material was dissolved in $CHCl_3$, washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Filtration through a plug of silica gel, eluting with 20-30% EtOAc/hexane, afforded, after concentration of appropriate fractions, a mixture of starting nitrobenzene derivative and the title compound. This material taken-up in 20% H_2O/THF (50 mL) and treated with W-2 Raney nickel (ca. 0.400 g). The reaction mixture was shaken on a Parr apparatus under 45 psi H_2. After 3 h the reaction mixture was filtered through Celite® and the filtrate cooled to 0 °C and treated with $NaHCO_3$ (2.00 g, 23.8 mmol) followed by benzyl chloroformate (0.600 mL, 4.19 mmol). After 0.5 h the reaction mixture was concentrated under reduced pressure and the residue chromatographed over silica gel (125 g), eluting with 10-20% EtOAc/hexane, to afford, after concentration of appropriate fractions, 2.20 g (95%) of the title compound as a yellow solid mp 91-93 °C and MS(EI) 358 (M^+).

Step 3: (*R*)-[3-[4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methanol

A solution of N-(carbobenzyloxy)-4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluoroaniline (0.359 g, 1.00 mmol) in dry THF (4 mL) under N_2 was cooled to -78 °C and then treated with *n*-butyllithium (0.633 mL of a 1.6 M solution in hexane, 1.01 mmol). The reaction mixture was stirred at -78 °C for 15 min and then treated with (*R*)-glycidyl butyrate (0.151 mL, 1.00 mmol). When the addition was complete, the cooling bath was removed and the reaction mixture allowed to warm to ambient temperature overnight. TLC analysis (5% MeOH/$CHCl_3$) indicated the reaction was

complete but a small amount of the butyrate ester of the title compound was present. The addition of 5 drops of a 25 wt.% solution of NaOMe/MeOH, followed by stirring for 20 min at room temperature, was effective in converting this intermediate to the title compound. The reaction mixture was treated with saturated aqueous NH_4Cl (10 drops) and then concentrated under reduced pressure to an oil. This material was dissolved in CH_2Cl_2 and washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a crude product. Chromatography over silica gel (50 g), eluting with 1-3% MeOH/$CHCl_3$, afforded, after concentration of appropriate fractions, 0.132 g (41%) of the title compound as an oil. Trituration with EtOAc afforded a precipitate, which was isolated and dried *in vacuo* to give an off-white solid with mp 156-157 °C and MS(EI) 324 (M^+).

Step 4: (*R*)-[[3-[4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]methanesulfonate

A solution of (*R*)-[3-[4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methanol (1.68 g, 5.19 mmol) in dry CH_2Cl_2 (100 mL) under N_2 was cooled to 0 °C and treated with Et_3N (0.793 mL, 5.70 mmol) followed by methanesulfonyl chloride (0.442 mL, 5.70 mmol). After 0.5 h at this temperature, the reaction appeared to be complete by TLC analysis (5% MeOH/$CHCl_3$). The mixture was washed with H_2O, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give 1.65 g (79%) of the title compound as a white solid with mp 139-142 °C and MS(EI) 402 (M^+).

Step 5: (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A mixture of (*R*)-[[3-[4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]methanesulfonate (1.56 g, 3.88 mmol), 1:1 THF/*i*-PrOH (4 mL) and 30% NH_4OH (4 mL) was heated to 95 °C in a sealed tube for 14 h and then cooled to ambient temperature. TLC analysis (5% MeOH/$CHCl_3$) revealed the reaction to be complete. The mixture was diluted with CH_2Cl_2 (75 mL), washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a syrup. The crude 5-(aminomethyl)oxazolidinone intermediate was dissolved in CH_2Cl_2 (75 mL) and treated with pyridine (0.345 mL, 4.27 mmol) and acetic anhydride (0.403 mL, 4.27 mmol) at ambient temperature. After 1 h, TLC analysis (5% MeOH/$CHCl_3$)

indicated the acetylation to be complete. The reaction mixture was washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to an amber solid. Chromatography over silica gel (125 g), eluting with 1-3% MeOH/$CHCl_3$, afforded, after concentration of appropriate fractions, 1.23 g (87%) of the title oxazolidinone antibacterial agent as a solid with mp 90-95 °C and MS(EI) 365 (M^+).

EXAMPLE 3: (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-2,2-dioxo-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A solution of (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (0.300 g, 0.82 mmol) in 25% H_2O/acetone (16 mL) was treated at ambient temperature with 4-methylmorpholine-N-oxide (0.288 g, 2.47 mmol) followed by osmium tetroxide (0.102 mL of a 2.5 wt.% solution in *tert*-butanol, 0.008 mmol). After 18 h, TLC analysis (10% MeOH/$CHCl_3$) revealed the oxidation was complete. The reaction mixture was treated with saturated aqueous $NaHSO_3$ and then extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed over silica gel (10 g), eluting with 1-3% MeOH/$CHCl_3$, to afford, after concentration of appropriate fractions, 0.321 g (98%) of the title oxazolidinone antibacterial agent as a white solid with mp 95-105 °C.

EXAMPLE 4: (*S*)-*N*-[[3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5(3*H*)-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1: *cis*-1-(Phenylmethyl)-3,4-pyrrolidinedimethanol

(*cis*)-1-(Phenylmethyl)-3,4-pyrrolidinedicarboxylic acid, dimethyl ester was prepared according to the procedure of Y. Terao, et al (*Chem. Pharm. Bull.*, **1985**, *33*, 2762-66). To a stirred solution of this diester (12.14 g, 43.8 mmol) in dry THF (175 mL) under N_2 cooled to 0 °C was added dropwise a solution of lithium aluminum hydride (1M in THF, 87 mL, 87 mmol) over 15 min. The reaction mixture was stirred at 0 °C for 1 h, then at RT for 18 h. The reaction mixture was cooled to 0 °C and quenched with successive addition of H_2O (3.2 mL), 5 N NaOH (3.2 mL) and H_2O (11.7 mL). The reaction mixture became very thick and stirring was difficult. The reaction mixture was diluted with ether (500 mL) and filtered through a small pad of celite. The filter cake was washed with ether (250 mL). The filtrate was washed

with H_2O (1 x 300 mL) and the organics were dried ($MgSO_4$), filtered and concentrated to afford 9.3 g (41.8 mmol, 96%) of the desired diol and a thick yellow oil. Used without further purification. HRMS (FAB) calcd for $C_{13}H_{19}NO_2$+H 222.1494, found 222.1490.

Step 2: *cis*-1-(Phenylmethyl)-3,4-di(methylsulfonyloxy)methylpyrrolidine

To a stirred solution of *cis*-1-(phenylmethyl)-3,4-pyrrolidinedimethanol (9.2 g, 41.6 mmol) in CH_2Cl_2 (240 mL) cooled to 0 °C was added triethylamine (29 mL, 208.1 mmol) followed by methanesulfonyl chloride (8.1 mL, 104.0 mmol). The reaction mixture was stirred at 0 °C for 15 min, then at RT for 1.5 h. The reaction mixture was poured into H_2O (240 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (1 x 100 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography using ethyl acetate as the eluent to afford 14.2 g (37.5 mmol, 90%) of the desired bis-mesylate as a thick yellow oil. HRMS (EI) calcd for $C_{15}H_{23}NO_6S_2$ 377.0967, found 377.0958.

Step 3: Hexahydro-5-(phenylmethyl)-1*H*-thieno[3,4-c]pyrrole

To a stirred solution of *cis*-1-(phenylmethyl)-3,4-di(methylsulfonyloxy)methylpyrrolidine (9.2 g, mmol), in dry DMSO (48 mL) was added anhydrous sodium sulfide (5.7 g, 73.3 mmol). The dark reaction mixture was heated at 120 °C for 18 h. The cooled reaction mixture was poured into ice H_2O (150 mL). The resulting mixture was extracted with ether (3 x 200mL). The combined organics were dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by flash chromatography using ethyl acetate as the eluent to afford 4.2 g (19.1 mmol, 78%) of the desired product as a thick yellow oil. HRMS (EI) calcd for $C_{13}H_{17}NS$ 219.1082, found 219.1080. Anal. Calcd for $C_{13}H_{17}NS$: C, 71.19; H, 7.81; N, 6.39. Found: C, 70.82; H, 7.83; N, 6.35.

Step 4: Hexahydro-1*H*-thieno[3,4-c]pyrrole, hydrochloride

To a stirred solution of hexahydro-5-(phenylmethyl)-1*H*-thieno[3,4-c]pyrrole (1.2 g, 5.3 mmol) in CH_2Cl_2 (21 mL) cooled to 0 °C was added dropwise *via* syringe 1-chloroethylchloroformate (1.15 mL, 10.7 mmol). The reaction mixture was stirred at 0 °C for 20 min, then at RT for 90 min. The reaction mixture was concentrated. The resulting residue was purified by flash chromatography using 25 % ethyl acetate in hexane as the eluent to afford 611.3 mg (2.6 mmol, 49%) of 1-

chloroethylcarbamate. The column was then washed with 20% methanolic ammonia in $CHCl_3$ to afford 160.5 mg (1.24 mmol, 23 %) of desired amine as the free base. The 1-chloroethylcarbamate (611.3 mg, 2.6 mmol) was dissolved in methanol (15 mL) and heated at reflux for 90 min. The cooled reaction mixture was concentrated to afford 408.0 mg (2.5 mmol, 47%) of the desired amine as the HCl salt (based on chlorocarbamte). mp 149-151 °C; HRMS (EI) calcd for $C_6H_{11}NS$ 129.0612, found 129.0614. Anal. Calcd for $C_6H_{12}ClNS$: C, 43.50; H, 7.30; N, 8.45; Cl: 21.39; S: 19.35. Found: C, 43.39; H, 7.23; N, 8.24; Cl: 21.08; S: 19.12.

Step 5: 5-(2-Fluoro-4-nitrophenyl)-hexahydro-1*H*-thieno[3.4-c]pyrrole

To a stirred suspension of hexahydro-5-1*H*-thieno[3,4-c]pyrrole, hydrochloride (147.3 mg, 0.89 mmol) in acetonitrile (5 mL) was added 3,4-fluoronitrobenzene (0.11 mL, 0.98 mmol) followed by diisopropylethyl amine (0.36 mL, 2.05 mmol). The homogeneous reaction mixture was heated at reflux for 18 h. The cooled reaction mixture was concentrated. The resulting residue was diluted with EtOAc (50 mL) and washed with saturated aqueous NH_4Cl (1 x 25 mL). The aqueous layer was extracted with EtOAc (1 x 30 mL). Combined organics were washed with saturated $NaHCO_3$ (1 x 40 mL), brine (1 x 40 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography using 20 % EtOAc in hexane as the eluent to afford 202.5 mg (0.75 mmol, 89%) of the desired nitro compound as a bright yellow solid. mp 107-109 °C; Anal. calcd for $C_{12}H_{13}FN_2O_2S$: C, 53.72; H, 4.88; N, 10.44; S: 11.95. Found: C, 53.38; H, 5.03; N, 10.34; S: 11.89.

Step 6: 3-[3-Fluoro-4-(tetrahydro-1*H*-thieno[3.4-c]pyrrol-5(3*H*)-yl)phenylcarbamic acid, phenylmethylester

To a stirred suspension of 5-(2-fluoro-4-nitrophenyl)-hexahydro-1*H*-thieno[3,4-c]pyrrole (1.44 g, 5.4 mmol) in ethanol (70 mL) was added 2 M aqueous $CuSO_4$ (2.9 mL). This mixture was cooled to 0 °C and sodium borohydride (1.10 g, 26.8 mmol) was added portionwise. (Caution: Very exothermic!) The dark reaction mixture was then heated at reflux for 2 h. The cooled reaction mixture was partitioned between EtOAc and H_2O. The phases were separated. The aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated. The resulting dark residue was dissolved in acetone/H_2O (2:1, 60 mL). This stirred solution was cooled to 0 °C and solid $NaHCO_3$ (1.35 g, 16.1 mmol) was added followed by benzylchloroformate (1.9 mL, 13.4 mmol). The reaction mixture was stirred at 0 °C for 15 min, then at RT for 2 h. The reaction

mixture was quenched by careful addition of 10 % aqueous $NaHSO_4$ (30 mL). The reaction mixture was poured into EtOAc (250 mL) and the phases were separated. The aqueous layer was extracted with EtOAc (1 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography using 20% EtOAc in hexane to afford 1.6 g (4.3 mmol, 81 %) of the desired carbamate: mp 101-102 °C; Anal. Calcd for $C_{20}H_{21}FN_2O_2S$: C, 64.50; H, 5.68; N, 7.52; S: 8.61. Found: C, 64.33; H, 5.56; N, 7.53; S: 8.61.

Step 7: (5*R*)-3-[3-Fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5(3*H*)-yl)phenyl]-5-(hydroxymethyl)-2-oxazolidinone

To stirred solution of 3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5(3*H*)-yl)phenylcarbamic acid, phenylmethyl ester (1.36 g, 3.6 mmol) dry THF (14 mL) under N_2 cooled to -78 °C was added n-butylithium (1.6 M in hexane, 2.4 mL, 3.8 mmol). The reaction mixture was stirred at -78 °C for 35 min and then *R*-(-)-glycidylbutyrate (0.54 mL, 3.8 mmol) was added. The reaction mixture was stirred at -78 °C for 30 min, then at RT overnight. A thick precipitate had formed. The reaction mixture was quenched with saturated aqueous NH_4Cl (14 mL) and poured into EtOAc (50 mL). The phases were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (1 x 30 mL), brine (1 x 30 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography using EtOAc as the eluent to afford 801.6 mg (2.4 mmol, 65%) of the desired product. mp 165-167 °C; Anal. Calcd for $C_{16}H_{19}FN_2O_3S$: C, 56.79; H, 5.66; N, 8.28; S: 9.48. Found: C, 56.88; H, 5.74; N, 8.21; S: 9.33.

Step 8: (5*R*)-3-[3-Fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5(3*H*)-yl)phenyl]-5-[[(methylsulfonyl)oxy]methyl]-2-oxazolidinone

To a stirred solution of (5*R*)-3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5(3*H*)-yl)phenyl]-5-(hydroxymethyl)-2-oxazolidinone (656.5 mg, 1.9 mmol) in CH_2Cl_2 (20 mL) cooled to 0 °C was added triethylamine (0.41 mL, 2.9 mmol) followed by methanesulfonylchloride (0.18 mL, 2.3 mmol). The reaction mixture was stirred at 0 °C for 15 min, then at RT for 18 h. The reaction mixture was poured into H_2O (20 mL). the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (1 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. the residue was triturated with ether/hexane and solid was isolated by filtration and dried to afford 773.9 mg (1.9 mmol, 96%) of the desired mesylate. mp 148-150 °C; Anal. Calcd for $C_{17}H_{21}FN_2O_5S_2$: C, 49.03; H, 5.08; N, 6.73; S:

15.40. Found: C, 48.56; H, 5.12; N, 6.48; S: 15.41. Found: C, 48.46; H, 5.25; N, 6.38.

Step 9: (*S*)-*N*-[[3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5(3*H*)-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A stirred suspension of (5*R*)-3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5-(3*H*)-yl)phenyl]-5-[[(methylsulfonyl)oxy]methyl]-2-oxazolidinone (208.5 mg, 0.5 mmol) in THF (3 mL) and methanolic ammonia (3 mL) was heated in a sealed tube at 100 °C for 48 h. (The reaction mixture became homogenous at about 80 °C.) The cooled reaction mixture was concentrated and the resulting residue was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. To this stirred suspension was added pyridine (0.12 mL, 1.5 mmol) followed by acetic anhydride (60 µL, 0.6 mmol). The homogeneous reaction mixture was stirred at 0 °C for 15 min, then at RT for 1 h then concentrated. The residue was purified by flash chromatography using 7 % methanol in EtOAc as the eluent to afford 148.2 mg (0.4 mmol, 78%) of the desired acetamide. mp 143-144 °C; KF-H_2O: 0.52% Anal. Calcd for $C_{18}H_{22}FN_3O_3S$ plus 0.52% H_2O: C, 56.68; H, 5.87; N, 11.01; S: 8.40. Found: C, 56.31; H, 5.90; N, 10.74; S: 8.30.

EXAMPLE 5: (*S*)-*N*-[[3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5(3*H*)-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, S-oxide

To a stirred solution of (S)-N-[[3-[3-fluoro-4-(tetrahydro-1H-thieno[3,4-c]pyrrol-5(3H)-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide (216.8 mg, 0.57 mmol) in methanol (4 mL) and H_2O (4 mL) cooled to 0 °C was added sodium metaperiodate (134.4 mg, 0.63 mmol). The reaction mixture was stirred at 0 °C for 1 h, then at RT for 18 h. The solid precipitation was removed by filtration. The solid was washed with $CHCl_3$ (50 mL). The filtrate was washed with H_2O (1 x 30 mL). The aqueous layer was extracted with $CHCl_3$ (2 x 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography using 7% methanol in CH_2Cl_2 as the eluent to afford 195.7 mg (0.5 mmol, 87 %) of the desired sulfoxide. mp 162-164 °C; HRMS (EI) calcd for $C_{18}H_{22}FN_3O_4S$ 395.1315, found 395.1309. KF-H_2O: 2.87 % Anal. Calcd for $C_{18}H_{22}FN_3O_4S$ plus 2.87 % H_2O: C, 53.09; H, 5.76; N, 10.32; S: 7.87. Found: C, 53.07; H, 6.01; N, 10.20; S: 7.87.

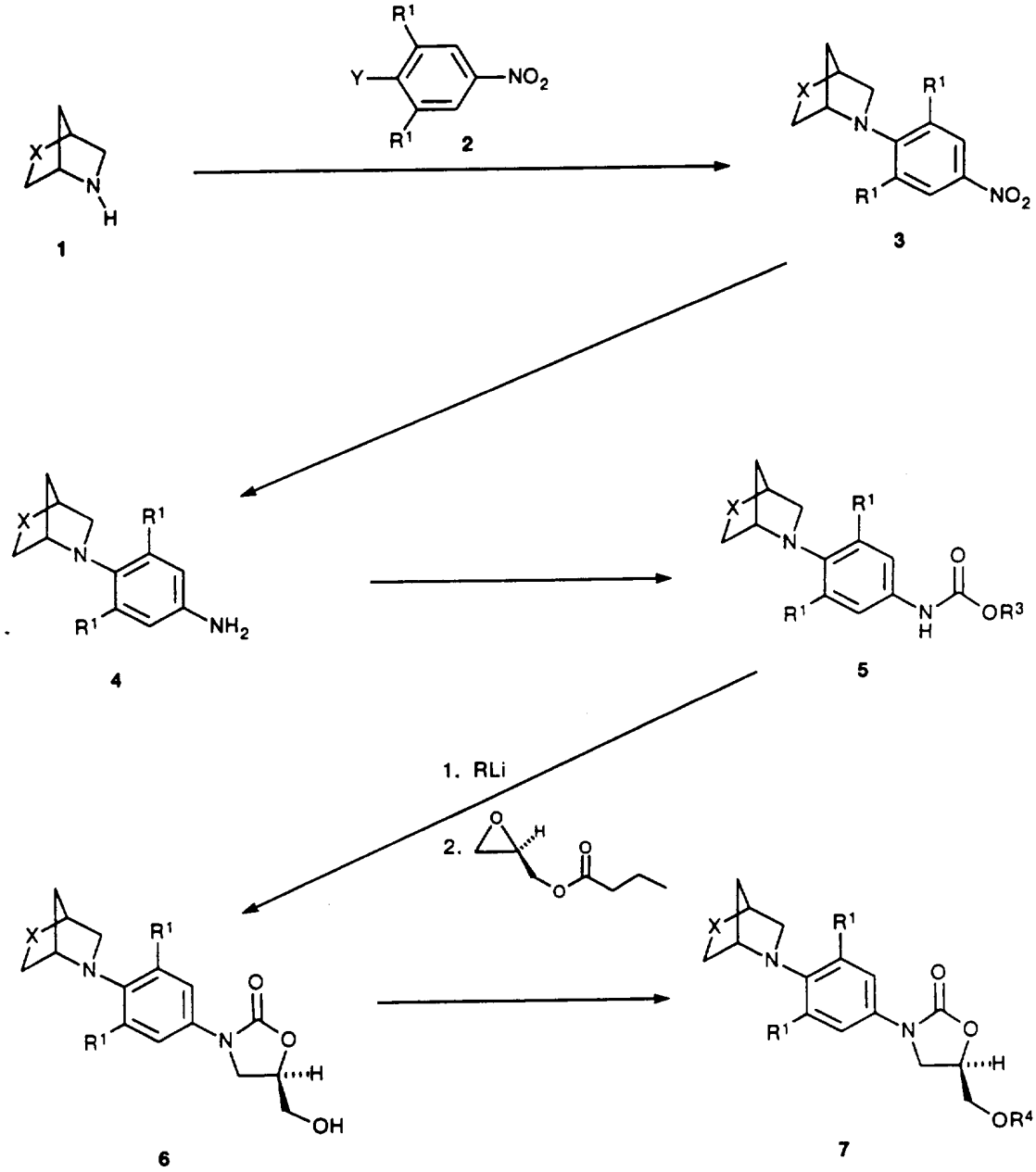
EXAMPLE 6: (*S*)-*N*-[[3-[3-fluoro-4-(tetrahydro-1*H*-thieno[3,4-c]pyrrol-5(3*H*)-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, S,S-dioxide

To a stirred solution of (S)-N-[[3-[3-fluoro-4-(tetrahydro-1H-thieno[3,4-c]pyrrol-5(3H)-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide (213.9 mg, 0.56 mmol) in 25 % acetone/H_2O (8 mL) was added N-methylmorpholine-N-oxide (198.1 mg, 1.7 mmol) followed by osmium tetroxide in *tert*-butanol (2.5 % by wt.) (30 μL, 0.08 mmol). The reaction mixture was stirred at RT for 18 h. The reaction mixture was quenched by careful addition of saturated sodium bisulfite (8 mL). The mixture was poured into CH_2Cl_2 (50 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with brine (1 x 30 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography using 7 % methanol in $CHCl_3$ as the eluent to afford 194.3 mg (0.47 mmol, 84 %) of desired sulfone. mp 135-137 °C; HRMS (EI) calcd for $C_{18}H_{22}FN_3O_5S$ 411.1264, found 411.1263. KF-H_2O: 1.10 %. Anal. Calcd for $C_{18}H_{22}FN_3O_5S$ plus 1.10 % H_2O: C, 51.96; H, 5.45 N, 10.10; S: 7.71. Found: C, 51.73; H, 5.62; N, 9.96; S: 7.75.

EXAMPLE 7: cis-(S)-N-[[3-[3-fluoro-4-[3-oxa-7azabicyclo[3.3.0]octane-7-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Following the general procedure of EXAMPLE 2 and making noncritical variations but substituting hexahydro-1H-furo(3,4-c)pyrrole (Miller, A.D. *U.S. Patent 3,975,532* **1976**). (2.33 g, 20.66 mmol) for (1S, 4S)-2-thia-5-azabicyclo[2.2.1]heptane, the title compound is obtained, mp 124-126°C.

Chart I


R1
Y
NO2
R1
2
X
N
H
1
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N
R1
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NH2
4
X
N
R1
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OR3
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1. RLi
2.
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7

Chart II

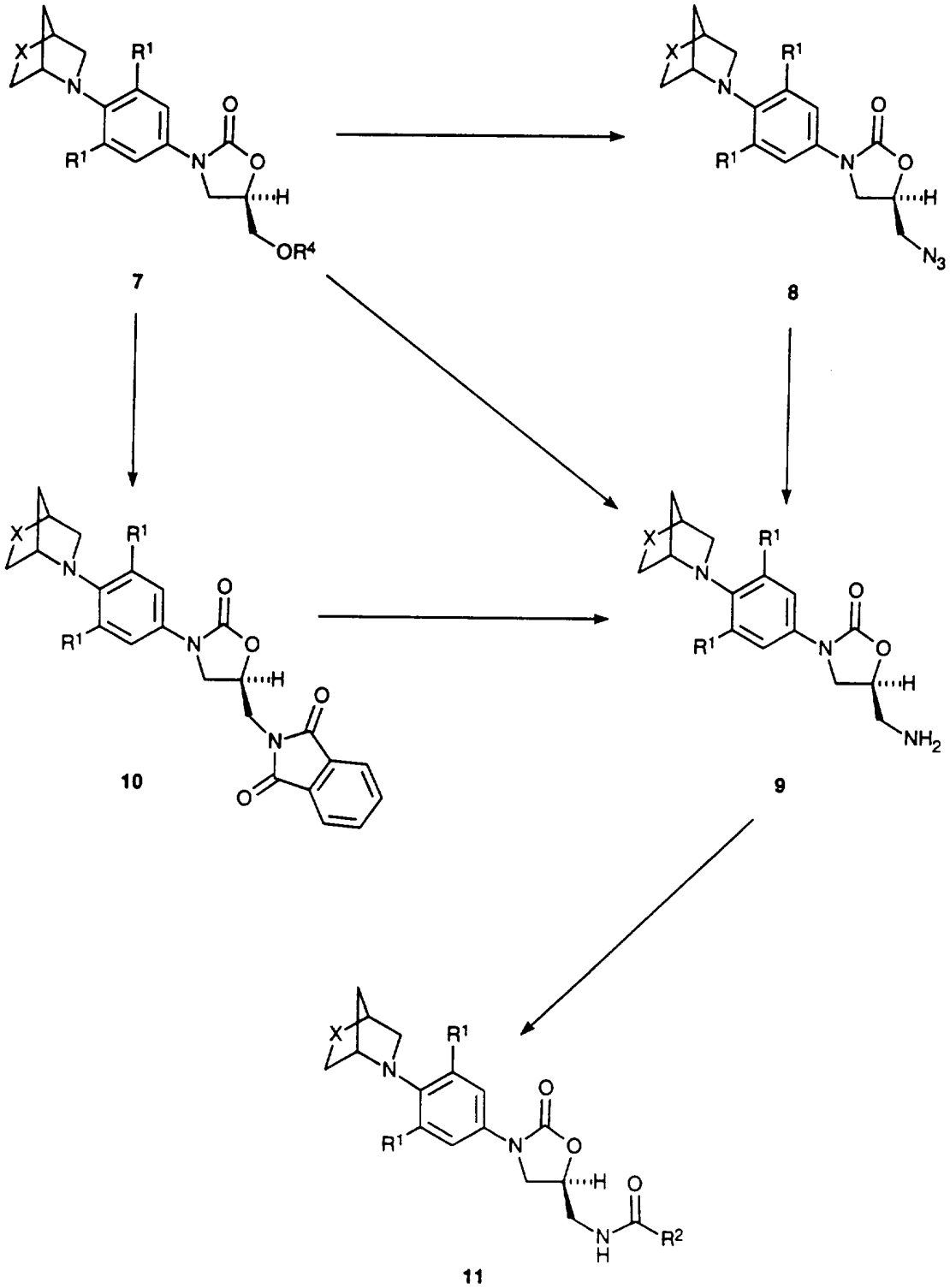

Chart III

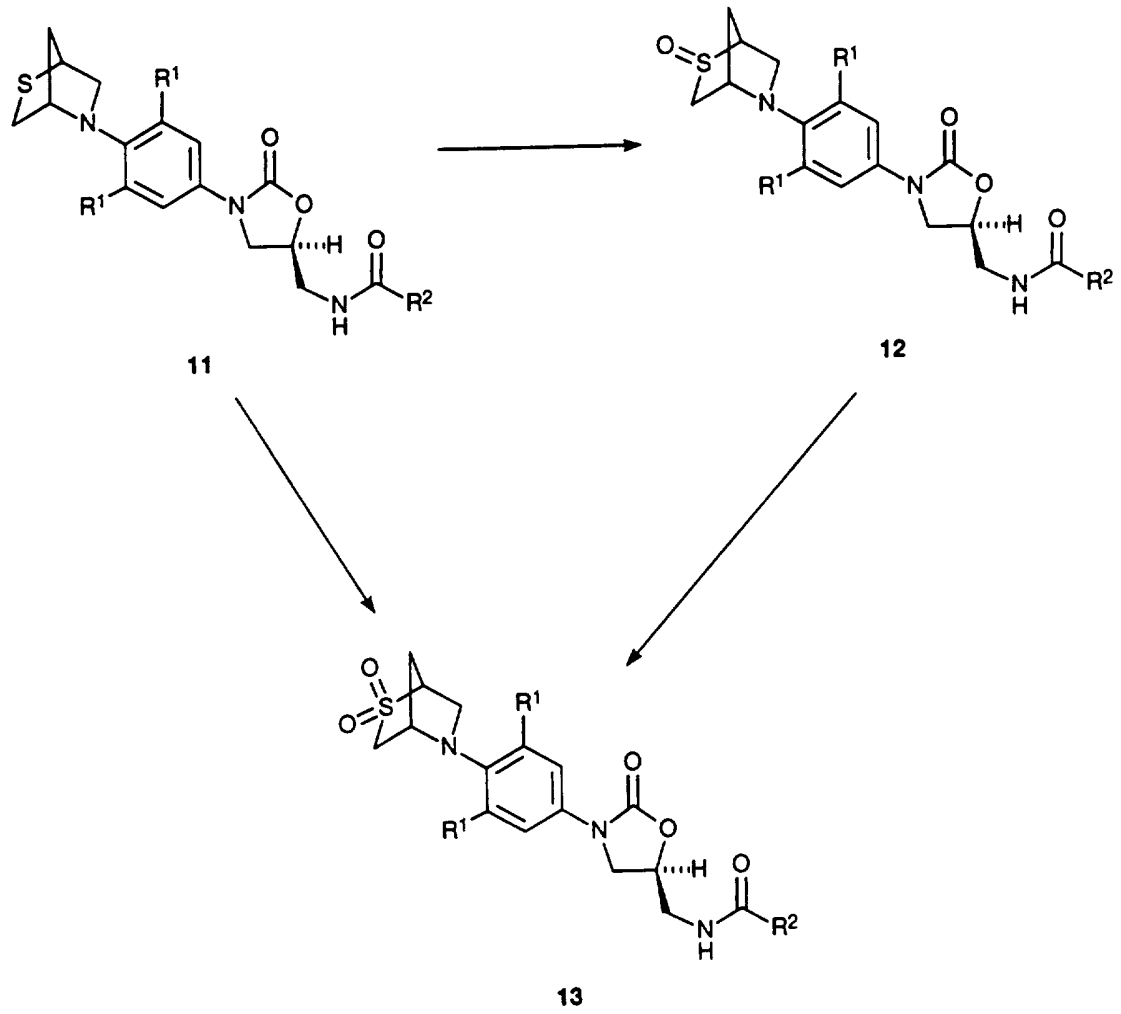

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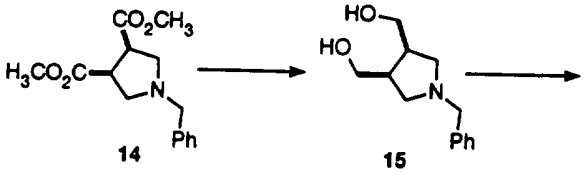
CHART IV



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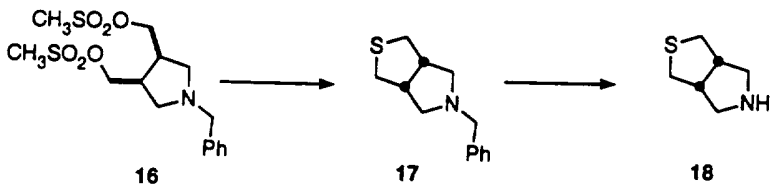
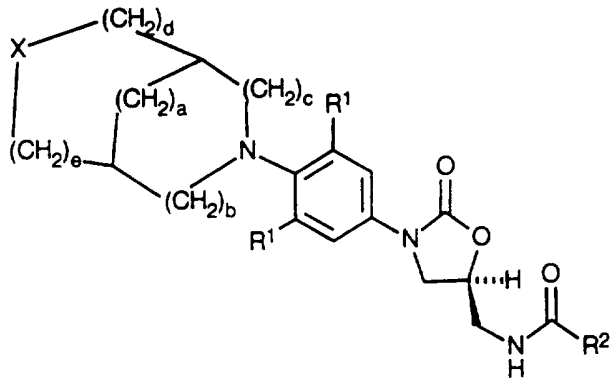


16 17 18

What is Claimed:

1. A compound of structural Formula I:



Formula I

or a pharmaceutically acceptable salt thereof wherein:

X is (a) O,
(b) S,
(c) SO,
(d) SO_2;

R^1 is independently H, F, Cl or OMe;

R^2 is (a) hydrogen,
(b) C_1-C_8 alkyl optionally substituted with one or more of the following: F, Cl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy,
(c) C_3-C_6 cycloalkyl,
(d) amino,
(e) C_1-C_8 alkylamino,
(f) C_1-C_8 dialkylamino,
(g) C_1-C_8 alkoxy;

a is 0 to 3; b is 0 to 2; c is 0 to 2 (provided b and c cannot both be 0); d is 0 to 2; and e is 0 to 2 (provided d and e cannot both be 0).

2. The compound of Claim 1 wherein X is S.

3. The compound of Claim 1 wherein each R^1 is independently H or F.

4. The compound of Claim 3 wherein each R^1 is F.

5. The compound of Claim 1 wherein R^2 is hydrogen, a C_1-C_8 alkoxy, or a C_1-C_8 alkyl optionally substituted with one or more Cl or OH.

6. The compound of Claim 1 wherein R^2 is methyl, dichloromethyl, hydroxymethyl, or methoxy.

7. The compound of Claim 1 which is:

a) (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

b) (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; or

c) (*S*)-N-[[3-[3-fluoro-4-[(1*S*,4*S*)-2-thia-2,2-dioxo-5-azabicyclo[2.2.1]heptan-5-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

8. The compound of Claim 1 which is the S-enantiomer form.

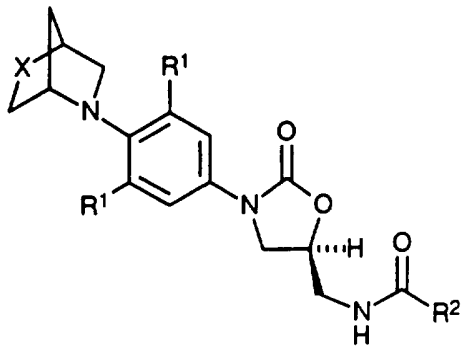
9. The compound of Claim 1 wherein c and b are both 1.

10. The compound of Claim 9 wherein d and e are both 1.

11. The compound of Claim 10 wherein a is 0.

12. The use of a compound of Formula I to prepare a medicament useful in treating microbial infections in a patient in need thereof by administering an effective amount of a compound of Formula I.

13. A compound of structural Formula II:



Formula II

or pharmaceutically acceptable salts thereof wherein:

X.is (a) O,

(b) S,

(c) SO,

(d) SO_2;

R^1 is independently H, F, Cl or OMe; and

R^2 is (a) hydrogen,

(b) C_1-C_8 alkyl optionally substituted with one or more of the following: F, Cl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy,

(c) C_3-C_6 cycloalkyl,

(d) amino,

(e) C_1-C_8 alkylamino,

(f) C_1-C_8 dialkylamino,

(g) C_1-C_8 alkoxy.

14. The compound of Claim 13 which is the S-enantiomer form.

15. The use of a compound of Formula II to prepare a medicament useful in treating microbial infections in warm-blooded animals by administering to a patient in need thereof an effective amount of a compound of Formula II.

INTERNATIONAL SEARCH REPORT

Interr. ıal Application No
PCT/US 95/12751

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D491/048 C07D491/08 C07D495/04 C07D495/08 A61K31/42
//(C07D491/048,307:00,209:00),(C07D491/08,307:00,209:00),
(C07D495/04,333:00,209:00),(C07D495/08,333:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,93 23384 (UPJOHN) 25 November 1993 see claims 1,11	1,12,13,15
A	JOURNAL OF MEDICINAL CHEMISTRY., vol.33, no.9, 1990, WASHINGTON US pages 2569 - 2578 W. A. GREGORY ET AL 'Antibacterials. Synthesis and structure-activity studies of 3-aryl-2-oxooxazolidines. 2. The "A" group' cited in the application see table VI	1,12,13,15
P,X	WO,A,95 07271 (UPJOHN) 16 March 1995 cited in the application see claims 1,15	1,12

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 February 1996	14.02.1996

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Voyiazoglou, D

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INTERNATIONAL SEARCH REPORT

Intern. nal Application No
PCT/US 95/12751

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO,A,95 14684 (UPJOHN) 1 June 1995 see claims 1,9	1,12,13, 15

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. ..onal Application No
PCT/US 95/12751

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9323384	25-11-93	AU-B-	4287793	13-12-93
		CN-A-	1079964	29-12-93
		CZ-A-	9402505	16-08-95
		EP-A-	0640077	01-03-95
		FI-A-	945246	08-11-94
		JP-T-	7506829	27-07-95
		NO-A-	944237	04-01-95
		SK-A-	133794	07-06-95
WO-A-9507271	16-03-95	AU-B-	7557094	27-03-95
WO-A-9514684	01-06-95	AU-B-	8010394	13-06-95

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doi:10.1155/2012/159285

D2

Review Article

Current Updates on Oxazolidinone and Its Significance

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Oxazolidinone is a five-member heterocyclic ring exhibiting potential medicinal properties with preferential antibacterial activity. Scientists reported various synthetic procedures for this heterocyclic structure. Current review articles tried to cover each and every potential aspect of oxazolidinone like synthetic routes, pharmacological mechanism of action, medicinal properties, and current research activities.

1. Introduction

The oxazolidinones are a new class of antimicrobial agents which have a unique structure and good activity against gram-positive pathogenic bacteria. Oxazolidinones are a class of compounds containing 2-oxazolidine in the structure. Oxazolidinones represent a new class of synthetic antibacterial agents active against multiple-resistant gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant streptococci, and vancomycin-resistant enterococci [1].

1.1. Chemical Structure [2]. Oxazolidinones are a class of azoles, oxazolidines with the carbon between the nitrogen and oxygen oxidized to a ketone, hence oxazolidinone (Figure 1).

1.2. Nomenclature. The antibacterial oxazolidinone template has a common nomenclature specially for aryl-5-(substituted) methyl-2-oxazolidinone. Throughout the paper, a consistent numbering system has been employed for description of the various oxazolidinone examined [3].

2. Synthetic Schemes

Earlier reviews have comprehensively covered the many synthetic approaches available for construction of the oxazolidinone ring. The most recent literature is replete with accounts of oxazolidinone templates that have seen extensive use as chiral auxiliaries.

(1) *Chiral Resolution Method.* Early work relied upon chiral resolution as a means to optically active oxazolidinone. The amino-diol resulting from reaction of an aniline with glycidol was resolved using (R)-mandelic acid. Diethylcarbonate effected cyclization to the 5-(R)-hydroxymethyl-3-phenyl-2-oxazolidinone. Numerous approaches had been employed for converting the 5-(R)-methylalcohol moiety to the 5-(S)-acetamidomethyl group. Here tosylation of the alcohol was followed by azide displacement, reduction, and acylation of the amine [4] (Figure 2).

(2) *Iodocyclocarbamation.* Many of the Upjohn SAR studies were carried out with racemic oxazolidinone, synthesized by iodocyclocarbamation. A key modification was the addition of pyridine, crucial for circumventing untoward alkylative side reaction [5] (Figure 3).

(3) *DuPONT Asymmetric Synthesis. The Herweh-Kauffmann/Speranza-Peppel Method.* This method involved high-temperature catalyst-mediated cyclization of an aryl isocyanate with an epoxide where LiBr catalyst was solubilized in refluxing xylene by tributylphosphine oxide. As demonstrated for DuP721 (R)-glycidol butyrate was cyclized with 4-acetylphenyl isocyanate, giving the oxazolidinone butyrate ester. Saponification provided the 5-(R)-hydroxymethyl oxazolidinone which was further

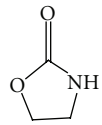


Figure 1: General Structure of oxazolidinone.

methylated and then converted to the acetamide, as described next for tosylate [5] (Figure 4).

(4) Synthesis of oxazolidin-2-ones derivatives was carried out starting from urea and ethanolamine reagents using microwave irradiation in a chemical paste medium in which a catalytic amount of nitromethane absorbed the microwaves and generated hot spots [6] (Figure 5).

(5) An efficient, versatile, and practical gram-scale preparation of oxazolidinone, imidazolidinone, and dioxolanone was achieved [6] (Figure 6).

(6) A mild and efficient gold (I)-catalyzed rearrangement of propargylic *tert*-butylcarbamates allowed the synthesis of various 5-methylene-1, 3-oxazolidin-2-ones, which would be less conveniently obtained using other methods [7] (Figure 7).

(7) Various *N*-Boc-protected alkynylamines were converted into the corresponding alkylidene 2-oxazolidinones or 2-oxazinones under very mild reaction conditions in the presence of a cationic Au (I) complex in high yield regardless of the substitution at nitrogen and alkyne terminus [8] (Figure 8).

(8) A nickel-catalyzed cycloaddition of aziridines with isocyanates proceeded smoothly to give iminooxazolidine derivatives in good yields. A longer reaction time allowed the isomerization of the iminooxazolidine to the corresponding imidazolidinone derivatives [9] (Figure 9).

(9) *Synthesis of Oxazolidinones by the Use of Halomethyloxirane, Primary Amine, and Carbonate Salt*. Primary amines reacted with carbonate salts (Na_2CO_3, K_2CO_3, Cs_2CO_3, and Ag_2CO_3) and halomethyloxiranes in the presence of a base such as DBU or TEA to give oxazolidinones in high yields. The use of K_2CO_3 among these carbonate gave the best yield in this synthesis. A reaction mechanism was proposed that the oxazolidinone was obtained from an oxazinanone intermediate via a bicyclo [2.2.1] intermediate. The present reaction can be widely applied to convenient synthesis of useful N-substituted oxazolidinones and chiral oxazolidinones [10] (Figure 10).

(10) *Direct Catalytic Asymmetric Amination of Aldehydes: Synthesis of Evans, Oxazolidinones and α-Amino Acids* [11] (Figure 11).

(11) *Conversion of Chiral α-Hydrazino Alcohols and N-Amino Oxazolidinone to Evans Auxiliaries [11]*(*Figure 12*).

(12) *Solid-Phase Synthesis of Oxazolidinones by Cycloaddition of Resin-Bound Epoxides with Isocyanates.* The first solid-phase synthesis of oxazolidinones by cycloaddition of resin-bound epoxides with isocyanates is described. Synthesis of the title compounds was achieved by alkylation of resin-bound carbamates with glycidyl tosylate, followed by cycloaddition of the resulting epoxides with isocyanates at elevated temperature in high yields and purity. Because *N*-aryloxazolidinones have been known to possess various biological activities, this method is useful from the viewpoint of drug discovery [12] (Figure 13).

(13) *A Convenient Diastereoselective Synthesis Of Oxazolidinone: Approach to Unusual Amino Acid Statine* [13] (Figures 14 and 15).

(14) *Synthesis of* [5, 14, 14]-*Tricyclic Fused Oxazolidinone [15] (Figure 16).*

3. Pharmacological Background

Mechanism of Action. Oxazolidinones inhibit protein synthesis by binding at the P site at the ribosomal 50S subunit. Resistance to other protein synthesis inhibitors does not affect oxazolidinone activity; however rare development of oxazolidinone resistance cases, associated with 23S r-RNA alterations during treatment, has been reported. Linezolid (Figure 17), the first oxazolidinone available, has already taken its place in the clinic for treatment of gram-positive infections.

It selectively inhibits bacterial protein synthesis through binding to sites on the bacterial ribosome and prevents the formation of a functional 70S-initiation complex. Specifically, linezolid binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit and prevents the formation of a functional 70S initiation complex (Figure 18), which is an essential component of the bacterial translation process [16].

4. Pharmacokinetic Parameter [17, 18]

(i) *Absorption*. It is rapidly and extensively absorbed after oral dosing. Maximum plasma concentrations are reached approximately 1 to 2 hours after dosing, and the absolute bioavailability is approximately 100%.

(ii) *Toxicity*. Clinical signs of acute toxicity lead to decreased activity, ataxia, vomiting and tremors.

(iii) *Protein Binding*. 31%.

(iv) *Biotransformation.* It is primarily metabolized by oxidation of the morpholine ring, which results in two inactive ring-opened carboxylic acid metabolites: the aminoethoxyacetic acid metabolite, and the hydroxyethyl glycine metabolite.

(v) *Half-Life.* 4.5–5.5 hours.

(vi) *Excretion*. Renal and fecal (Table 1).

4.1. Available Marketed Formulation [19]

4.1.1. Bacterial Resistace and the Search for Novel Antibacterial Structural Templates [5]

(i) The alarming escalation seen worldwide in the incidence of bacterial resistance to previously effective antibiotics continues to provide the impetus for the medicinal chemist to search for entirely new classes of antibacterial agents, that can cure bacterial infection by novel mechanism. As numerous bacteria have

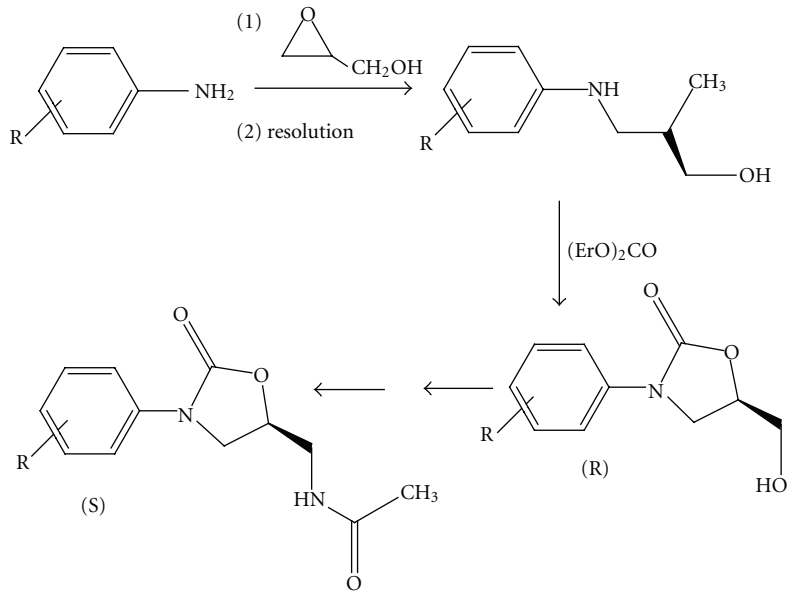


Figure 2: Chiral resolution method.

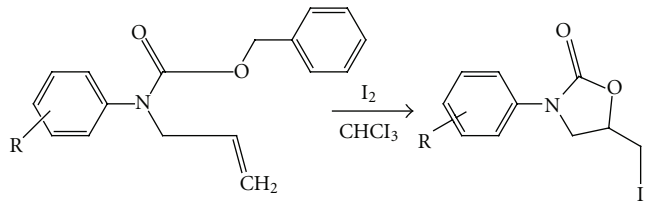


Figure 3: Iodocyclocarbamation.

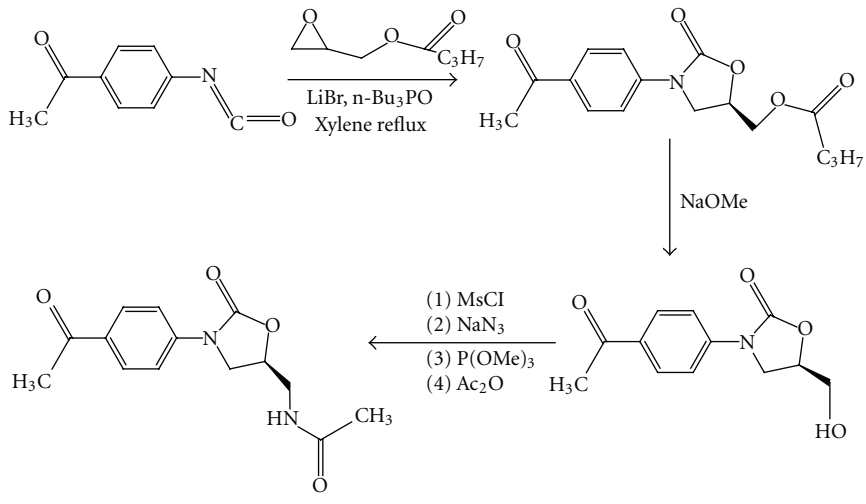


Figure 4: Du PONT asymmetric synthesis.

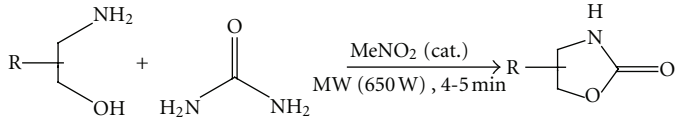


Figure 5: Oxazolidinones using urea and ethanolamine.

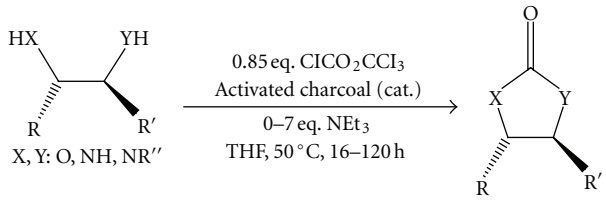


Figure 6: Efficient synthesis of oxazolidinone, imidazolidinone, and dioxolane.

Table 1: Available marketed formulation of oxazolidinone.

Brand name	Dosage form	Dosage	Company
Infulid	TAB	600 mg	Neiss
Linosept	TAB	600 mg	Micro Eros
Linospan	TAB	600 mg	Cipla
	IV	200 mg/100 mL	
Linox	TAB	600 mg	Unichem
Lizbid	TAB	600 mg	Piramal HC
Linezolid	TAB	600 mg	Glenmark (Integrace)
	IV BAG	600 mg	
Lizomed	TAB	600 mg	Aglowmed
	D-SYR	100 mg	

increasingly evidenced the evolution of multiple-antibiotic resistance, health care provides have been seriously challenged to provide effective therapy for the often life-threatening infection caused by these pathogens. Numerous reviews have recently appeared emphasizing the extent and severity of the resistance problem as it exists today, and the dim prospects envisioned for the future.

(ii) Some of the most problematic organism has been the multi-drug-resistant gram-positive bacteria. These include the highly virulent organism, methicillin-resistant *Staphylococcus aureus* MRSA, and penicillin- and cephalosporin-resistant *Streptococcus pneumoni.*

(iii) The enterococci have become increasingly of concern; there have been isolated problems of infection with vancomycin-resistant enterococci VREae. A major concern is that VRE will transfer the vancomycin-resistance genes encoded on a plasmid, to much more virulent organism *S. aureus,* as Nobel et al. have demonstrated to be feasible in an experimental setting.

Still another problem microorganism for which resistance has generated considerable medical concern is multidrug-resistant *M. tuberculosis* MDRTB.

This loss of antibacterial activity among drugs once efficacious against these pathogens has led to a summoning from numerous experts for the discovery and development of new antibiotic classes, so that health care practitioners will not be left benefit of effective therapeutic modalities. The oxazolidinone antibacterial agents are capable to provide an answer for these problems in new age.

5. Bacteriostatic versus Bactericidal Nature of Oxazolidinones [20]

Time-kill studies indicate that both Dup-721 (Figure 19) and Dup-105 (Figure 19) were bacteriostatic against all organism tested, expect the diphtheroids but U-100592 (Figure 19) and U-100766 (Figure 19) are bactericidal for *S. pneumoniae* and bacteriostatic for most staphylococci and enterococci.

5.1. Combination Therapy with Other Antibiotics [21]

(i) Antagonism between Dup-721 and ciprofloxacin or norfloxacin was reported for MRSA, *S. epidermidis* and *E. faecalis.*

(ii) In *In vivo* combination therapy studies, both drugs were found additive with vancomycin, gentamycin, or rifampin against *S. aureus*. Similarly, in a mixed *S. aureus* and *E. coli* infection model combination therapy with aztreonam or gentamycin as well as vancomycin, was found to be effective.

(iii) Oxazolidinones are a new class of totally synthetic antimicrobial agents against multidrug-resistant gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis* (MRSE), penicillin-resistant *Streptococcus pneunomiae* (PRSP) and vancomycin-resistant enterococci (VRE) [22–25]. Oxazolidinone has:

(a) a novel mechanism of action,
(b) selectively binding,
(c) uniquely binding to the 50S ribosomal subunit,
(d) inhibiting bacterial translation at the initiation phase of protein synthesis,
(e) consequently, the drug would not show cross resistance with existing antibacterial agents.

The unique mechanism of action of oxazolidinones has attracted interest to develop derivatives with potent activity and broad spectrum.

6. Structure Activity Relationship (SAR) [26, 27]

To find out the most potent and comparatively less toxic compounds, we need to to do exhaustive study of SAR.

This paper cites the modifications directed for the different parts of the oxazolidinone template as shown in Figure 20. The "A" part manifests oxazolidinone ring, which bears aryl system on the 3rd position of the oxazolidinone ring termed as B region and the 4th position of the aryl group is extended by amine functionality that has been termed as C region. Oxazolidinone ring exclusively possess C5 side chain in the (*S*)-configuration, which has been optimized for the better efficacy.

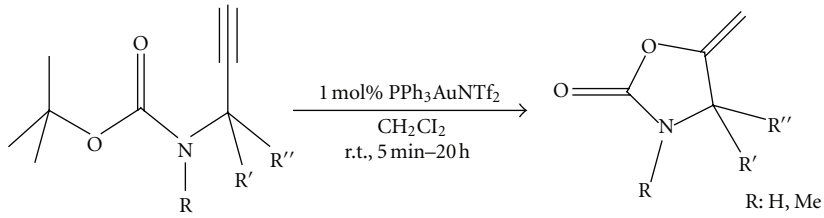


Figure 7: Gold catalyzed rearrangement in oxazolidinone synthesis.

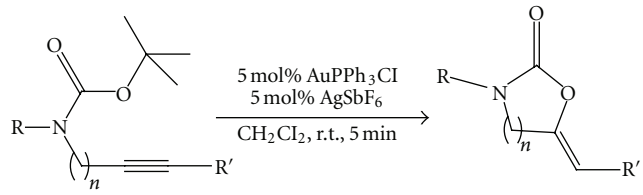


Figure 8: N-Boc protected oxazolidinone synthesis.

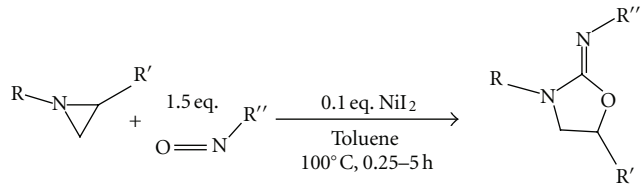


Figure 9: Nickel catalyzed cycloaddition in oxazolidinone synthesis.

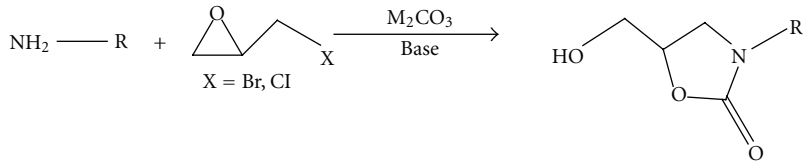


Figure 10: Use of halomethyloxirane, primary amine, and carbonate salt in oxazolidinone synthesis.

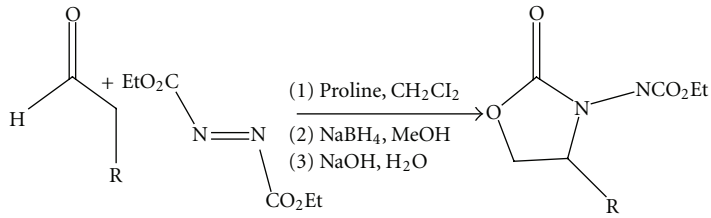


Figure 11: Direct catalytic asymmetric amination of aldehydes: synthesis of Evans, oxazolidinones and α-amino acids.

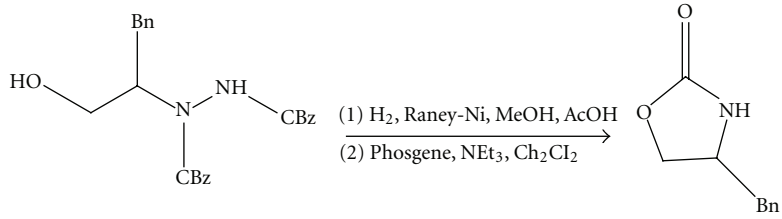


Figure 12: Conversion of chiral α-hydrazino alcohols and N-amino oxazolidinone to evans auxiliaries.

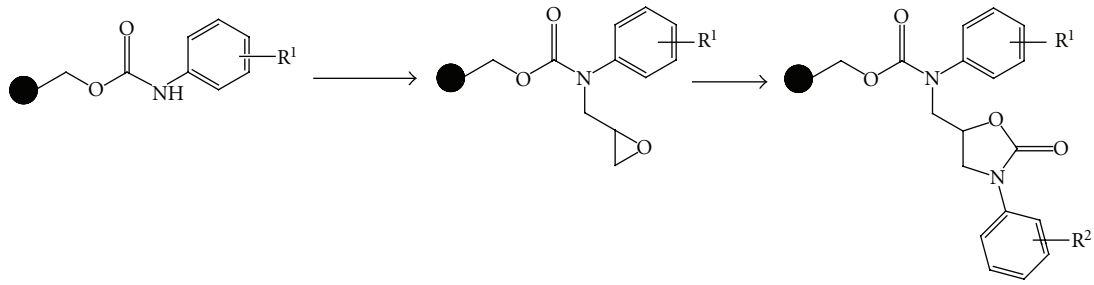
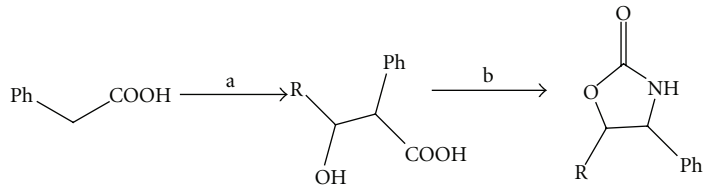


Figure 13: Solid-phase synthesis of oxazolidinones.



R = 2-thiophene
a = −78°C, THF
b = $(Pho)_2PON_3$, Et_3N, t-BuOH, 80°C

Figure 14: Diastereoselective synthesis of oxazolidinone part-I.

6.1. Synthesized Derivative of Oxazolidinone by Modification

(1) *Modifications in the Region A with C5*

(i) The thioanalogs of linezolid and eperezolid, **6** (Figure 21) and **7** (Figure 21), do not seem to bind to the 50S ribosomal subunit of the bacteria and thereby are unable to inhibit bacterial protein synthesis. The molecular modeling study supported this unexpected finding of oxazolidine-2-thione [16]. The similar trend of antibacterial activity has been reported in the early investigation for compound **8** (Figure 21), a thioanalogue of DuP 721 [28, 29].

(ii) Quesnelle et al. have reported isoxazolidinone agents having various substitutions at the C-region and most of the compounds have been found to be potent against gram-positive strains [30]. The compounds **9** (Figure 21) and **10** (Figure 21) have shown broad-spectrum antibacterial activity, additionally the sulfoxide **9** exhibited less toxicity compared to the linezolid in a seven-day study in rats.

(iii) Wang et al. have reported series of compounds with scaffolds **11**, **12**, and **13** (Figure 21) containing chiral 1, 3 oxazinan-2-ones and oxazolidinones as basic core structures having tertiary amines core containing two aryl substituents [31].

(2) *Modifications in the Region B and at the C5* [32]. Bosch et al. have reported convenient synthesis of conformationally constrained analog of linezolid **14** (Figure 21) having a tricyclic moiety; however, no antibacterial activity has been disclosed for this compound.

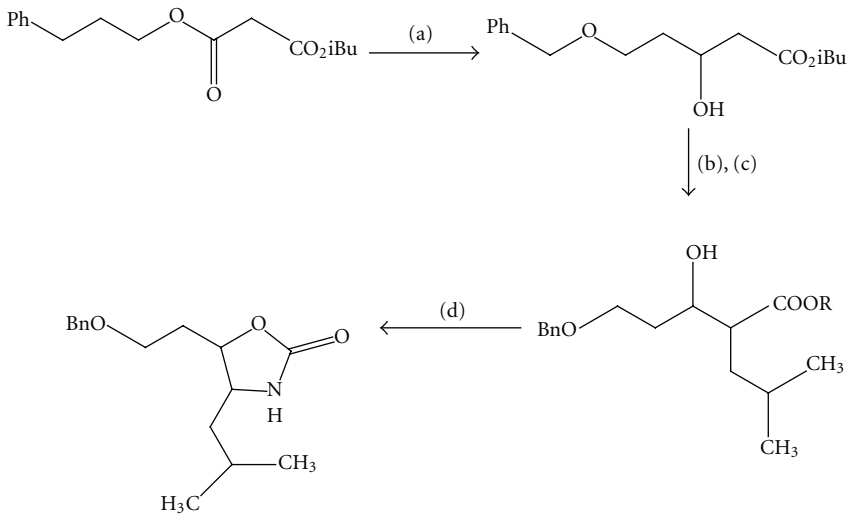
Merck has described novel oxazolidinone derivatives **15** and **16** substituted with cyclopropyl moiety [33]. The compounds **15** (Figure 22) and **16** (Figure 22) exhibited impressive *in vitro* antibacterial activities against different strains **15**.

Selvakumar et al. have reported constrained analogues of linezolid such as hexahydroazolo-quinoxaline and tetrahydroazolo-benzothiazine compounds [34]. Amongst the compound of this class the tetrahydroazolo-benzothiazine and thiocarbamate at C5 side chain **17** (Figure 22) have shown antibacterial activity in the range of 0.25–1 μg/mL against resistant and sensitive gram-positive strains.

Choy et al. from Pfizer reported the synthesis of conformationally restricted oxazolidinone compounds [35]. The compound **18** (Figure 22) was found to be more potent and exhibited broad-spectrum antibacterial activity with MIC values in the range of <0.06–0.25 μg/mL for gram-positive organisms and 1-2 μg/mL for fastidious gram-negative organisms.

(3) *Modifications in the Region C with C5* [36]. A series of *N*-phenyl piperazinyl derivatives of oxazolidinone **19** (Figure 22) in which the nitrogen atom at 4-position of piperazinyl ring is substituted by different cinnamoyl groups. This optimization resulted in few potent compounds, which were found to be active against several gram-positive pathogens. In this class of compound some substituents were well tolerated on the phenyl ring of cinnamoyl group.

There is a reported synthesis of a few Mannich ketones of piperazinyl phenyl oxazolidinone derivatives and their antibacterial activity in various Gram-positive organisms such as *Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis,* and *Enterococcus faecalis* [37]. A moderately



(a) = Baker's yeast, sucrose, 25°C, 3 days

(b) = −78°C, THF

(c) = NaOH, EtOH

(d) = $(PhO)_2PON_3$, Et_3N, tBuOH, 80°C

Figure 15: Diastereoselective synthesis of oxazolidinone part-II.

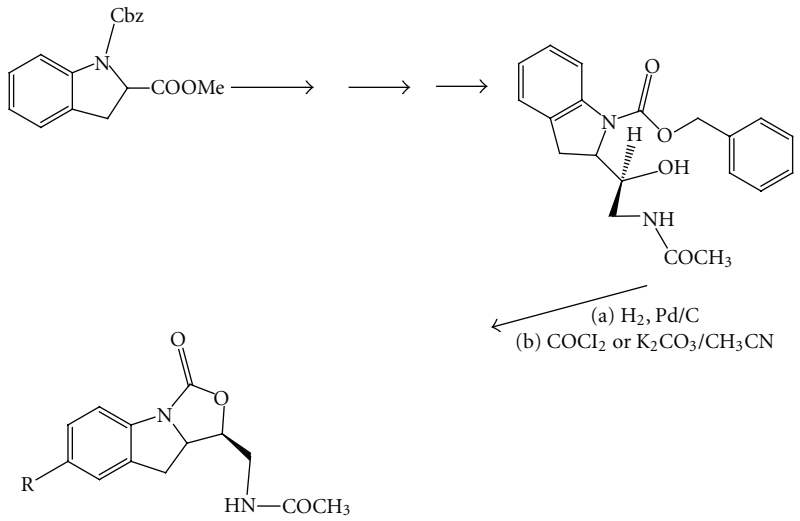


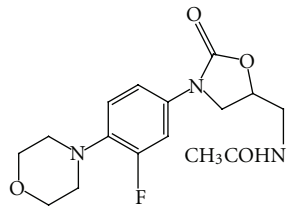
Figure 16: Diastereoselective synthesis of oxazolidinone part-II.

active compound **20** (Figure 22) has been transformed to active compound **21** (Figure 22). The compound **22** (Figure 22) having cyclohexanone has shown antibacterial activities against various gram-positive strains with MIC values in the range of 1–4 μg/mL, which is comparable to that of linezolid (0.5–4 μg/mL).

Ranbaxy has reported synthesis of oxazolidinones modified at the C region. The optimization of the series afforded a potent compound **23** (Figure 22) (Ranbezolid, RBx7644), which is under clinical development [38]. They have further modified the compound **23** to get the compound 24 (Figure 23), wherein nitrofuran ring is attached to the 2° nitrogen of the aminopiperidine.

In another embodiment a group of scientists from Merck has published a patent describing novel oxazolidinone derivatives possessing cyclopropyl moiety [33]. The disclosed compounds **25** and **26** (Figure 23) have shown excellent *in vitro* antibacterial activity against broader panel of both susceptible and resistant strains.

Scientists from Orchid have described novel oxazolidinones **27** (Figure 23) having variations in the regions B, C, and at the C5 side chain of oxazolidinone [39].



Linezolid

Figure 17

Pfizer has reported a series of oxazolidinone compounds **28** (Figure 23) containing dihydrothiopyran substituent at the C region and instead of acetamide other variations such as halogenated amide and thioamide derivatives were studied at the C5 side chain [40]. The *in vitro* activities of the C5 modified derivatives were found to be superior compared to the corresponding C5 acetamide derivative. The compounds of this class have shown better antibacterial activities towards Gram-positive *Staphylococcus pneumoniae*, *Enterococcus faecium,* and Gram-negative *Haemophilus influenzae* as compared to the compound **29** (Figure 23) (PNU-288034).

Zhai et al. have reported novel oxazolidinone derivatives having modified C-5 side chain. The compounds **30**, **31**, and **32** (Figure 24) have shown inferior *in vitro* antibacterial activities in MIC assay against various strains [41].

Trius Therapeutics has announced the initiation of Phase 1 clinical trials of TR-701 **33** (Figure 24) for the treatment of patients with serious Gram-positive bacterial infections, including those caused by methicillin-resistant *Staphylococcus aureus* and other drug-resistant strains [42].

A group of scientists from Ranbaxy has patented novel substituted phenyl oxazolidinone derivatives [43]. The compound **34** (Figure 24) of this series has shown significant *in vitro* antibacterial activity in the MIC assay against different strains such as methicillin-resistant *Staphylococcus aureus* (4.0 μg/mL; linezolid 2.0 μg/mL), vancomycin-resistant *Enterococci* (2.0 μg/mL; linezolid 2.0 μg/mL).

A series of arylcarbonyl and arylsulfonyl-piperizinyl-5-triazolylmethyl oxazolidinones **35** (Figure 24) with improved activity against Gram-positive bacterial clinical isolates than Gram-negative bacterial clinical isolates [44].

Fan et al. have reported triazolyl oxazolidinones as antibacterial agents. Most of the analogues displayed activity superior to the linezolid and the vancomycin in various Gram-positive bacteria [45]. In the antibacterial MIC assay, the compounds **36**, **37**, and **38** (Figure 24) were found to be potent and further studied for their *in vivo* efficacies in mice model; however none of the compounds showed *in vivo* activity.

Selvakumar et al. have reported novel chalcone oxazolidinone hybrids with antibacterial activity. Of these, the compound **39** (Figure 24) containing chalcone substituent in the C region showed significant antibacterial activities with MIC values of 4 μg/mL against methicillin-resistant *Staphylococcus aureus* strain [46]. The acetamide group at C-5 was converted to thiocarbamate to get compound **40** (Figure 25), which exhibited *in vitro* activity in the range of 0.25–2 ug/mL against resistant strains.

Reck et al. at AstraZeneca have reported substituted (pyridin-3-yl) phenyloxazolidinones as antibacterial agents with reduced activity against monoamine oxidase A [47]. The compound **41** (Figure 25) showed excellent activity against Gram-positive bacteria; however the compound **41** lacks the monoamine oxidase A inhibition and inhibits cytochrome P450 (CYP) due to its poor solubility.

Liu et al. have reported novel substituted oxotriazolylphenyl derivatives. Of the many compounds described, the compound **42** (Figure 25) has shown potent antibacterial activity against pathogens *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Streptococcus enteritidis, and Streptococcus nonhemolyticus* at 0.10–6.25 μg/mL [48] O Vara Prasad et al. have reported new series of oxazolidinones with C5 carboxamide functionality, that is, reverse amides, which blocks the bacterial protein synthesis. These compounds have also exhibited less potency against monoamine oxidase enzymes, indicative for the lower side effects. The compound **43** (Figure 25) has shown reduction of myelotoxicity in a 14-day safety study in rodents and compared with linezolid [49].

Rudra et al. have reported series of heterocyclic oxazolidinones as antibacterial agents with identification of RBx 8700 as potent compound [50]. Systematic modification of the linker between the five-membered heterocycle and the piperazinyl ring of RBx 7644 and its thienyl analogue **44** (Figure 25) resulted in the identification of an expanded spectrum compound.

Reck et al. reported novel acyclic substituted (pyridin-3-yl) phenyl oxazolidinones **45**–**47** [51] (Figure 25). The acyclic 6-substituted pyridin-3-yl phenyl oxazolidinones **46** and **47** having bulky substituent demonstrated excellent antibacterial activity against Gram-positive organisms, including linezolid resistant *Streptococcus pneumonia* (1.0 μg/mL). The compounds with bulkier substituents showed reduced MAO-A activity (Ki = 40 μM; Ki = 19 μM) compared to the corresponding unsubstituted parent compound **48** (Figure 25) (Ki < 0.3 μM) and the improved solubility.

The high-molecular-weight novel oxazolidinone derivatives having variations in the regions B, C, and at the C5 side chain have been patented by a group of scientists from Ferrer International Company [52].

(4) *Hybrid Molecules* [53]. Morphochem AG has published a patent mentioning oxazolidinone-quinolone hybrid **49** (Figure 26). However, no discloser has been made for their antibacterial activities. Further, in another report they have described different variant of oxazolidinone-quinolone hybrids of type **50**. The disclosed derivatives **50** (Figure 26) possess the pharmacophore of quinolone and oxazolidinone linked together through a linker and the hybrid has been used as an antibacterial agent. However, there is no mention of the antibacterial activities for the disclosed oxazolidinone-quinolone hybrids.

(5) *Computational Studies.* Extensive studies on the syntheses of oxazolidinone antibacterial agents and their SAR have been reported; however only few QSAR studies have been published. The first QSAR study was reported in the year 1999, comprised a 3D-QSAR study on a small data

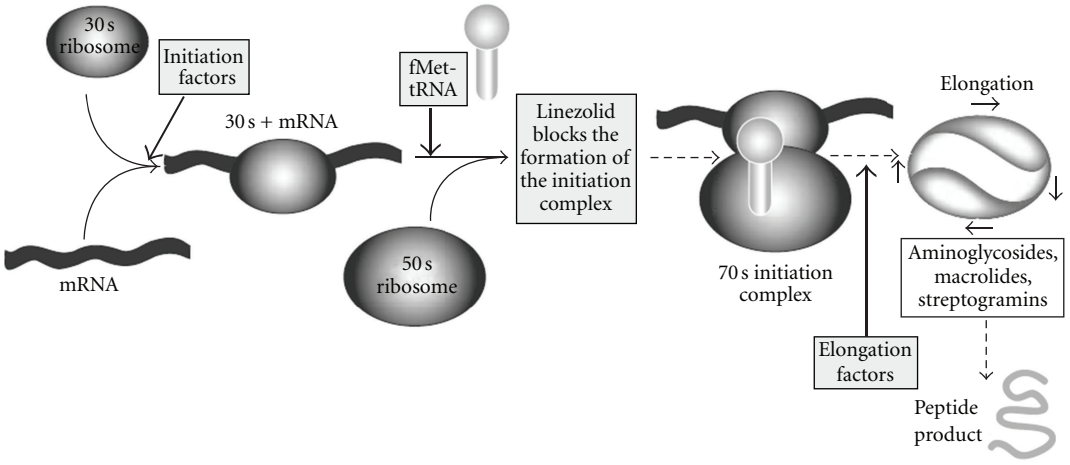


Figure 18

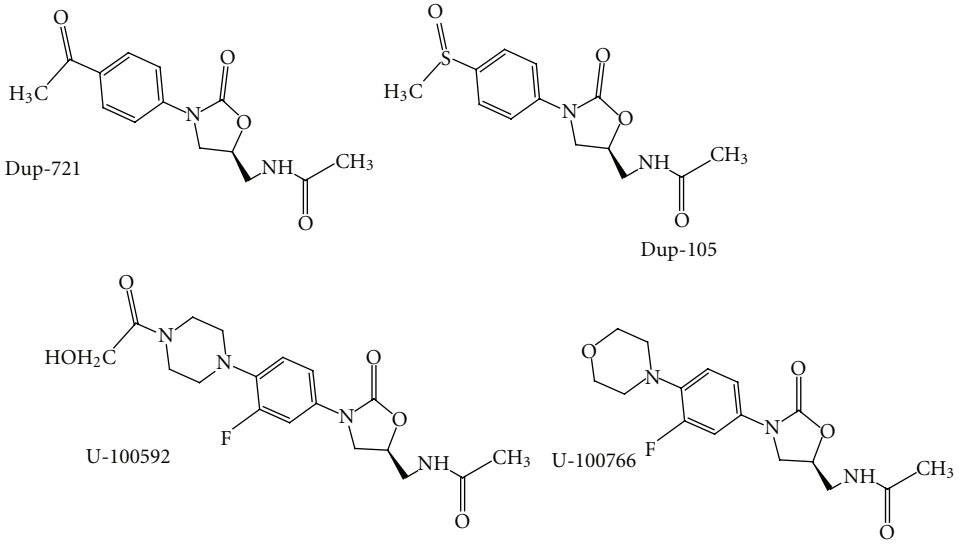


Figure 19

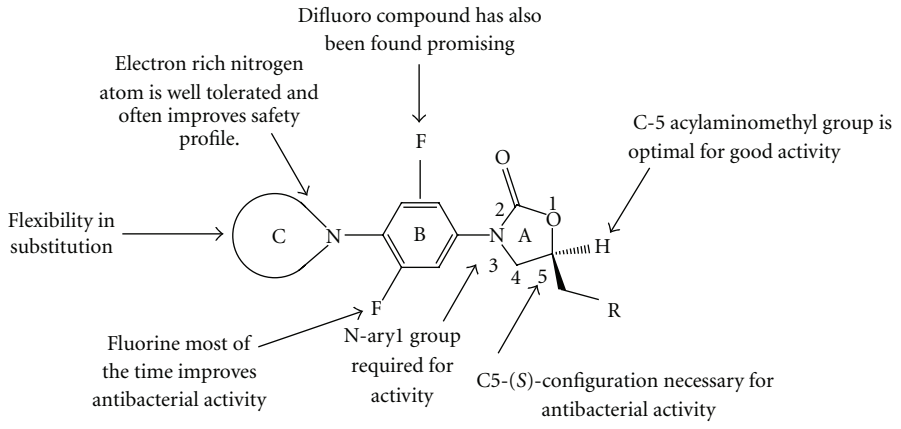


Figure 20

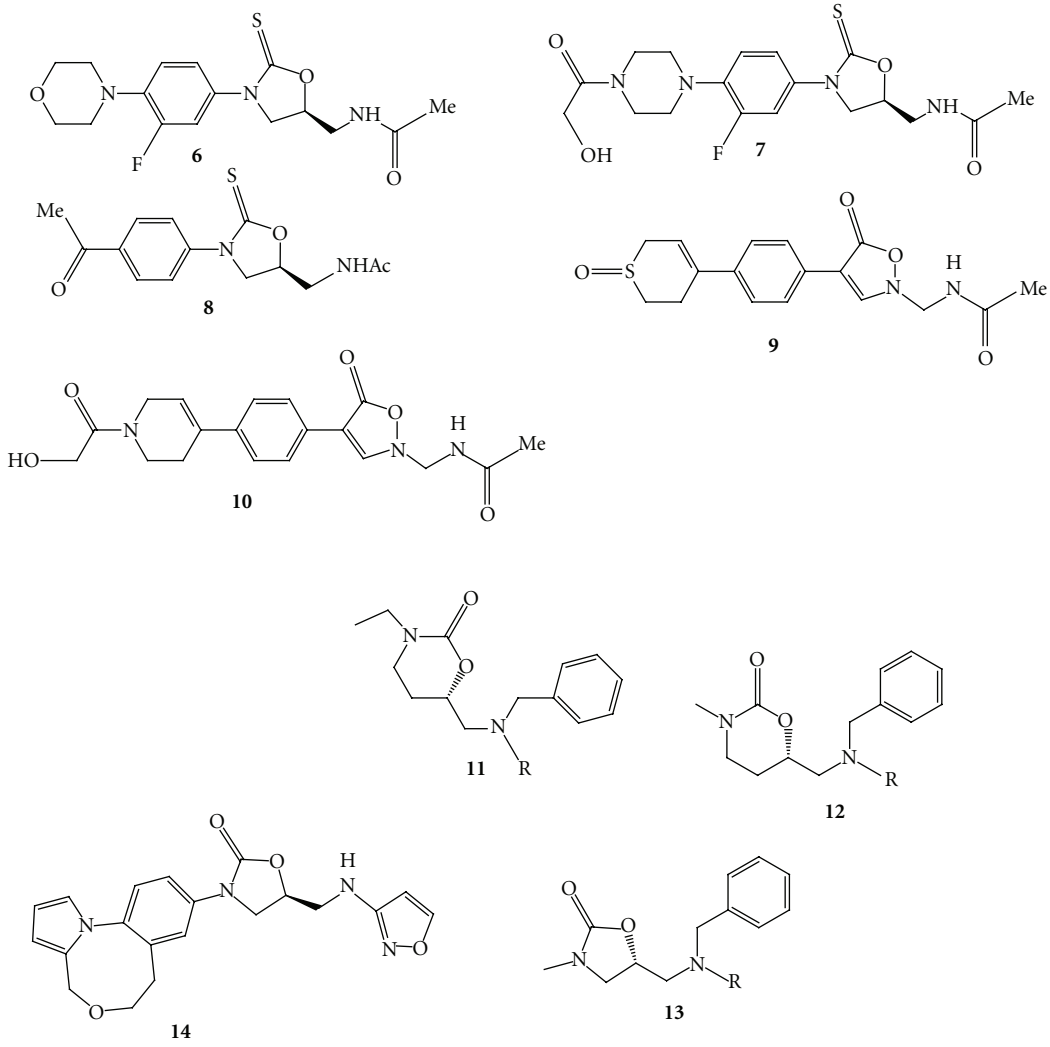


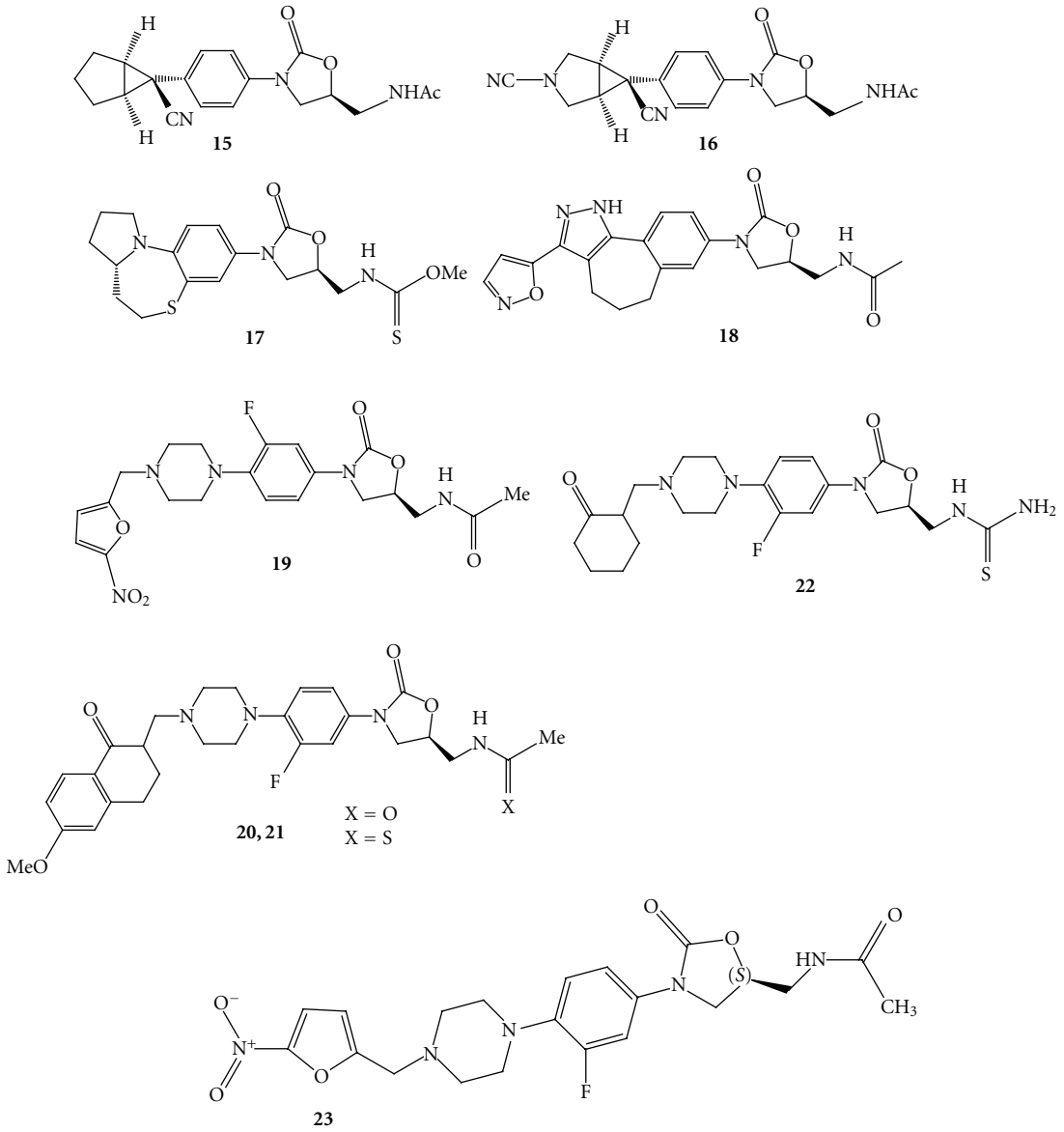
Figure 21

sets of two novel series of oxazolidinone antibacterial agents using "Comparative Molecular Field Analysis" (CoMFA), wherein a training set of 17 compounds with two reference compounds have been used. The CoMFA steric, electrostatic fields, and ClogP were used as descriptors, and the activities against methicillinresistant *Staphylococcus aureus* 88 (MRSA 88) as dependents were developed. The cross-validated r2cv (0.653) and conventional r2 (0.984) from the Partial Least Square (PLS) and CoMFA analyses indicated considerable reliability for predicting the antibacterial activities of oxazolidinone antibacterial agents.

The second 3D-QSAR studies, reported by Karki and Kulkarni in the year 2001, used a genetic function algorithm with a data set of 60 compounds. The QSAR models were developed using a training set of 50 compounds and the *in vitro* MIC against *Staphylococcus aureus* SFCO-1. The r2 values reported for the models range from 0.629 to 0.732. The predictive ability of the QSAR model was evaluated with a test set of 10 compounds. The results obtained concluded that the antibacterial activity of the 3-aryloxazolidin-2-ones is strongly dependent on the electronic factor as expressed by lowest unoccupied molecular orbital energy (LUMO) and the spatial factor as expressed by density and thermodynamic factors accounted for molar refractivity and the heat of formation. The SAR study by Tokuyama et al. revealed that the antibacterial activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci on 5 thiocarbonyl oxazolidinones was significantly affected by the lipophilicity, especially the calculated log *P* value, the balance between 5-hydrophilic (or hydrophobic) substituents and hydrophobic (or hydrophilic) substituents on the benzene ring (Table 2).

6.2. Oxazolidinone in Clinical Trials

6.2.1. Oxazolidinone: Biological Activity. The development of resistance by the antibiotics in the Gram-positive pathogenic bacteria over the last twenty years and continuing today



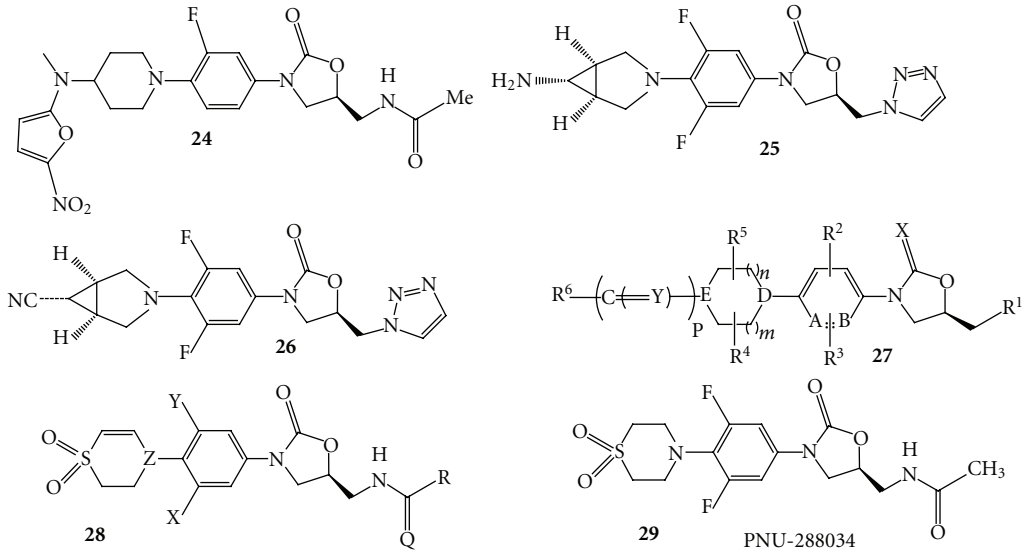
Ranbezolid, RBx7644

(a)

Figure 22

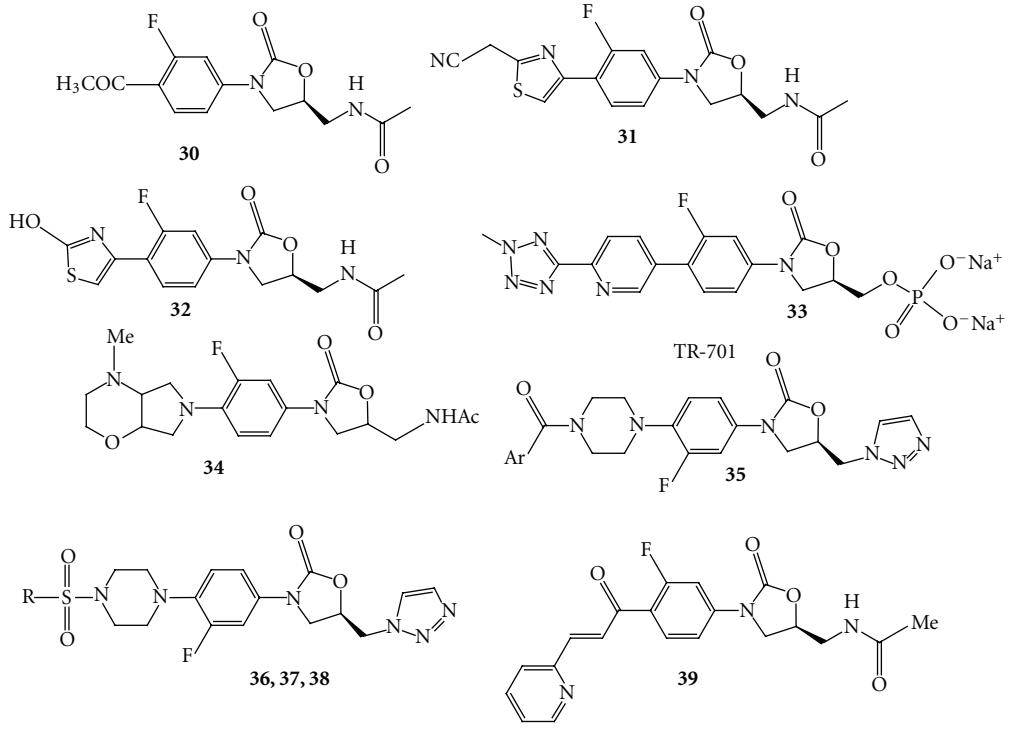
has created a need for new antibiotic classes, which may be unaffected by existing bacterial resistance. The oxazolidin-2-ones not only represent a new class with a novel mechanism of action, but also satisfy the requirement for overcoming the resistance mechanisms. Both linezolid and eperezolid, the first chemical candidates, arose from the piperazine subclass, with the first one being chosen further development because of its enhanced pharmacokinetic properties. The main attractive traits of the oxazolidinone series have encouraged further work in the area, and the patent literature reveals that extensive chemical investigation is currently being made. The unexpected early resistance development emphasizes the need for further exploration of features of the oxazolidinone to eliminate these deficiencies. Recently, several changes, involving the C5 side chain as well the N-phenyl heterocyclic ring, give promise for such improvement. Various biological activity show by oxazolidinone derivatives like the following.

(1) *Antibacterial Activity* [54]. Linezolid is an oxazolidinone developed by Pharmacia (formerly Pharmacia & Upjohn) for the treatment of multiresistant Gram-positive infections 187765, 317456. Linezolid resistance due to a 23S rRNA mutation may emerge in Enterococci during therapy with this antimicrobial and may be associated with clinical failure 368652. Following FDA approval, linezolid was launched in May 2000 368526, 368652. In April 2000, the FDA approved linezolid injection, tablets,



X = H, F; Y = H, F
Z = CH, N; Q, S
R = CH_3, CHF_2, $CHCl_2$

Figure 23



R = *m*-F-Ph
R = *m*-NO_2-Ph
R = *m*-NH_2-Ph

Figure 24

Table 2

S. no.	Compound name	Clinical phase	Sponser	Conditions
(1)	Rivaroxaban (BAY59-7939)	phase-III	Bayer's Johnson & Johnson Pharmaceutical Research Development	Deep vein thrombosis (DVT) or Pulmonary embolism (PE)
(2)	Radezolid	phase-II Complete	Rib-X pharmaceutics	Uncomplicated skin infection
(3)	Torezolid	phase-II	Trius Therapeutics	Complicated skin and skin-structure infections (cSSSI)
(4)	DA-7218	phase-III	Dong-A Pharmaceutical	Acute bacterial skin and skin-structure infections (ABSSSI)
(5)	MRX-1	phase-I	MicuRx Pharmaceutical	Bacterial infection
(6)	Radezolid	phase-II	Rib-X pharmaceutics	Community-acquired pneumonia
(7)	PNU-100480	phase- IIa	Pfizer pharmaceutical	Pulmonary Tuberculosis
(8)	RX-1741	phase- II	Rib-X pharmaceutics	Infectious skin disease

and oral suspension for the treatment of patients with infections caused by Gram-positive bacteria. It is indicated for adults in the treatment of nosocomial pneumonia, community-acquired pneumonia (CAP), complicated and uncomplicated skin and skin structure infections and vancomycin-resistant enterococcus (VRE) infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), VRE, faecium and penicillin-susceptible *Streptococcus pneumoniae* 363503.

Vancomycin resistance was reported in only 0.6 and 3.0% of *Enterococcus faecalis* and *E. faecium*, respectively. Penicillin resistance occurred in 25.1% of *Streptococcus pneumonia*, 4.9% at the high level (≥2 mg/L). The MIC_{90} for linezolid was 1 mg/L for streptococci and 2 mg/L for enterococci and staphylococci. Using the US FDA- and EUCAST-recommended susceptible breakpoints for linezolid, there were no confirmed reports of linezolid resistance minimum inhibitory concentration (MIC), ≥8 mg/L. The distribution of linezolid MIC values was unimodal and varied between 0.25 and 1 mg/L for streptococci (>90% of isolates) and between 1 and 2 mg/L for staphylococci (>90%) and enterococci (>95%).

Favorable clinical results shown by linezolid prompted many pharmaceutical industries and academic institutions to explore the possibilities of expansion of antibacterial spectrum of this class. A large number of publications, reviews, and patents testify to the interest of the various research groups in the oxazolidinone class of antibacterials. Furazolidone as shown in Figure 27 is the first member of the oxazolidinone class discovered in 1950 and appears to be the initial candidate responsible for the genesis of further work on oxazolidinone antibacterials.

YC-20 [55] (Figure 28) and linezolid were active against all Gram-positive organisms isolated, including strains resistant to other classes of antibiotics. YC-20 exhibited MIC50 and MIC90 values of <0.5 and 2 mg/L against all isolates. Overall, the activity of YC-20 is slightly superior to that of linezolid. The present study confirms and expands previous findings of the good *in vitro* activity of YC-20 against Gram-positive organisms. YC-20 has a potential role in the treatment of infections caused by Gram-positive pathogens, especially for multidrug-resistant Gram-positive bacteria (Table 3).

Radezolid (RX-1741) [56, 57] (Figure 28) is a novel oxazolidinone with broader spectrum of coverage and increased activity against Gram-positive organisms as compared to other oxazolidinones. Radezolid has recently completed successfully two Phase 2 clinical trials: one for community-acquired pneumonia (CAP) and the second for uncomplicated skin and skin structure infections (Usssi) (Table 4).

The spectrum of activity of torezolid (TR-700) (Figure 28), the active moiety of torezolid phosphate (TR-701), and proposes tentative MIC and disk diffusion breakpoints as well as quality control ranges [58]. The *in vitro* susceptibilities of 1,096 bacterial isolates, representing 23 different species or phenotypic groups, were determined for torezolid, linezolid, cefotaxime, and levofloxacin using Clinical and Laboratory Standards Institute (CLSI) broth microdilution MICs, minimum bactericidal concentrations (MBCs), agar dilution, and disk diffusion testing methods. Torezolid was very active against the majority of Gram-positive strains, including methicillin-susceptible and -resistant *Staphylococcus aureus* (MIC_{50} = 0.25 μg/mL, MIC_{90} ≤ 0.5 μg/mL), coagulase-negative staphylococci (CNS; MIC_{50} = 0.25 μg/mL, MIC_{90} ≤ 0.5 μg/mL), enterococci (MIC_{50} and MIC_{90} ≤ 0.5 μg/mL), and streptococci (MIC_{50} and MIC_{90} ≤ 0.25 μg/mL). Based upon MIC_{90}s, torezolid was 4-fold more active than linezolid against *S. aureus*, coagulase-negative staphylococci, and the enterococci and 8-fold more active than linezolid.

In 2002 AstraZeneca introduced posizolid (AZD2563) (Figure 28). Results indicate that posizolid has excellent, targeted bactericidal activity against all common gram-positive bacteria, regardless of resistance to other classes of antibiotics [59].

The *in vitro* activity of AZD2563, a novel oxazolidinone, was assessed against 595 Gram-positive cocci, comprising recent surveillance isolates and a collection of resistant

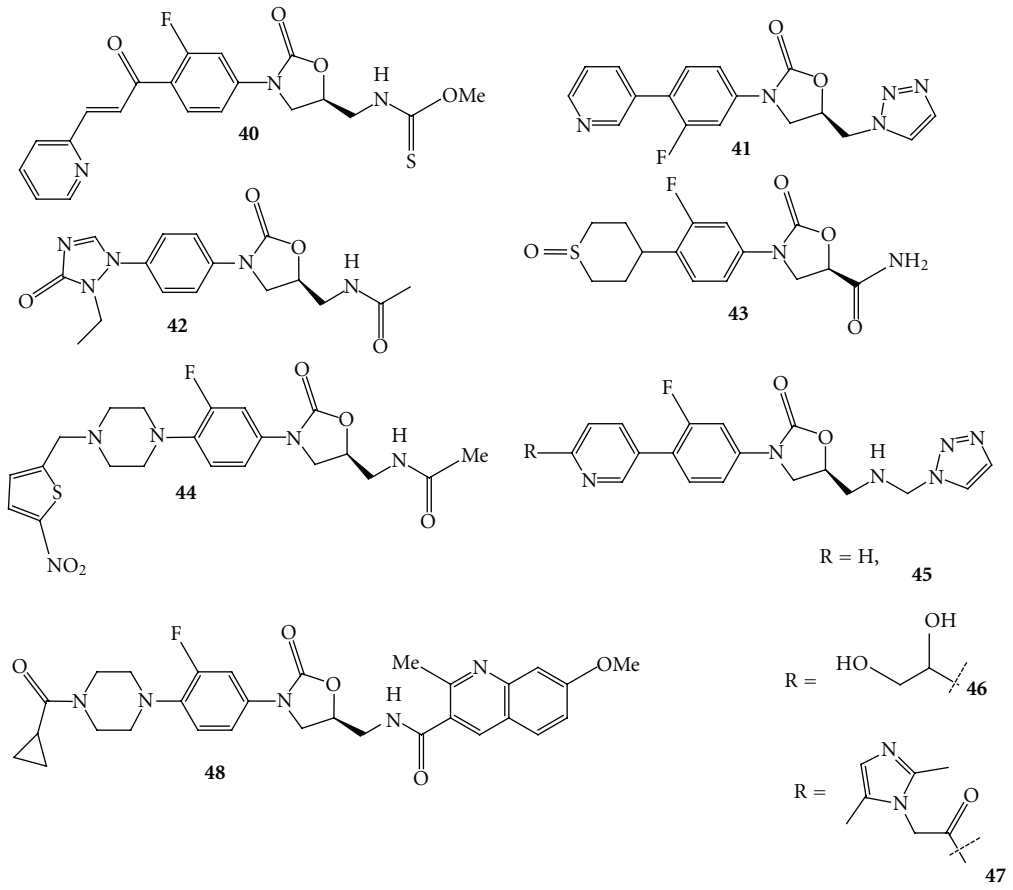


Figure 25

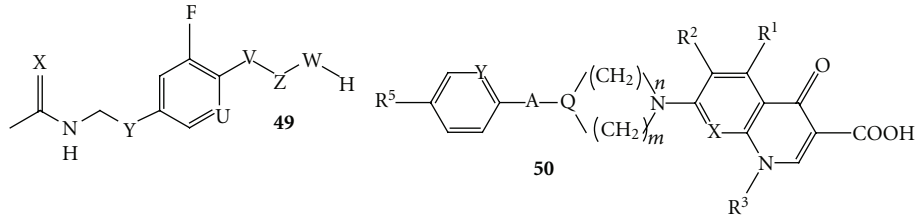
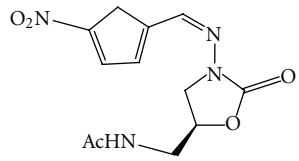


Figure 26

Table 3: Antimicrobial activity of YC-20 against 522 Gram-positive organisms from clinical samples.

Organism/antimicrobial agent	50% MIC (mg/L)	90% MIC (mg/L)	Range MIC (mg/L)
Staphylococcus aureus, MSSA (80)			
YC-20	0.25	0.5	0.06–0.5
Linezolid	0.25	1	0.25–1
Vancomycin	0.5	1	0.25–1
Ampicillin	1.0	2	0.25–4
Cefazolin	0.5	4	0.125–4
evofloxacin	0.125	1	0.06–2



Furazolidone

Figure 27

Table 4: Antimicrobial activity of Radezolid against 522 Gram-positive organisms from clinical samples.

Bacteria	Linezolid (MICs in mg/L)	Radezolid (MICs in mg/L)
S. pneumonia	0.5–2	<0.25
S. pyogenes	2–4	0.03–0.125
E. faecalis	1–16	<0.25– 4
H. influenza	2–64	0.25–2
S. aureus	2–4	.5–4
L. pneumophila	4–16	1–4
C. trachomatis	8–16	.5–1

(including multiresistant), epidemiologically diverse isolates [60]. The MICs of AZD2563 for staphylococci, pneumococci, and enterococci had narrow ranges, 0.25–2 mg/L, with modal MICs of 1 mg/L for staphylococci and pneumococci, and 1–2 mg/L for enterococci. AZD2563 was equally active against the surveillance isolates and those that had been selected for their multiresistance to other agents. The MICs of AZD2563 were either the same as those of linezolid or twofold lower.

A few Mannich ketones of piperazinyl oxazolidinone derivatives have been synthesized and their antibacterial activities in various Gram-positive organisms such as *Bacillus subtilis, Staphylococcus aureus, Staphylococcus epidermidis,* and *Enterococcus faecalis* were evaluated by MIC determination [61]. The analog showed inferior activity than linezolid as well as eperezolid. Thus in an attempt to improve potency, we prepared several analogues by modifying the ketone part A. However, all such resulting compounds lost their *in-vitro* antibacterial activity. It has been reported that thioacetamide at the 5th position of the oxazolidinone improves the activity. MIC was determined by microbroth dilution technique and values reported in table represent the highest MIC value obtained in triplicate. S.a1, *Staphylococcus aureus* ZYABL 006; S.a2, *Staphylococcus aureus* ATCC 33591; S.e, *Staphylococcus epidermidis* ATCC 12228, B.s, *Bacillus subtilis* ATCC 6633; E.f, *Enterococcus faecalis* ATCC 29212.

The compound library (Figure 28) was screened using a disk diffusion assay on the Gram-positive bacterial reference strains, *M. smegmatis* ATCC 14468, *Bacillus subtilis* ATCC 6633, and *Enterococcus faecalis* ATCC [62]. *Mycobacterium smegmatis* was inoculated into Middlebrook 7H9 containing 0.2% glycerol and ADC enrichment while the other strains were inoculated into Mueller–Hinton broth. The inocula of all strains were allowed to incubate for approximately 24 h at 37°C and 180 rpm. Minimum inhibitory concentrations (MICs) of compound was also determined against the same strains using a broth macrodilution assay using either Middlebrook 7H9 containing 0.2% glycerol and ADC enrichment or Mueller–Hinton broth 20. The highest concentration for each compound tested was 32 lg/mL, and each subsequent tube was a twofold dilution of the previous. The M. smegmatis tubes were incubated for 48 h at 37°C while the other strains were incubated for 24 h and then analyzed. Thiazolyl blue tetrazolium bromide (MTT) was dissolved in MeOH (10 mg/mL) and added to the solution (20 lL) to aid in bacteria visualization.

The *in vitro* antibacterial activities of the compound and vancomycin, ciprofloxacin, and linezolid as the reference drugs were determined by the conventional agar dilution method using Mueller–Hinton agar medium [63]. The tested Gram-positive organisms included two clinical isolates of *S. aureus* resistant to methicillin (MRSA), *S. aureus* ATCC 29737, and *S. epidermidis* ATCC 12229. Gram-negative bacteria used in the study were *E. coli* ATCC 8739, *S. typhimurium* ATCC 1639 and *P. aeruginosa* ATCC 9027. The tested compounds, vancomycin and ciprofloxacin, were dissolved in DMSO while linezolid was dissolved in water. Suspensions of each of bacteria were prepared to contain approximately 106 colony-forming units (CFU/mL) and applied to plates with twofold serially diluted compounds to be tested in distilled water in concentration ranging from 0.01 to 100 mg/mL and incubated at 37°C for 18 h. To ensure that the solvent had no effect on bacterial growth, a control test was performed with test medium supplemented with DMSO at the same dilution as used in the experiments.

Minimum inhibitory concentrations (MICs, mg/mL) were determined on Mueller–Hinton (MH) agar with medium containing dilutions of antibacterial agents ranging from 0.12 to 64 mg/mL [64]. The test compounds were dissolved in 20% water in DMSO, while linezolid and vancomycin were dissolved in 40% water in ethanol and water, respectively. The tests were performed using MH agar plates for all staphylococci and enterococci and on MH agar plates supplemented with 5% sheep blood to facilitate the growth of *S. pneumoniae*, *H. influenzae*,and *M. catarrhalis*. The Gram-positive clinical isolates utilized in this study consisted of methicillin-resistant *S. aureus* (MRSA, n = 1/4 10), methicillin-susceptible S. aureus (MSSA, n = 1/4 10), methicillin-resistant coagulase-negative staphylococci (MR-CNS, n = 1/4 3), methicillin-sensitive coagulase-negative staphylococci (MS-CNS, n = 1/4 6), S. pneumoniae (n = 1/4 3), vancomycin-sensitive (VSE, n = 1/4 6) and vancomycin-resistant (VRE, n = 1/4 4) enterococci. The Gram-negative clinical isolates tested included *H. influenzae* (n = 1/4 4) and *M. catarrhalis* (n = 1/4 1). The reference strains, *S. aureus* ATCC 25923, *S. epidermidis* ATCC 12228 and *E. faecalis* ATCC 29212, *E. coli* ATCC 25922, and *H. influenzae* ATCC 49247 were used as controls. The final bacterial concentration for inocula was 107 CFU/mL and was incubated at 35°C for 18 h. The test compounds were also evaluated against *S. aureus* ATTC 25923 in MH broth supplemented with 50% human plasma to assess the extent of plasma binding and/or plasma instability. The MIC was defined as the lowest drug concentration that completely inhibited growth of the bacteria.

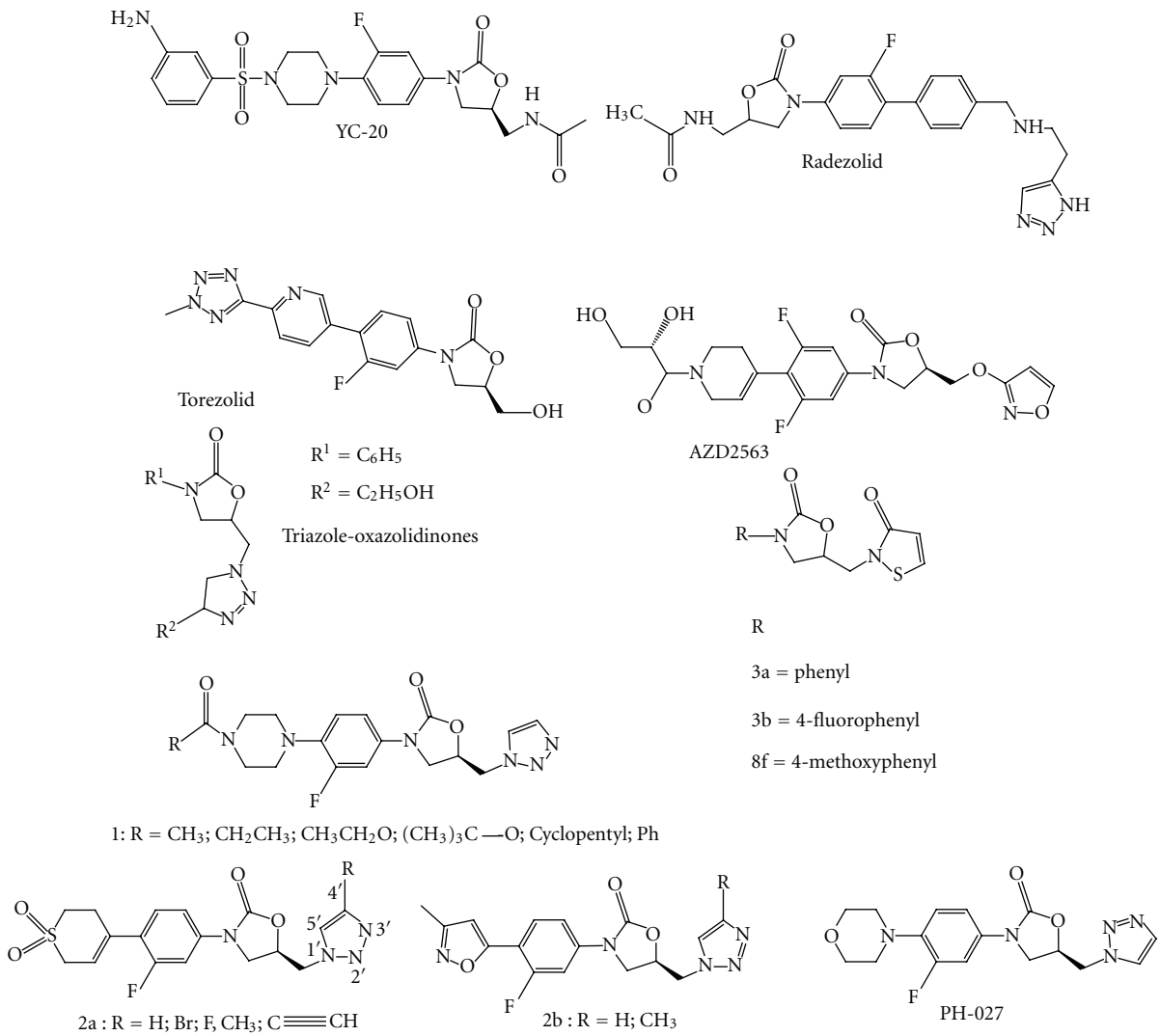


Figure 28

Against some of the gram-positive bacteria strains tested, the triazole oxazolidinone (Figure 28) PH-027 demonstrated MIC values comparable to or 1- to 2-fold lower that hose of linezolid and vancomycin [65]. In particular, the MIC values of PH-027 against vancomycin susceptible *E. faecium* (VSE), vancomycin-intermediate-resistant *E. faecalis* (VIRE), and vancomycin-resistant E. faecalis (VRE) were 0.5, 0.5, and 2 mg/mL, respectively, compared to an MIC of 2 mg/mL demonstrated by linezolid against these strains. However, the MIC's of vancomycin against the same strains were 4, 8 and >32 mg/mL, respectively. PH-027 demonstrated the most potent antibacterial activity against both sensitive and resistant gram-positive bacteria strains, including MRSA, MSSA, MS-CNS, MR-CNS, PRSP, and enterococci (*Enterococcus faecium* and *Enterococcus faecalis*).

The result of *in vitro* antibacterial activity against a spectrum of resistant and susceptible Gram-positive organisms [66] clearly shows that all compounds (Figure 29) bearing sulfonyl group have good antibacterial activity. Compound

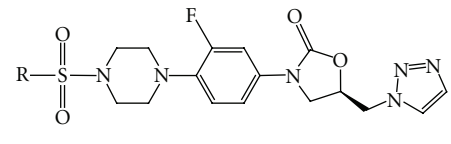


Figure 29

showed more potent antibacterial activity than linezolid and vancomycin. Obviously, the introduction of strong electron-withdrawing groups (e.g., CF3, F, and NO2) into the oxazolidinones can confer excellent antibacterial activity especially at the 3rd position of the phenylsulfonyl group, in addition, electron-donating groups (e.g., Cl).

(2) *Anticoagulant Activity* [67, 68]. Rivaroxaban (BAY 59–7939) (Figure 30) is an oral anticoagulant invented and manufactured by Bayer; in a number of countries it is

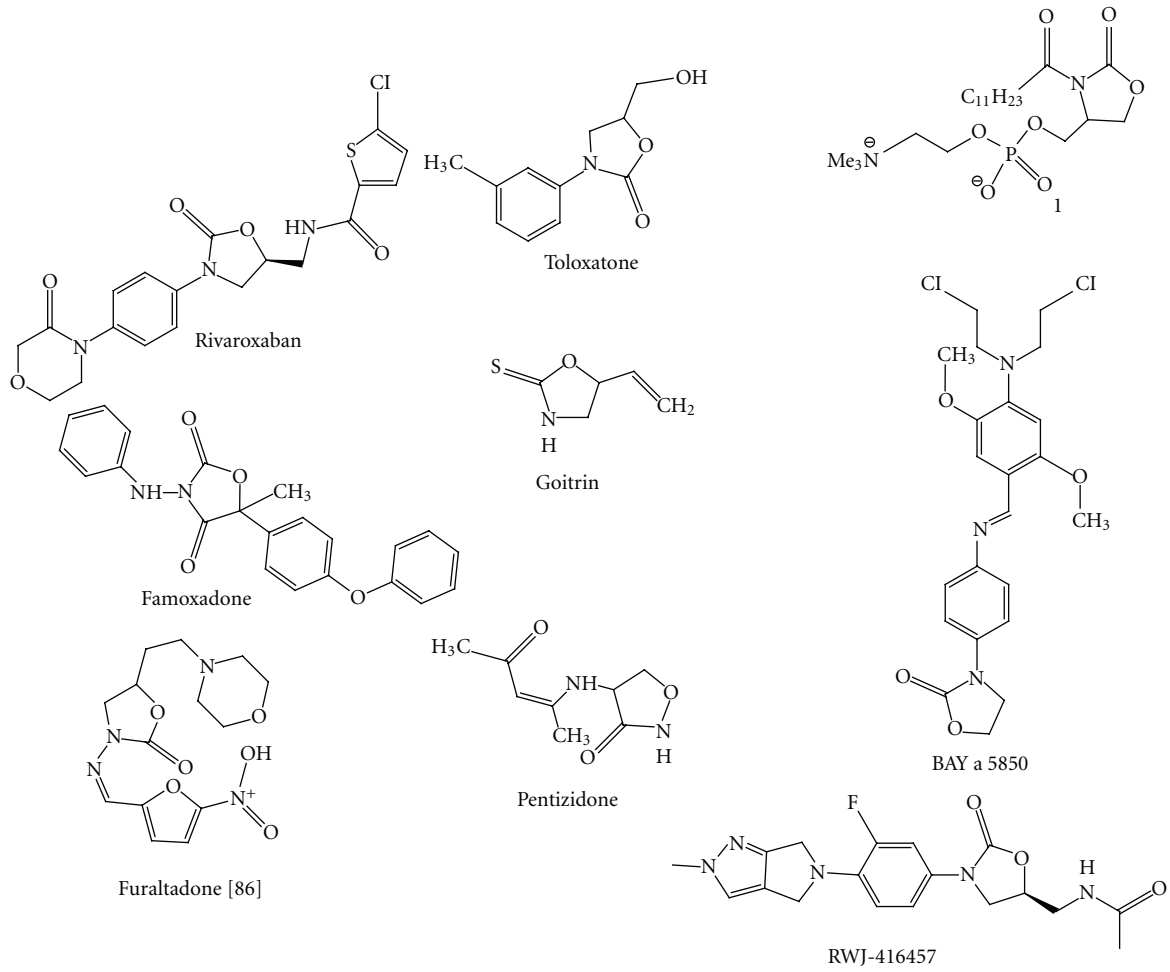


Figure 30

marketed as Xarelto. If approved by the United States FDA, it will be marketed by Ortho-McNeil Pharmaceutical. It is the first available orally active direct factor Xa inhibitor. Rivaroxaban is well absorbed from the gut and maximum inhibition of factor Xa occurs four hours after a dose. The effect lasts 8–12 hours, but factor Xa activity does not return to normal within 24 hours so once daily dosing is possible.

(3) *Antitubercular Activity*. During the course of investigation in the oxazolidinones antibacterial agent area was identified a subclass with especially potent in vitro activity against mycobacteria [69]. The salient structural feature of these oxazolidinone analogues, U-100480, U-101603, and U-101244, is their appended thiomorpholine. Potent activity against a screening strain of *M. tuberculosis* was determined by U-100480 and U-101603 (MIC = 0.125 mg/mL).

The activities of linezolid, eperezolid, and PNU-100480 were evaluated in a murine model of tuberculosis. Approximately 10 (7) viable *Mycobacterium tuberculosis* ATCC 35801 organisms were given intravenously to 4-week-old outbred CD-1 mice [70]. In the first study, treatment was started 1 day postinfection and was given by gavage for 4 weeks. Viable cell counts were determined from homogenates of spleens and lungs. PNU-100480 was as active as isoniazid. Linezolid was somewhat less active than PNU-100480 and isoniazid. Eperezolid had little activity in this model. In the next two studies, treatment was started 1 week postinfection. A dose-response study was performed with PNU-100480 and linezolid (both at 25, 50, and 100 mg/kg of body weight). PNU-100480 was more active than linezolid, and its efficacy increased with an escalation of the dose. Subsequently, the activity of PNU-100480 alone and in combination with rifampin or isoniazid was evaluated and was compared to that of isoniazid-rifampin. The activity of PNU-100480 was similar to that of isoniazid and/or rifampin in the various combinations tested. Further evaluation of these oxazolidinones in the murine test system would be useful prior to the development of clinical studies with humans.

(4) *Antidepressant or Psychotropic Activity*. Monoamine oxidase (MAO) inhibitors were developed as antidepressants but many drugs, including the novel oxazolidinone antibacterial agents, share similar molecular properties and have MAO inhibitory activity [71]. Factors important for binding antidepressants and modifications to decrease binding of oxazolidinones to avoid undesirable vascular effects are discussed [72].

In man, the antidepressant agent 3-(3-methylphenyl)-5-hydroxymethyl-2-oxazolidinone (toloxatone) (Figure 30) on oral dosing was mainly eliminated in urine (80% dose in 12 h).

Plasma concnentration of total radioactivity was max (5.8 μg equiv./mL) at 30 min to 1 h after administration and declined rapidly ($t_{1/2}$, 1.25 h). Unchanged drug accounted for 48, 32, and 13% of plasma radioactivity at 15 min, 1 h, and 6 h, respectively.

The drug was extensively metabolized. The major urinary metabolites were 3-(3-carboxyphenyl)-5-hydroxymethyl-2-oxazolidinone and a glucuronide of toloxatone. A minor urinary metabolite, characterized as a phenolic derivative, was also excreted conjugated.

On the basis of previous laboratory studies AS-8 (5-morpholinemethyl-3-(4-chlorobenzylideneamino)-2-oxazolidinone) was suggested to possess antidepressant-like activity. Forced swim test, learned helplessness, and conflict Vogel's test were performed after three prior administrations of AS-8 (24, 5, and 1 h before the test). The data have shown that AS-8 produces moderate antidepressant effect but did not induce anxiolytic-like action. Biochemical data revealed increased brain 5-HT and 5-HIAA levels following AS-8 administration [73]. The combined treatment of rats with AS-8 (100 mg/kg) and amitriptyline (5 mg/kg) or desipramine (1.25 mg/kg) significantly stimulated active behavior in the forced swim test above the level obtained with each of the drug given separately. The present data suggest the potential antidepressant efficacy of AS-8 in conjunction with small doses of tricyclic antidepressants.

(5) *Phospholipase Inhibitor* [74]. (S)- and (R)-3-dodecanoyl-4-phosphatidylcholinohydroxymethyl-2-oxazolidinone (**1**) (Figure 30), which are cyclic analogues of the amide phospholipid 7, were synthesized. The inhibitory activities of these analogues toward phospholipase A_2 were compared with that of the amide analogue 7. (S)- and (R)-3-dodecanoyl-4-phosphatidylcholinohydroxymethyl-2-oxazolidinone (1) were synthesized. The inhibitory activities of these analogues toward phospholipase A_2 were compared with that of the amide analogue.

(6) *Agriculture Fungicide* [75]. 5-Methyl-5-(4-phenoxyphenyl)-3-phenylamino-2,4-oxazolidinedione, DPX-JE874, is a new agricultural fungicide under development by DuPont. DPX-JE874 is a member of a new class of oxazolidinone fungicides which demonstrate excellent control of plant pathogens in the Ascomycete, Basidiomycete, and Oomycete classes which infect grapes, cereals, tomatoes, potatoes, and other crops. The synthesis, mode of action, and structure-activity relationships of two types of oxazolidinones, 2-thioxo-4-oxazolidinones and 2,4-oxazolidinediones, were discussed.

Famoxadone (3-anilino-5-methyl-5-(4-phenoxyphenyl)-1, 3-oxazolidine-2, 4-dione) (Figure 30), is a new agricultural fungicide recently commercialized by DuPont under the trade name Famoxate [76]. Famoxadone is a member of a new class of oxazolidinone fungicides that demonstrate excellent control of plant pathogens in the Ascomycete, Basidiomycete, and Oomycete classes that infect grapes, cereals, tomatoes, potatoes, and other crops.

Famoxadone is a preventative and curative fungicide recently commercialized for plant-disease control [77]. The molecule and its oxazolidinone analogs are potent inhibitors of mitochondrial ubiquinol: cytochrome c oxidoreductase (cytochrome bc_1) and they bind in the Q_0 site of the enzyme near the low potential heme of cytochrome b. Inhibitor binding constants for five mutant cytochrome bc_1 enzymes from *Saccharomyces cerevisiae* having single amino acid changes in their apocytochrome b located near the low potential heme were compared with their two parental wild-type enzymes. The five individual amino acid changes altered the inhibition constants for the inhibitors famoxadone, myxothiazol, azoxystrobin, and kresoxim-methyl in dissimilar fashion.

(7) *CNS Depressant* [78, 79]. A method of treating central nervous system diseases and disorders, the diseases and disorders being responsive to drugs possessing psychotropic activity. The method involves administering to a subject suffering from the disease or disorder a therapeutically effective amount of 5-morpholinomethyl-3-(4-chlorobenzylideneamine)-2-oxazolidinone or a pharmaceutically acceptable salt of 5-morpholinomethyl-3-(4-chlorobenzylideneamine)-2-oxazolidinone. The invention also relates to a pharmaceutical composition, the composition having pharmaceutically acceptable carriers and 5-morpholinomethyl-3-(4-chlorobenzylideneamine)-2-oxazolidinone and/or a pharmaceutically acceptable salt of 5-morpholinomethyl-3-(4-chlorobenzylideneamine)-2-oxazolidinone.

(8) *Centrally Acting Muscle Relaxants* [80]. The severity of anaemic decerebrate rigidity was quantitatively determined by measuring the frequency of electromyographic potentials in the rat. Some oxazolidinones markedly reduced the severity of this decerebrate rigidity in a dose-dependent manner, (4S,5R)-4-(2-methylpropyl)-3-[3-(perhydroazepin-1-yl)propyl]-5-phenyl-1,3-oxazolidin-2-one (MLV-6976) being the most potent. In addition to the oxazolidinones, an amino alcohol derivative, (1RS,2SR)-5-methyl-1-phenyl-2-(3-piperidinopropylamino)hexan-1-ol(MLV-5860) also reduced the rat decerebrate rigidity. In the oxazolidinone series, the optical isomers with absolute configuration (S) at the 4-position were more potent than the corresponding (4R)-isomers, while there was no significant difference in their LD50 values. Normal rats and mice receiving MLV-6976 at doses which reduced decerebrate rigidity showed no behavioural changes, impairment of motor coordination only appearing at extremely high doses. MLV-6976 and its derivatives did not affect spinal reflex potentials in cats. MLV-6976 reduced the severity of harmaline-induced tremor in mice in a dose-dependent manner, but slightly augmented tremorine-induced tremor. The frequency of the spike discharges induced by iontophoretically applied glutamate was reduced by MLV-6976 in a dose-dependent manner in rat cortical neurones. The amplitude of miniature endplate potentials of the rat diaphragm was decreased by MLV-6976 only at concentrations greater than 0.1 mM. It is concluded that MLV-6976 acts on the brainstem or/and higher levels of the brain rather than on the spinal cord

or the peripheral nervous system to reduce the excessive activities of the nervous system.

(9) *Antithyroid Agent* [81]. 5-Vinyloxazolidine-2-thione (VOT) administered orally to lactating rats was found to be efficiently transferred to the sucklings via the milk. In mothers the exposure to VOT resulted in an increased percentage of neutrophils, a decreased percentage of lymphocytes, and increases in the relative weights of liver and thyroid. Suckling rats showed a decreased number of leucocytes, increases in the relative weights of liver and thyroid and structural changes in the thyroid. Male sucklings were more affected than female pups. The antithyroid effects were clearly related to the maternally administered VOT doses.

RS-Goitrin (Figure 30) can be conveniently prepared by a simplification of the Ettlinger procedure. Goitrin is a moderate inhibitor of purified bovine adrenal dopamine beta-hydroxylase [82]. The administration of goitrin leads to a depression of brain norepinephrine and to an elevation of heart and adrenal dopamine.

Brassica vegetables are the major source of glucosinolates in the human diet. Certain glucosinolates are readily converted into goitrogenic species, notably 5-vinyloxazolidine-2-thione and thiocyanate ion [83]. The effect of dietary Brussels sprouts, a particularly rich source of such glucosinolates, on thyroid function has been examined.

(10) *Antiblastic Activity in Chemotherapy* [84]. Antiblastic activity means retardation of growth. 3-p-(2′, 5′-Dimethoxy-4′-(N,N-bis-(-chloroethyl)-amino)benzylideneamino)phenyl-2-oxazolidinone (GEA 29; BAY a 5850) (Figure 30) and its analogues use as antiblastic agent.

Some other oxazolidinone derivatives are used as anticancer in early clinical trial for example,

(i) 3-nitroso-5-methyl-2-oxazolidone,

(ii) 3-(2-hydroxy-3-(2-nitro-1H-imidazol-1-yl)propyl)-2-oxazolidinone,

(iii) 4-(4-(bis(2-chloroethyl)amino)-2,5-dimethoxyphenyl) methylene aminophenyl)-2-oxazolidinone.

(11) *Use in Urinary Tract Infection* [85]. The antimicrobial activity of linezolid, a recently developed antibiotic agent active against Gram-positive bacteria, was tested against pathogens from three different collections. (1) Uropathogens from hospitalized urological patients (1990/1991) with complicated and/or hospital-acquired UTIs; Urologic Clinic, Hospital St. Elisabeth, Straubing. (2) Uropathogens from a multicentre study (1995/1996) comprising 37 urological centres throughout Germany. (3) MRSA isolates of patients and staff (1999/2000) within the Hospital St. Elisabeth, Straubing. Genotyping of the latter isolates was performed by pulsed-field electrophoresis. The minimal inhibitory concentrations (MICs) of linezolid determined by an agar (Isosensitest) dilution method using a multipoint inoculator and an inoculum of 104 cfu per point ranged for methicillin susceptible *Staphylococcus aureus* (MSSA) ($n = 27$) between 2 and 4 mg/L, for methicillin resistant *S. aureus* (MRSA) ($n = 35$) between 1 and 2 mg/L, for methicillin susceptible coagulase-negative staphylococci (CNS) (MSSE) ($n = 67$) between 0.5 and 4 mg/L, for methicillin resistant CNS (MRSE) ($n = 19$) between 0.25 and 2 mg/L, for *Enterococcus. faecalis* ($n = 184$) between 0.5 and 4 mg/L, for *E. faecium* ($n = 3$) 2 mg/L, and for *Streptococcus* spp. ($n = 4$) between 0.25 and 1 mg/L, indicating that all strains were susceptible. According to the *in vitro* activity, linezolid may be considered a promising antibacterial agent for the treatment of complicated UTI caused by Gram-positive uropathogens. Thus, linezolid should be evaluated in a clinical study (Table 5).

Table 5

Product name	Furaltadone (Figure 30)
Synonyms	5-(Morpholinomethyl)-3-((5-nitrofurfurylidene)amino)-2-oxazolidinon; 5-morpholinomethyl-3-(5-nitro-2-furfurylidine-amino)-2-oxazolidinone; altabactina; altafur; f-150; furazolin; furazoline; furmethanol
MF	C13H16N4O6
Use	Use in UTI

(12) *Cycloserine Analogues* [86]. (R)-4-[(1-Methyl-3-oxo-1-butenyl)amino]isoxazolidin-3-one is used as cycloserine analogues. Synonym of this compound is Pentizidone (Figure 30).

D-Cycloserine is a broad-spectrum antibiotic used with other antibiotics to treat various forms of tuberculosis [87]. Its prodrug sodium (R)-4-[(1-methyl-3-oxo-1-butenyl)amino]-3-isoxazolidinone hemihydrate, developed for better aqueous stability and solubility, is combined with another broad-spectrum antibiotic, fludalanine.

6.2.2. Current Research Work on Oxazolidinone. Mathur et al. demonstrated RBx 11760 MICs were in the range of 0.5–1 mg/L for *C. difficile* isolates, and it demonstrated concentration-dependent killing of *C. difficile* ATCC 43255 and *C. difficile* 6387 up to 2–4x MIC (1–2 mg/L). RBx 11760, at concentrations as low as 0.25–0.5 mg/L, resulted in a significant reduction in *de novo* toxin production as well as sporulation in different *C. difficile* isolates [88]. In contrast, vancomycin, metronidazole, and linezolid had little or no effect on toxin production and appeared to promote the formation of spores. In the hamster infection model, treatment with RBx 11760 resulted in prolonged survival of animals as compared with vancomycin or metronidazole, which correlated well with the histopathology results. Macromolecular labelling results suggest that RBx 11760 is a potent inhibitor of bacterial protein synthesis. RBx 11760 showed excellent *in vitro* and *in vivo* activity against *C. difficile*, and it could be a promising novel candidate for future drug development against *C. difficile* infection.

Skripkin et al. have reported new and improved antibiotics are urgently needed to combat the ever-increasing number of multidrug-resistant bacteria [89]. In this study, we characterized several members of a new oxazolidinone family, Rχ-01. This antibiotic family is distinguished by having *in vitro* and *in vivo* activity against hospital-acquired,

as well as community-acquired, pathogens. We compared the 50S ribosome binding affinity of this family to that of the only marketed oxazolidinone antibiotic, linezolid, using chloramphenicol and puromycin competition binding assays. The competition assays demonstrated that several members of the Rχ-01 family displace, more effectively than linezolid, compounds known to bind to the ribosomal A site. We also monitored binding by assessing whether Rχ-01 compounds protect U2585 (*Escherichia coli* numbering), a nucleotide that influences peptide bond formation and peptide release, from chemical modification by carbodiimide. The Rχ-01 oxazolidinones were able to inhibit translation of ribosomes isolated from linezolid-resistant *Staphylococcus aureus* at submicromolar concentrations. This improved binding corresponds to greater antibacterial activity against linezolid-resistant enterococci. Consistent with their ribosomal A-site targeting and greater potency, the Rχ-01 compounds promote nonsense suppression and frameshifting to a greater extent than linezolid. Importantly, the gain in potency does not impact prokaryotic specificity as, like linezolid, the members of the Rχ-01 family show translation 50% inhibitory concentrations that are at least 100-fold higher for eukaryotic than for prokaryotic ribosomes.

Hilliard et al. have reported RWJ-416457 is an investigational pyrrolopyrazolyl-substituted oxazolidinone with activity against antibiotic-susceptible and -resistant gram-positive pathogens [90]. Efficacies of RWJ-416457, linezolid, and vancomycin against methicillin-susceptible *Staphylococcus aureus* (MSSA) and community-associated methicillin-resistant *S. aureus* (CA-MRSA) in murine skin and systemic infections were compared, as were efficacies against *Streptococcus pneumoniae* in a lower respiratory infection. In staphylococcal systemic infections, RWJ-416457 was equipotent to twofold more potent than linezolid, with 50% effective dose values ranging from 1.5 to 5 mg/kg of body weight/day. RWJ-416457 was two- to fourfold less potent than vancomycin against MSSA but up to fourfold more potent than vancomycin against CA-MRSA. In MSSA and CA-MRSA skin infections, RWJ-416457 demonstrated an efficacy similar to that of linezolid.

Locke et al. have reported that TR-700 (torezolid), the active moiety of the novel oxazolidinone phosphate prodrug TR-701, is highly potent against gram-positive pathogens, including strains resistant to linezolid (LZD) [91]. Here we investigated the potential of *Staphylococcus aureus* strains ATCC 29213 (methicillin-susceptible *S. aureus* MSSA) and ATCC 33591 (methicillin-resistant *S. aureus* MRSA) to develop resistance to TR-700. The spontaneous frequencies of mutation of MSSA 29213 and MRSA 33591 resulting in reduced susceptibility to TR-700 at 2x the MIC were 1.1×10^{-10} and 1.9×10^{-10}, respectively. These values are ~16-fold lower than the corresponding LZD spontaneous mutation frequencies of both strains. Following 30 serial passages in the presence of TR-700, the MIC for MSSA 29213 remained constant (0.5 μg/mL) while increasing eightfold (0.25 to 2.0 μg/mL) for MRSA 33591. Serial passage of MSSA 29213 and MRSA 33591 in LZD resulted in 64- and 32-fold increases in LZD resistance (2 to 128 μg/mL and 1 to 32 μg/mL, resp.). Domain V 23S rRNA gene mutations (*Escherichia coli* numbering) found in TR-700-selected mutants included T2500A and a novel coupled T2571C/G2576T mutation, while LZD-selected mutants included G2447T, T2500A, and G2576T. We also identified mutations correlating with decreased susceptibility to TR-700 and LZD in the *rplC* and *rplD* genes, encoding the 50S ribosomal proteins L3 and L4, respectively.

Resistance to linezolid (LZD) occurs through mutations in 23S rRNA and ribosomal proteins L3 and L4 or through methylation of 23S rRNA by Cfr [92]. Here we report novel L3 mutations, ΔSer145/His146Tyr and ΔMet169-Gly174, cooccurring with *cfr* in LZD-resistant *Staphylococcus aureus* isolates recovered from a hospital outbreak in Madrid, Spain. LZD MIC values (16, 32, or 64 μg/mL) correlated with the presence and severity of the L3 mutation. All isolates had TR-700 (torezolid) MIC values of ≤ 2 μg/mL.

The crystal structure of the antibiotic drug candidate RWJ-416457 (Figure 30) (systematic name: *N*-{(5*S*)-3-[4-(5,6-dihydro-2*H*,4*H*-2-methylpyrrolo [3,4-*c*]pyrazol-5-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}acetamide), $C_{18}H_{20}FN_5O_3$, which belongs to the first new class of antibiotics discovered in the past 30 years, has been determined at 150 K [93]. Each molecule of this drug donates one hydrogen bond to a neighboring molecule and accepts one hydrogen bond to give $(O{=}C{-}R{-}N{-}H\cdots O{=}C{-}R{-}N{-}H\cdots)_n$ linkages along the *b*-axis direction. The compound contains a pyrrolopyrazole ring, which, owing to its uncommon structure, has been shown to have particular effectiveness against multidrug-resistant bacteria.

Locke et al. have reported that staphylococcal resistance to linezolid (LZD) is mediated through ribosomal mutations (23S rRNA or ribosomal proteins L3 and L4) or through methylation of 23S rRNA by the horizontally transferred Cfr methyltransferase [94]. To investigate the structural basis for oxazolidinone activity against LZD-resistant (LZD^r) strains, we compared structurally diverse, clinically relevant oxazolidinones, including LZD, radezolid (RX-1741), TR-700 (torezolid), and a set of TR-700 analogs (including novel CD-rings and various A-ring C-5 substituents), against a panel of laboratory-derived and clinical LZD^r *Staphylococcus aureus* strains possessing a variety of resistance mechanisms. Potency against all strains was correlated with optimization of C- and D-rings, which interact with more highly conserved regions of the peptidyl transferase center binding site. Activity against *cfr* strains was retained with either hydroxymethyl or 1,2,3-triazole C-5 groups but was reduced by 2- to 8-fold in compounds with acetamide substituents.

This phase 4, randomized, double-blind, multicenter trial compared the efficacy and safety of Zyvox with vancomycin in the treatment of nosocomial pneumonia proven to be caused by MRSA, a serious and difficult-to-treat bacterial infection that is resistant to many antibiotics [95]. The study randomized 1,225 patients between 2004 and 2010. The study was designed as a noninferiority study with nested superiority, meaning the primary endpoint would be tested for superiority if it met non-inferiority criteria. In the study, Zyvox was noninferior and statistically superior to vancomycin in achieving both clinical and microbiologic success. The primary endpoint was clinical outcome at

end of study in the per-protocol population. Secondary analyses included clinical outcome at end of treatment in the per-protocol population, clinical outcomes in the modified intent-to-treat population at end of study and end of treatment, microbiologic outcomes at end of study and end of treatment in the per-protocol and modified intent-to-treat populations, and safety and tolerability in the intent-to-treat population. Patients were randomized to receive Zyvox IV 600 mg every 12 hours or vancomycin 15 mg/kg every 12 hours over the course of seven to 14 days; vancomycin doses could be titrated at the investigator's discretion based on creatinine clearance and vancomycin trough levels.

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(54) Title: ANTIMICROBIAL [3.1.0] BICYCLIC OXAZOLIDINONE DERIVATIVES

(57) Abstract: The present invention provides certain [3.1.0] bicyclic oxazolidinone derivatives of Formulea I and II, described herein, or pharmaceutically acceptable salts or prodrugs thereof that are antibacterial agents, pharmaceutical compositions containing them, methods for their use, and methods for preparing these compounds.

ANTIMIBICROBIAL [3.1.0] BICYCLIC OXAZOLIDINONE DERIVATIVES

Field of the Invention

The present invention relates to novel [3.1.0] bicyclic oxazolidinone derivatives, pharmaceutical compositions thereof, methods for their use, and methods for preparing the bicyclic derivatives. These compounds display potent activities against gram-positive and gram-negative bacteria.

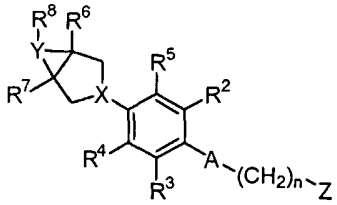
Background

Due to ever-increasing antibiotic resistance, structurally novel antibacterials with a new mode of action have become increasingly important in the treatment of bacterial infections. Effective antibacterials should exhibit potent activity against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiply-resistant staphylococci and streptococci, anaerobic organisms such as bacteroides and clostridia species, and acid-fast organisms such as *Mycobacterium tuberculosis* and *Mycobacterium avium*. The present invention provides structurally novel pharmaceutical compounds with expanded spectrum of antibacterial activity, including the activity against aerobic gram-negative organisms.

Among newer antibacterial agents, oxazolidinone compounds are the most recent synthetic class of antimicrobials active against a number of pathogenic microorganisms. However, oxazolidinones generally do not demonstrate useful levels of activity against aerobic gram-negative organisms. Thus, the use of these oxazolidinone antibacterial agents is limited to infectious states caused by gram-positive bacteria. We have now discovered that [3.1.0] bicyclic oxazolidinone derivatives of oxazolidinones of the present invention possess enhanced anti-gram-positive activity and/or expand the spectrum of antimicrobial activity to include gram-negative organisms such as *Haemophilus influenza* and *Moraxella catarrhalis*.

SUMMARY OF THE INVENTION

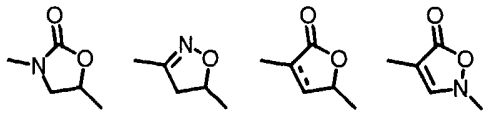
The present invention provides a compound of Formula I



I

wherein:

A is a structure i, ii, iii, or iv



i ii iii iv

where the dashed line in formula iii represents an optional double bond;

n is 0 or 1;

X is N or CH;

Y is N, O, or S;

Z is $NHC(=O)R^1$, $NHC(=S)R^1$, $CONHR^1$, $NHC(=NCN)R^1$, NH–het^1, O-het^1, S-het^1 or het^2;

R^1 is H, NH_2, NHC_{1-4}alkyl, C_{1-4}alkyl, C_{2-4}alkenyl, $(CH_2)_mC(=O)C_{1-4}$alkyl, OC_{1-4}alkyl, SC_{1-4}alkyl, $(CH_2)_mC_{3-6}$cycloalkyl, CH=CH-aryl, CH=CH-het^1, $CH_2C(=O)$-aryl, or $CH_2C(=O)$-het^1;

R^2 and R^3 are independently H or F;

R^4 and R^5 are independently H, Cl, F, CH_3, NH_2, or OH;

R^6 and R^7 are independently H, F, OH, C_{1-4}alkyl, or C_{1-4}heteroalkyl;

R^8 is H, F, OH, CN, $NR^{10}R^{11}$, C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{1-4}heteroalkyl, aryl, het^1, OC_{1-4}alkyl, C_{1-4}alkylOR^{10}, C_{1-4}alkyl$NR^{10}R^{11}$, $O(C=O)C_{1-4}$alkyl, $C(=O)C_{1-4}$alkyl, $C(=O)OH$, $C(=O)NR^{10}OR^{11}$, $C(=NOC_{1-4}alkyl)H$, $C(=NOC_{1-4}alkyl)C_{1-4}$alkyl, $C(=O)$het^1, $C(=NOC_{1-4}alkyl)$het^1, $(CH_2)_mC(=O)NR^{10}R^{11}$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}C(=O)C_{1-4}$alkyl, $NR^{10}C(=O)C_{3-6}$cycloalkyl, $NR^{10}C(=O)OH$, $NR^{10}C(=O)H$, or OC_{1-4}alkyl$CONR^{10}R^{11}$, provided that when Y is is O or S, then R^8 is absent,

further wherein

each R^{10} and R^{11} are independently H, C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, het^1, $C(=O)$aryl, $C(=O)$het^1, SO_2C_{1-4}alkyl, or SO_2NH_2;

het^1 is a C-linked five- (5) or six- (6) membered heterocyclic ring having 1-4 heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen;

het^2 is a N-linked or C-linked five- (5) or six- (6) membered heterocyclic ring having 1-4 heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen;

each m is independently 0, 1, or 2;

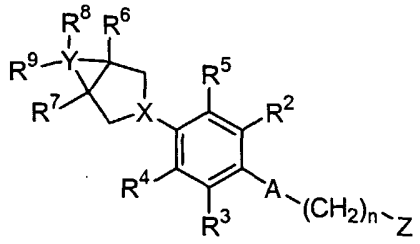
and a pharmaceutically acceptable salts thereof;

with the further provisos that

when Z is $NHC(=O)R^1$ or $NHC(=S)R^1$; n is 1; A is structure (i); R^2, R^3, R^6 and R^7 are H; X is N; Y is N; then R^8 is not $C(=O)het^1$; and

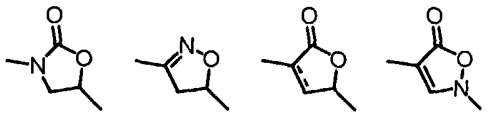
when Z is $NHC(=O)R^1$ or $NHC(=S)R^1$; n is 1; A is structure (i); R^2, R^3, R^6 and $R^7$are H; X is N; Y is N; and R^8 is $NR^{10}R^{11}$ or $C_{1-4}alkylNR^{10}R^{11}$; then R^{10} and R^{11} are not het^1, aryl, C(=O)aryl, or $C(=O)het^1$.

In another aspect the invention features compounds of Formula II



II

wherein A is a structure i, ii, iii, or iv



i ii iii iv

where the dashed line in formula iii represents an optional double bond;

n is 0 or 1;

X is N or CH;

Y is C;

Z is $NHC(=O)R^1$, $NHC(=S)R^1$, $CONHR^1$, $NHC(=NCN)R^1$, NH–het^1, O-het^1, S-het^1, or het^2;

R^1 is H, NH_2, NHC_{1-4}alkyl, C_{1-4}alkyl, C_{2-4}alkenyl, $-(CH_2)_mC(=O)C_{1-4}$alkyl, OC_{1-4}alkyl, SC_{1-4}alkyl, $(CH_2)_mC_{3-6}$cycloalkyl, CH=CH-aryl, CH=CH-het^1, $CH_2C(=O)$-aryl, or $CH_2C(=O)$-het^1;

R^2 and R^3 are independently H or F,

R^4 and R^5 are independently H, Cl, F, CH_3, NH_2, or OH;

R^6 and R^7 are independently H, F, OH, C_{1-4}alkyl or C_{1-4}heteroalkyl;

R^8 and R^9 are independently H, F, OH, CN, $NR^{10}R^{11}$, C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{1-4}heteroalkyl, aryl, het^1, OC_{1-4}alkyl, C_{1-4}alkylOR^{10}, C_{1-4}alkyl$NR^{10}R^{11}$, $O(C=O)C_{1-4}$alkyl, $C(=O)C_{1-4}$alkyl, C(=O)OH, $C(=O)NR^{10}OR^{11}$, $C(=NOC_{1-4}$alkyl)H, $C(=NOC_{1-4}$alkyl)C_{1-4}alkyl, $C(=O)het^1$, $C(=NOC_{1-4}$alkyl)het^1, $(CH_2)_mC(=O)NR^{10}R^{11}$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}C(=O)C_{1-4}$alkyl, $NR^{10}C(=O)C_{3-6}$cycloalkyl, $NR^{10}C(=O)OH$, $NR^{10}C(=O)H$, or OC_{1-4}alkyl$CONR^{10}R^{11}$, with the following provisos:

when both R^8 or R^9 are present they are not both OH or $NR^{10}R^{11}$;

when both R^8 or R^9 are present and R^8 is CN then R^9 is not OH or $NR^{10}R^{11}$;

further wherein

each R^{10} and R^{11} are independently H, C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, het^1, C(=O)aryl, $C(=O)het^1$, SO_2C_{1-4}alkyl, or SO_2NH_2;

het^1 is a C-linked five- (5) or six- (6) membered heterocyclic ring having 1-4 heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen;

het^2 is a N-linked or C-linked five- (5) or six- (6) membered heterocyclic ring having 1-4 heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen;

each m is independently 0, 1, or 2;

and a pharmaceutically acceptable salts thereof;

with the further provisos that

when Z is $NHC(=O)R^1$ or $NHC(=S)R^1$; n is 1; A is structure (i); R^2, R^3, R^6 and $R^7$are H; X is N; Y is C; and R^9 is H; then R^8 is not $C(=O)het^1$;

when Z is $NHC(=O)R^1$ or $NHC(=S)R^1$; n is 1; A is structure (i); R^2, R^3, R^6 and $R^7$are H; X is N; Y is C; R^9 is H; R^8 is $NR^{10}R^{11}$ or C_{1-4}alkyl$NR^{10}R^{11}$; then R^{10} and R^{11} are not het^1, aryl, C(=O)aryl, or $C(=O)het^1$.

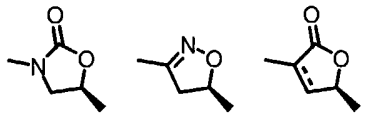
In another aspect, the present invention provides for pharmaceutical compositions comprising a compound of Formulea I or II, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In yet another aspect, the present invention provides for a method for the treatment of microbial infection in a mammal comprising administration of an effective amount of the compound of Formulea I or II, or a pharmaceutically acceptable salt thereof, to said mammal.

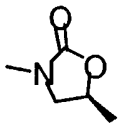
In still another aspect, the present invention also provides for a method for treating gram-negative microbial infections in humans or other warm-blooded animals by administering to the subject in need a therapeutically effective amount of a compound of Formulea I or II, or a pharmaceutically acceptable salt thereof.

The present invention also provides novel intermediates and processes that are useful for preparing compounds of Formulea I or II.

Embodiments of the invention may include one or more of the following. A is an optical configuration of structure i, ii, or iii:



i ii iii . A is an optical configuration of structure



i: i . R^1 is C_{1-4} alkyl. R^1 is methyl, difluoromethyl, ethyl, 2-fluoroethyl, or 2,2-difluoroethyl. R^4 and R^5 are independently H or F. R^6 and R^7 are H. R^8 and R^9 are H. n is 0.

Specific embodiments of the invention include, but are not limited to,

N-({(5S)-3-[3,5-difluoro-4-(6-oxa-3-azabicyclo[3.1.0]hex-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-({(5S)-3-[3,5-difluoro-4-(6-oxa-3-azabicyclo[3.1.0]hex-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanamide;

N-({(5S)-3-[4-(3,6-diazabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-({(5S)-3-[4-(6-acetyl-3,6-diazabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-({(5S)-3-[4-(6-methoxyacetyl-3,6-diazabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

2-[3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}2-fluorophenyl)-3,6-diazabicyclo[3.1.0]hex-6-yl]-2-oxoethyl acetate; and

N-((5S)-3-{3,5-Difluoro-4-[exo-(1R,5S)-6-(2-hydroxy-ethyl)-3-aza-bicyclo[3.1.0]hex-3-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide.

DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, C_{1-7} alkyl refers to alkyl of one to seven carbon atoms, inclusive.

The terms alkyl, alkenyl, etc. refer to both straight and branched groups, but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to. The alkyl, alkenyl, etc. group may be optionally substituted with one, two, or three substituents, preferably halo, aryl, het^1, or het^2. Representative examples include, but are not limited to, difluoromethyl, 2-fluoroethyl, CH=CH-aryl, CH=CH-het^1, CH_2-phenyl, and the like.

The term "cycloalkyl" means a cyclic saturated monovalent hydrocarbon group of three to seven carbon atoms, e.g., cyclopropyl, cyclohexyl, and the like. The cycloalkyl group may be optionally substituted with one, two, or three substituents, preferably halo, aryl, het^1, or het^2.

The term "heteroalkyl" means an alkyl or cycloalkyl group, as defined above, having a substituent containing a heteroatom selected from N, O, or $S(O)_q$, where q is 0, 1 or 2, including for example, hydroxy (OH), alkoxy, amino, thio, and the like. Representative substituents include $-NR_aR_b$, $-OR_a$, or $-S(O)_q R_c$, wherein R_a is hydrogen, alkyl, cycloalkyl, optionally substituted aryl, optionally substituted heterocyclic, or -COR (where R is alkyl); R_b is hydrogen, alkyl, $-SO_2R$ (where R is alkyl or hydroxyalkyl), $-SO_2NRR'$ (where R and R' are independently of each other hydrogen or alkyl), -CONR'R" (where R' and R" are independently of each other hydrogen or alkyl); n is an integer from 0 to 2; and R_c is hydrogen, alkyl, cycloalkyl, optionally substituted aryl, optionally substituted heterocyclic, amino, monosubstituted amino, or disubstituted amino. Representative examples include, but are not limited to 2-methoxyethyl ($-CH_2CH_2OCH_3$), 2-hydroxyethyl ($-CH_2CH_2OH$), hydroxymethyl ($-CH_2OH$), 2-aminoethyl ($-CH_2CH_2NH_2$), 2-dimethylaminoethyl ($-CH_2CH_2NHCH_3$), 2-morpholinoethyl, benzyloxymethyl, and the like.

The term "halo" refers to fluoro (F), chloro (Cl), bromo (Br), or iodo (I).

Aryl refers to phenyl, biphenyl, or naphthyl, optionally substituted with halo, C_{1-4} alkyl, OH, OC_{1-4} alkyl, $S(O)_qC_{1-4}$alkyl wherein q is 0, 1, or 2, H_2NC_{1-4}alkyl, -C(=O)H, or $-C=N-OR_d$ wherein R_d is hydrogen or alkyl.

The term heterocyclic group or ring refers to an aromatic ring or a saturated or unsaturated ring that is not aromatic of 3 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur within the ring. The heterocyclic ring may be optionally substituted with halo, C_{1-4} alkyl, OH, OC_{1-4} alkyl, $S(O)_qC_{1-4}$alkyl wherein q is 0, 1, or 2, H_2NC_{1-4}alkyl, -C(=O)H, or $-C=N-OR_d$ wherein R_d is hydrogen or alkyl. In addition, one of the carbon atoms of the heterocyclic ring may optionally be replaced by C=O or C=N. Examples of heterocyclic rings include, but are not limited to, azetidine, pyrrole, imidazole, pyrazole, 1,2,3-triazole, 1,3,4-triazole, oxazole, thiazole, isoxazole, isothiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,2,3-thiadiazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole,

dihydroindole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, isoxazolinone, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, thiadiazole tetrazole, thiazolidine, thiophene, benzo[b]thiophene, morpholine, thiomorpholine, (also referred to as thiamorpholine,), piperidine, pyrrolidine, tetrahydrofuran, and the like.

Specifically, het^1 refers to a C-linked five- (5) or six- (6) membered heterocyclic ring. Representative examples of "het^1" include, but are not limited to, pyridine, thiophene, furan, pyrazole, pyrimidine, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazinyl, 4-oxo-2-imidazolyl, 2-imidazolyl, 4-imidazolyl, 3-isoxaz-olyl, 4-is-oxaz-olyl, 5-isoxaz-olyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 4-oxo-2-oxazolyl, 5-oxazolyl, 1,2,3-oxathiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazole, 4-isothiazole, 5-isothiazole, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 3-isopyrrolyl, 4-isopyrrolyl, 5-isopyrrolyl, 1,2,3,-oxathiazole-1-oxide, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 5-oxo-1,2,4-oxadiazol-3-yl, 1,2,4-thiadiazol-3-yl, 1,2,5-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 3-oxo-1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-oxo-1,3,4-thiadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,2,3,4-tetrazol-5-yl, 5-oxazolyl, 3-isothiazolyl, 4-isothiazolyl and 5-isothiazolyl, 1,3,4,-oxadiazole, 4-oxo-2-thiazolinyl, or 5-methyl-1,3,4-thiadiazol-2-yl, thiazoledione, 1,2,3,4-thiatriazole, or 1,2,4-dithiazolone

Specifically, het^2 refers to a C-linked or N-linked five- (5) or six- (6) membered heterocyclic ring having 1 to 4 nitrogen atoms, and optionally having one oxygen or sulfur atom. Representative examples of "het^2" include, but are not limited to pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3,4-tetrazolyl, and isoxazolidinonyl group.

A C-linked heterocyclic ring is a heterocyclic group as defined above wherein the group is attached via a carbon atom within of the heterocyclic ring.

An N-linked heterocyclic ring is a heterocyclic group as defined above wherein the group is attached via a nitrogen atom of the heterocyclic ring.

"Optional" or "optionally" means that the subsequently described event or circumstance may, but need not, occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "aryl group optionally mono- or di- substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the aryl group is mono- or disubstituted with an alkyl group and situations where the aryl group is not substituted with the alkyl group.

Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers".

Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)- stereoisomers

or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 1992).

A "pharmaceutically acceptable carrier" means a carrier that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier" as used in the specification and claims includes both one and more than one such carrier.

A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an

aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

"Treating" or "treatment" of a disease includes:

preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease,

inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms, or

relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

A "therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

"Leaving group" has the meaning conventionally associated with it in synthetic organic chemistry i.e., an atom or group capable of being displaced by a nucleophile and includes halogen, alkylsulfonyloxy, ester, or amino such as chloro, bromo, iodo, mesyloxy, tosyloxy, trifluorosulfonyloxy, methoxy, N,O-dimethylhydroxyl-amino, and the like.

"Pro-drugs" mean any compound that releases an active parent drug according to a compound of the subject invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of the subject invention are prepared by modifying functional groups present in a compound of the subject invention in such a way that the modifications may be cleaved *in vivo* to release the parent compound. Prodrugs include compounds of the subject invention wherein a hydroxy, sulfhydryl or amino group in the compound is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxyl, amino, or sulfhydryl group,

respectively. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate, and benzoate derivatives), carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds of the subject invention, and the like.

Mammal refers to human or warm-blooded animals including livestock and companion animals.

The compounds of the present invention are generally named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill in the art may be used (e.g. "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "h" for hour or hours and "rt" for room temperature).

Illustrative Embodiments

Within the broadest definition of the present invention, certain compounds of the compounds of formula I may be preferred. Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

Specifically the term C_{1-4}alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, and their isomeric forms thereof.

Specifically, C_{2-4}alkenyl can be vinyl, propenyl, allyl, butenyl, and their isomeric forms thereof.

Specifically, C_{3-6}cycloalkyl can cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and their isomeric forms thereof.

Specifically, R^1 is C_{1-4}alkyl, optionally substituted with one, two, or three fluoro (F) or chloro (Cl).

Specifically, R^1 is difluoromethyl, dichloromethyl, fluoroethyl, or difluoromethyl.

Specifically, R^1 is CH_3, CHF_2, CF_3, or $CHCl_2$, CH_2CF_3, CH_2CH_3, CH_2CHF_2, CH_2CH_2F.

Specifically, R^1 is CH=CH-aryl.

Specifically, R^1 is CH=CH-het^1.

Specifically, R_1 is $CH_2C(=O)C_{1-4}$alkyl.

Specifically, R^4 and R^5 are independently H or F.

Specifically, Y is N or O.

Specifically, Y is C.

Specifically, Z is $C(=O)NH_2$.

Specifically, m is 1.

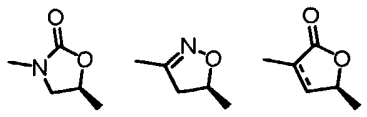
Specifically, R^6, R^7 and R^8 are H.

Specifically, R^4 and R^5 are independently H or F and R^6, R^7, and R^8 are H.

Specifically, het^1 is isoxazolyl, 1,2,5-thiadiazolyl, or pyridyl.

Specifically, het ^{2} is 1,2,3-triazolyl.

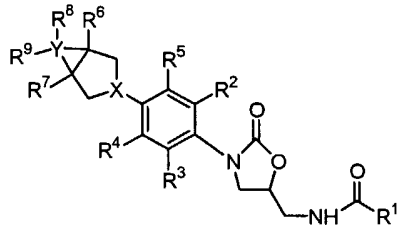
Specific compounds of the present invention are those wherein structure i, ii, or iii has an optical configuration as depicted below:



i ii iii

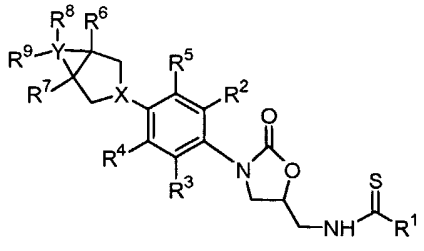
The dotted line within structure iii indicates an optional double bond at that position. It will be appreciated by those skilled in the art that compounds of the present invention may have additional chiral centers and be isolated in optically active and racemic forms. The present invention encompasses any racemic, optically active, tautomeric, or stereoisomeric form, or mixture thereof, of a compound of the invention.

Other specific compounds of the present invention are the compounds of Formula IIa:



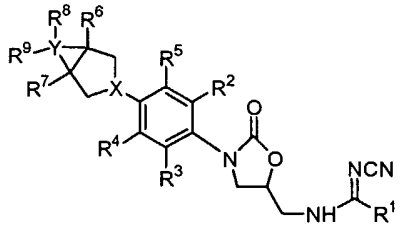
IIa

Other specific compounds of the present invention are the compounds of Formula III



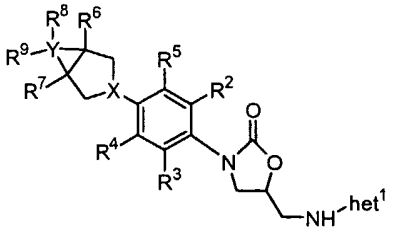
III

Other specific compounds of the present invention are the compounds of Formula IV



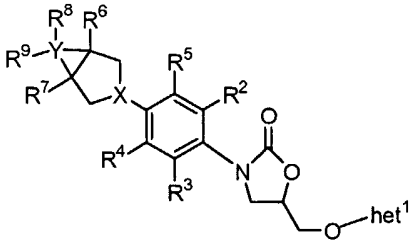
IV

Other specific compounds of the present invention are the compounds of Formula V



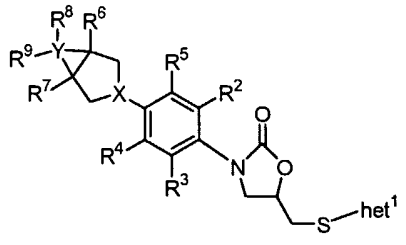
V

Other specific compounds of the present invention are the compounds of Formula VI



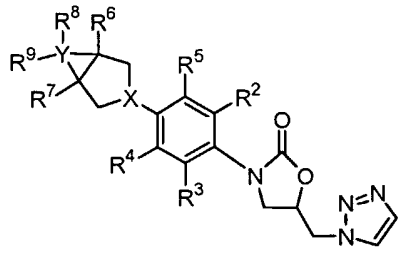
VI

Other specific compounds of the present invention are the compounds of Formula VII



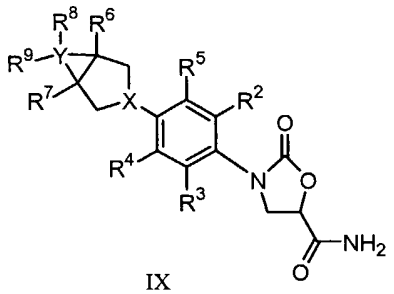
VII

Other specific compounds of the present invention are the compounds of Formula VIII



VIII

Other specific compounds of the present invention are the compounds of Formula IX



IX

A particularly preferred group of compounds includes the following:

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}phenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

exo-(1R,5S)-3-[4-((5S)-5-{[(difluoroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

exo-(1R,5S)-3-[4-((5S)-5-{[(difluoroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)phenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

exo-(1R,5S)-3-[4-((5S)-5-{[(2,2-difluoroethanethioyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)phenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

exo-(1R,5S)-3-(2,6-difluoro-4-{(5S)-2-oxo-5-[(propionylamino)methyl]-1,3-oxazolidin-3-yl}phenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

exo-(1R,5S)-3-[4-((5S)-5-{[(dichloroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

exo-(1R,5S)-3-[4-((5S)-5-{[(2,2-difluoroethanethioyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

exo-(1R,5S)-3-{4-[(5R)-5-(aminocarbonyl)-2-oxo-1,3-oxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

exo-(1R,5S)-3-{2,6-difluoro-4-[(5R)-2-oxo-5-(1H-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-3-yl]phenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

exo-(1R,5S)-3-[4-((5S)-5-{[(dichloroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)phenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

exo-(1R,5S)-3-[4-((5S)-5-{[(difluoroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

exo-(1R,5S)-3-[4-((5S)-5-{[(dichloroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

exo-(1R,5S)-3-[4-((5S)-5-{[(2,2-difluoroethanethioyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide;

N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide;

N-[((5S)-3-{4-[endo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide;

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxamide;

N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2,2-difluoroacetamide

N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2,2-difluoroacetamide;

N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2,2-dichloroacetamide;

N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2,2-difluoroethanethioamide;

N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2,2-dichloroacetamide;

N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarboxamide;

N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]propanamide;

N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2,2-difluoroethanethioamide;

methyl exo-(1R,5S)-3-[4-((5S)-5-{[(dichloroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylate;

methyl exo-(1R,5S)-3-[4-((5S)-5-{[(difluoroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylate;

2-(diethylamino)-2-oxoethyl exo-(1R,5S)-3-[4-((5S)-5-{[(dichloroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylate;

2-(diethylamino)-2-oxoethyl exo-(1R,5S)-3-[4-((5S)-5-{[(difluoroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylate;

(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl exo-(1R,5S)-3-[4-((5S)-5-{[(dichloroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylate;

(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl exo-(1R,5S)-3-[4-((5S)-5-{[(difluoroacetyl) amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0] hexane-6-carboxylate;

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxamide;

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N,N-dimethyl-3-azabicyclo[3.1.0]hexane-6-carboxamide;

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-(2-furylmethyl)-3-azabicyclo[3.1.0]hexane-6-carboxamide;

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-(6-methoxypyridin-3-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide;

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-(pyridin-2-ylmethyl)-3-azabicyclo[3.1.0]hexane-6-carboxamide;

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-[(2R)-2-hydroxypropyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide;

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-(1,3-thiazol-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide;

N-({(5S)-3-[3,5-difluoro-4-(exo-(1R,5S)-6-{[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}-3-azabicyclo[3.1.0]hex-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-(1,3-benzodioxol-5-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide;

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-(2-mercapto-1,3-benzothiazol-6-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide;

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-(1H-pyrazol-3-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide;

N-[exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-2-hydroxyacetamide;

N-[((5S)-3-{3-fluoro-4-[exo-(1R,5S)-6-(formylamino)-3-azabicyclo[3.1.0]hex-3-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide;

N-[((5S)-3-{3,5-difluoro-4-[exo-(1R,5S)-6-(formylamino)-3-azabicyclo[3.1.0]hex-3-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide;

Methyl exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylcarbamate;

N-[((5S)-3-{4-[exo-(1R,5S)-6-(acetylamino)-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide;

N-{[(5S)-3-(3,5-difluoro-4-{exo-(1R,5S)-6-[(methylsulfonyl)amino]-3-azabicyclo[3.1.0]hex-3-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

exo-(1R,5S)-3-{2,6-difluoro-4-[(5R)-2-oxo-5-(1H-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-3-yl]phenyl}-3-azabicyclo[3.1.0]hexane-6-carboxamide;

exo-(1R,5S)-3-[4-((5S)-5-{[(2,2-difluoroethanethioyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxamide;

exo-(1R,5S)-3-{4-[(5R)-5-(aminocarbonyl)-2-oxo-1,3-oxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxamide;

N-({(5S)-3-[4-(exo-(1R,5S)-6-acetyl-3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-{[(5S)-3-(3,5-difluoro-4-{exo-(1R,5S)-6-[N-methoxyethanimidoyl]-3-azabicyclo[3.1.0]hex-3-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

N-({(5S)-3-[3,5-difluoro-4-(exo-(1R,5S)-6-{[(methylsulfonyl)amino]carbonyl}-3-azabicyclo[3.1.0]hex-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

tert-butyl 3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3,6-diazabicyclo[3.1.0]hexane-6-carboxylate;

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-hydroxy-3-azabicyclo[3.1.0]hexane-6-carboxamide;

N-[((5S)-3-{3,5-difluoro-4-[exo-(1R,5S)-6-hydroxy-3-azabicyclo[3.1.0]hex-3-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide;

N-({(5S)-3-[4-(exo-(1R,5S)-6-{[(2S)-3-(acetylamino)-2-hydroxypropyl]oxy}-3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-({(5S)-3-[4-(3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-[((5S)-3-{4-[exo-(1R,5S)-6-cyano-3-azabicyclo[3.1.0]hex-3-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide;

N-{[(5S)-3-(3-fluoro-4-{exo-(1R,5S)-6-[(hydroxyamino)(imino)methyl]-3-azabicyclo[3.1.0]hex-3-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

N-({(5S)-3-[3-fluoro-4-(6-oxa-3-azabicyclo[3.1.0]hex-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-({(5S)-3-[3,5-difluoro-4-(6-oxa-3-azabicyclo[3.1.0]hex-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-({(5S)-3-[3,5-difluoro-4-(6-oxa-3-azabicyclo[3.1.0]hex-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanamide;

N-({(5S)-3-[3,5-difluoro-4-(6-oxa-3-azabicyclo[3.1.0]hex-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2,2-difluoroethanethioamide;

(5S)-3-[3-Fluoro-4-(6-oxa-3-aza-bicyclo[3.1.0]hex-3-yl)-phenyl]-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one;

(5S)-3-[3-Fluoro-4-(6-oxa-3-aza-bicyclo[3.1.0]hex-3-yl)-phenyl]-2-oxo-oxazolidine-5-carboxamide;

(5S)-3-[3,5-Difluoro-4-(6-oxa-3-aza-bicyclo[3.1.0]hex-3-yl)-phenyl]-2-oxo-oxazolidine-5-carboxamide;

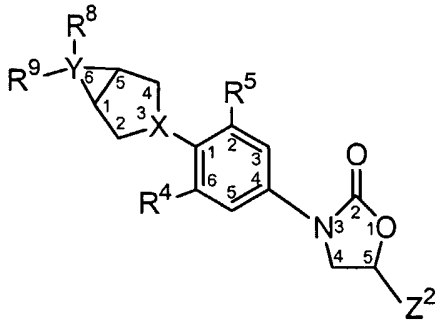
exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-(benzyloxy)-3-azabicyclo[3.1.0]hexane-6-carboxamide;

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-methyl-3-azabicyclo[3.1.0]hexane-6-carboxamide;

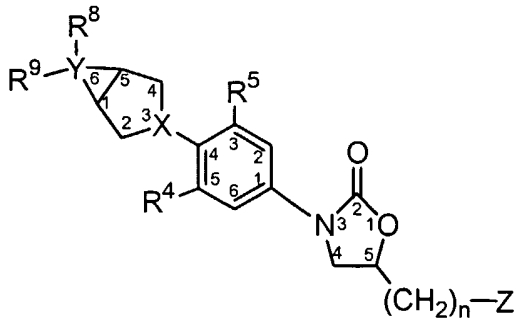
N-{[(5S)-3-(4-{exo-(1R,5S)-6-[(anilinocarbonyl)amino]-3-azabicyclo[3.1.0]hex-3-yl}-3,5-difluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide; and

N-({(5S)-3-[4-(3-azabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide.

The compounds discussed herein are named according to one of the structures set forth below in which the ring positions are numbered according to convention:



3-{4-[(Z^2)-2-oxo-oxazolidin-3-yl]-substituted-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-(R^8 and/or R^9); or



N-{3-[4-[6-(Y-(R^8 and/or R^9))-3-aza-bicyclo[3.1.0]hex-3-yl]-substitued-phenyl]-2-oxo-oxazolidin-5-yl$(CH_2)_n$))}-(Z).

General Synthetic Schemes

The compounds of this invention can be prepared in accordance with one or more of the Schemes discussed below. Syntheses of [3.1.0] bicyclic compounds are precedented in the prior art, although no oxazolidinones derivatives of this class have been reported.

The starting materials, intermediates, and final compounds described in this invention were prepared using common procedures and techniques that are well known to persons of ordinary skill in organic chemistry. These compounds were prepared in accordance with one or more of the following Schemes as described below.

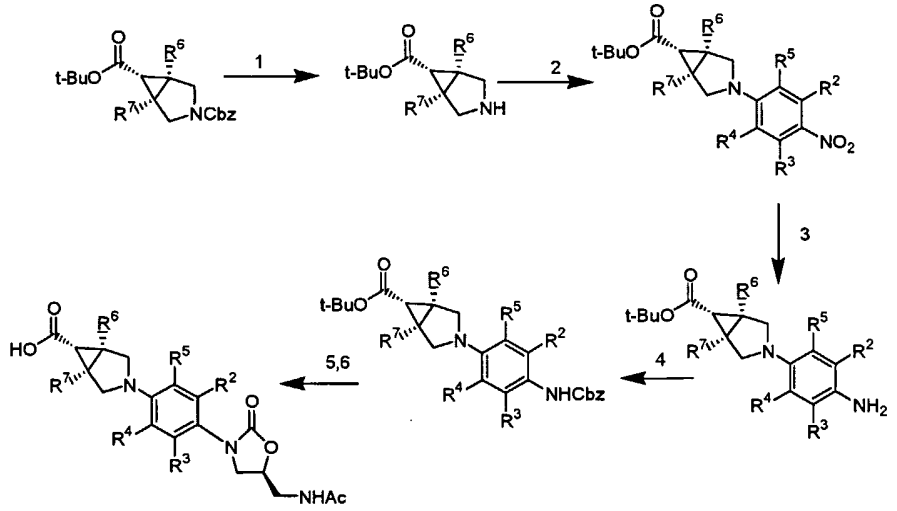
It will be appreciated that some of the processes described herein require the use of protective groups to prevent the undesired reactivity of certain substituents. A person skilled in organic chemistry will recognize when such protection may be required and how such groups may be installed and subsequently removed. For examples of protecting groups and procedures for their introduction and removal see one of the general texts on the subject such as "Protecting Groups" by Philip J. Kocienski (publisher: Georg Thieme Verlag: Stuttgart, 1994).

Chiral intermediates of enantiomeric purity may be prepared using various asymmetric reaction methodologies, or alternatively by resolution of the racemic mixtures. A skilled chemist will appreciate that the azabicyclo[3.1.0]hexyl ring

systems described herein, when substituted at the terminal carbon atom of the cyclopropane ring, can exist as either *endo* or *exo* diastereomers. When formed as mixtures, these diastereomers can be separated by standard techniques of organic chemistry, for example by silica gel chromatography.

Scheme I illustrates a general synthesis of aryloxazolidinone compounds bearing a carboxylic acid substituent on the appended azabicyclo[3.1.0]hexane ring. The starting material shown was prepared as described by Brighty *et al.* (in *Synlett* 1996, p. 1097) but using *tert*-butyl diazoacetate in the cyclopropanation reaction rather than ethyl diazoacetate. The desired *endo* isomer (Scheme I) was obtained after purification by silica gel column chromatography. In step **1** of the synthesis, the benzyloxycarbonyl group is removed from the starting material by hydrogenolysis using a catalyst such as palladium on carbon or palladium hydroxide on carbon. These reactions are generally performed at ambient temperatures and hydrogen pressures and in solvents such as methanol, ethanol, or ethyl acetate (alone or as mixtures). Optionally, the hydrogenolysis may be conducted at elevated hydrogen pressures and temperatures.

Scheme I



Step **2** of Scheme I involves a nucleophilic aromatic substitution reaction of the first intermediate with a substituted fluoronitro aromatic compound such as 3,4-difluoronitrobenzene or 3,4,5-trifluoronitrobenzene. Nucleophilic aromatic substitution reactions are well known to a person skilled in the art and review articles describing these reactions are available (see Zoltewicz in *Top. Curr. Chem.*

1975, vol. 59, pp. 33-64). These transformations are generally performed at 40°C to 90°C using polar aprotic solvents such as acetonitrile or dimethylformamide and in the presence of acid-scavenging bases such as triethylamine or *N,N*-diisopropylethylamine.

Step **3** of Scheme I involves the reduction of the nitro substituent to an amino substituent. This reduction is generally accomplished by reacting the nitro intermediate with iron metal. The reaction is carried out at temperatures between 60°C and 90°C in mixtures of water and alcohol (methanol, ethanol, etc.) as solvent, and in the presence of ammonium chloride to buffer the reaction mixture. Optionally, reductions of this type are conducted by reaction with other metals such as tin or zinc or by hydrogenation under palladium or platinum catalysis (see Rylander *Hydrogenation Methods*; Academic Press: New York, 1985, pp. 104-116).

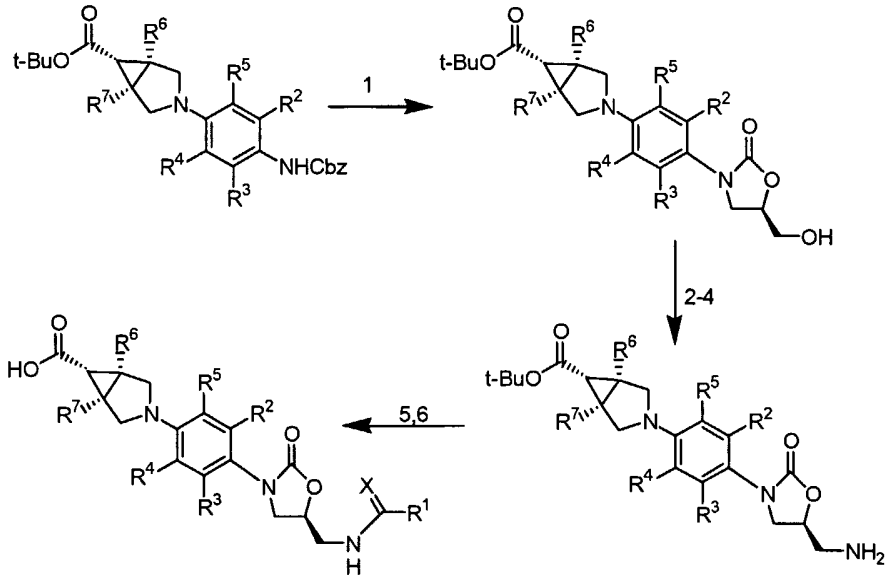
Step **4** of Scheme I involves the introduction of benzyloxycarbonyl protection on the aniline formed in step **3**. This is a standard transformation that is typically carried out by reaction of the amine with benzyl chloroformate or an equivalent reagent (see Kocienski *Protecting Groups*; Georg Thieme Verlag: Stuttgart, 1994, pp. 195-199). The reaction is typically conducted at temperatures between 0°C and 25°C in organic solvents such as dichloromethane in the presence of amines such as triethylamine or pyridine. Optionally the reaction may be performed in aqueous solutions in the presence of inorganic bases such as sodium hydroxide or sodium bicarbonate.

Step **5** of Scheme I illustrates the construction of the oxazolidinone group from the aryl carbamate prepared in step **4**. Transformations of this type are known to those skilled in the art (see, e.g., International Publication WO 95/07271, published on 16 March 1995). In step **5** the oxazolidinone synthesis is performed with *S*-acetic acid 2-acetylamino-1-chloromethyl-ethyl ester (prepared according to the procedure described in US patent application, Serial No. 09/982157) to afford the acetylaminomethyl-substituted oxazolidinone. The reaction is performed in the presence of an organic base such as lithium *tert*-butoxide, in a polar organic solvent such as dimethylformamide, at temperatures of about 0°C to 25°C. The synthesis

is then completed in step **6** by hydrolysis of the *tert*-butyl ester. This transformation is conveniently accomplished with trifluoroacetic acid in dichloromethane at a temperature in the range of about 0°C to 24°C; however, other deprotection conditions can be employed.

Scheme II describes a general synthesis of aryloxazolidinone compounds substituted at C-5 with substituents other than simple acetylaminomethyl. The synthesis begins with the carbonylbenzyloxy-protected aniline, described in Scheme I. Step **1** of Scheme II involves the construction of an oxazolidinone ring bearing a hydroxymethyl group at the C-5 position. This reaction is accomplished with *R*-(-)-glycidyl butyrate or a similar glycidyl ester. The reaction is performed in the presence of organic base such as lithium hexamethyldisilylamide in organic solvents such as tetrahydrofuran, at temperatures of about -78°C to 25°C.

Scheme II



Steps **2-4** of Scheme II describe the transformation of a hydroxymethyl substituent into an aminomethyl substituent. This transformation is performed by initial conversion of the hydroxy group into an activated form (step **2**, Scheme II) such as an alkyl or aryl sulfonate, halide, or optionally by activation in accordance with Mitsunobu-type activation (see Fabiano et. al. *Synthesis*, 1987, p.190). These reactions are well known to those skilled in the art and are preferably performed with reagents such as methanesulfonyl chloride, *p*-toluenesulfonyl chloride, or with

dialkyl azodicarboxylates (for Mitsunobu reactions). The reactions are preferably carried out in organic solvents such as dichloromethane or tetrahydrofuran, and in the presence of acid-scavenging amines such as triethylamine or *N,N*-diisopropylethylamine a temperature of about 0°C to 40°C.

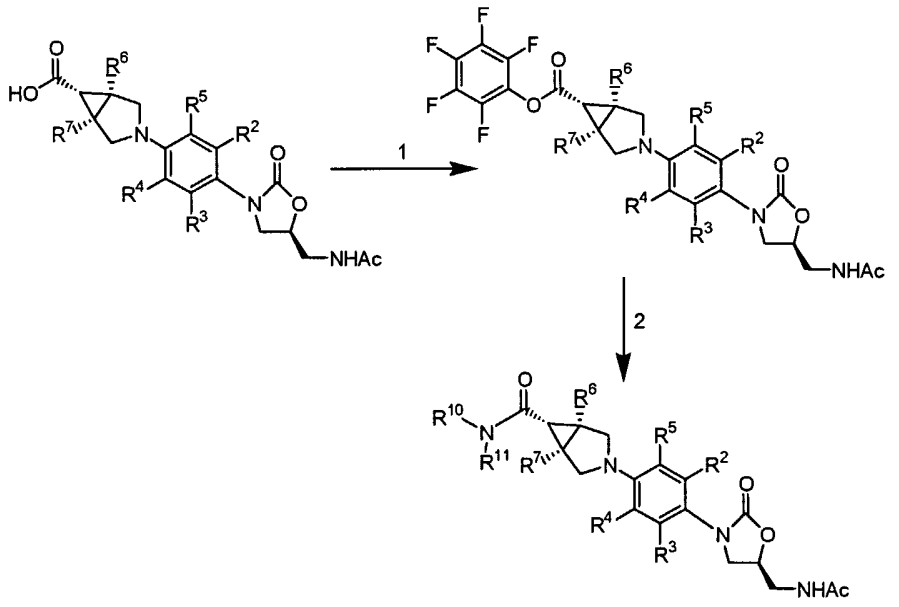
Step **3** of Scheme II involves reaction of the activated alcohol of step **2** with a nucleophilic nitrogen source. For reactions of alkyl or aryl sulfonates this is usually accomplished by reaction with an azide salt (e.g., sodium azide) in polar solvents such as acetone or dimethyl sulfoxide (optionally with added water) and at temperatures of about 50°C to 120°C. For Mitsunobu activation, hydrazoic acid is commonly employed as a nucleophilic nitrogen sources. The azide produced in step **3** is then reduced to the amine in step **4**. This transformation can be accomplished with a variety of inorganic reducing agents or by catalytic hydrogenation. An alternative and selective reduction of azides is accomplished by reaction with phosphines (Staudinger reaction). For example, reaction of the azidomethyl oxazolidinone with triphenylphosphine in an organic solvent such as tetrahydrofuran produces an iminophosphorane that is then hydrolyzed to the amine by the addition of water to the reaction mixture. The Staudinger reaction is preferably conducted at temperatures of about 20°C to 60°C.

Step **5** of Scheme II involves acylation or thioacylation of the amine intermediate using known art. Hence, acylations can be performed by reaction of the amine with carboxylic acid anhydrides, esters or acid chlorides. These transformations are usually performed at temperatures between 0°C and 50°C in solvents such as dichloromethane, acetonitrile, tetrahydrofuran, dimethylformamide, methanol, or mixtures thereof. These reactions are preferably performed in the presence of acid-scavenging amines such as triethylamine, pyridine, or potassium carbonate. Thioacylations are accomplished by reaction of the amines from step **4** with dithioesters or thionoesters in the presence of a tertiary amine base such as triethylamine. Preferred solvents for these reactions include tetrahydrofuran, dichloromethane or preferably methanol and the reactions are conducted in a temperature range from 20°C to 50°C. Other thiocarbonyl compounds of the Scheme II can be prepared according to procedures disclosed in PCT International

Publication WO 98/54161. Finally, the *tert*-butyl ester is hydrolyzed under similar conditions as described in step **6** of Scheme I.

Scheme III illustrates the preparation of aryloxazolidinone compounds bearing carboxamide substitution on the appended azabicyclo[3.1.0]hexane ring. The starting material for this Scheme is the carboxylic acid compound described in Scheme I. In step **1** of Scheme III this acid is activated as a pentafluorophenyl ester or similar activated ester. This ester is formed by reaction with pentafluorophenyltrifluoroacetate in the presence of an amine base such as pyridine and in a polar aprotic solvent such as dimethylformamide at temperatures of around 0°C and 40°C. In step **2** of Scheme III, the activated ester is reacted with an amine or other similar nucleophile. This transformation is preferably conducted in solvents such as dichloromethane, dimethylformamide, or ethyl acetate and in the presence of bases such as triethylamine, pyridine, or potassium carbonate.

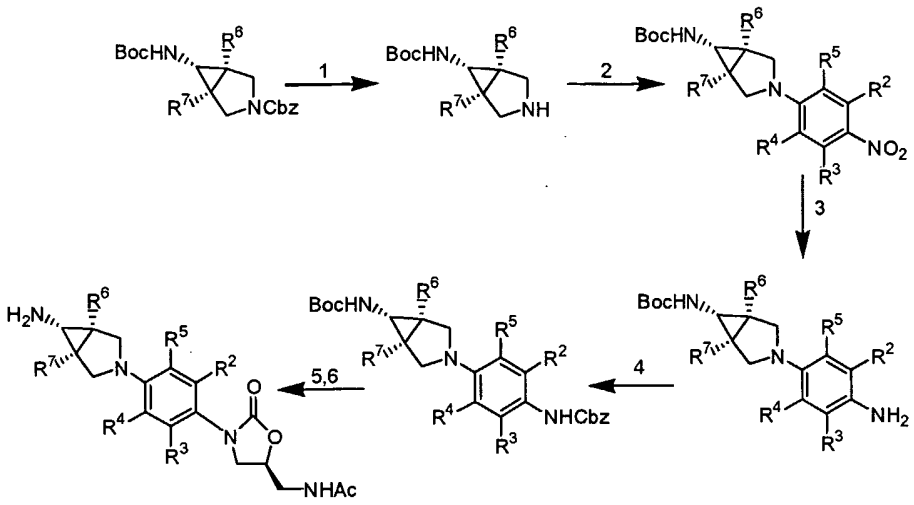
Scheme III



Scheme IV illustrates a general synthesis of aryloxazolidinone compounds bearing an amine substituent on the appended azabicyclo[3.1.0]hexane ring. The starting material shown is known art, prepared as described by Brighty *et al.* (in Synlett 1996, pp. 1097-1099). The desired *endo* isomer (Scheme I) was obtained after purification by silica gel column chromatography. In step **1** of the synthesis, the

benzyloxycarbonyl group is removed under conditions similar to those used in step **1** of Scheme I.

Scheme IV



Step **2** of Scheme IV involves a nucleophilic aromatic substitution reaction of the first intermediate with a substituted fluoronitro aromatic compound such as 3,4-difluoronitrobenzene or 3,4,5-trifluoronitrobenzene. This reaction is conducted under similar conditions as described in Scheme I.

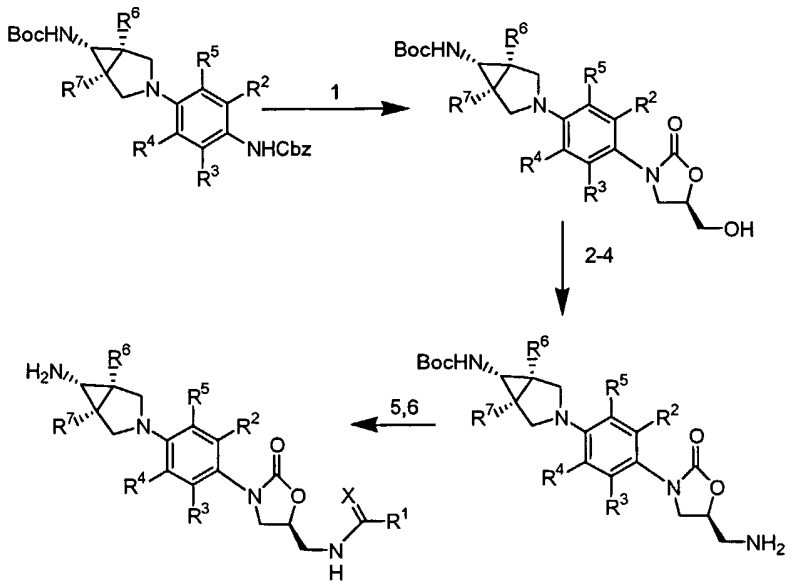
Step **3** of Scheme IV involves the reduction of the nitro substituent to an amino substituent. This reduction is accomplished under similar conditions as those described in Scheme I.

Step **4** of Scheme IV involves the introduction of benzyloxycarbonyl protection on the aniline formed in step **3**. This transformation is accomplished under similar conditions as those described in Scheme I.

Step **5** of Scheme IV illustrates the construction of the oxazolidinone group from the aryl carbamate prepared in step **4**. This transformation is accomplished under similar conditions as those described in Scheme I. The synthesis is then completed in step **6** by cleavage of the Boc-protected amine. This transformation is conveniently accomplished with hydrochloric acid in dioxane at a temperature in the range of about 0°C to 24°C; however, other deprotection conditions can be employed.

Scheme V describes a general synthesis of oxazolidinone compounds substituted at C-5 with substituents other than simple acetylaminomethyl. The synthesis begins with the carbonylbenzyloxy-protected aniline, described in Scheme IV. Step **1** of Scheme V involves the construction of an oxazolidinone ring bearing a hydroxymethyl group at the C-5 position. This reaction is accomplished using conditions similar to those described in Scheme II.

Scheme V



Steps **2-4** of Scheme V describe the transformation of the hydroxymethyl substituent into an aminomethyl substituent. This transformation is performed by initial conversion (step **2**) of the hydroxy group into an activated form using conditions similar to those described in Scheme II.

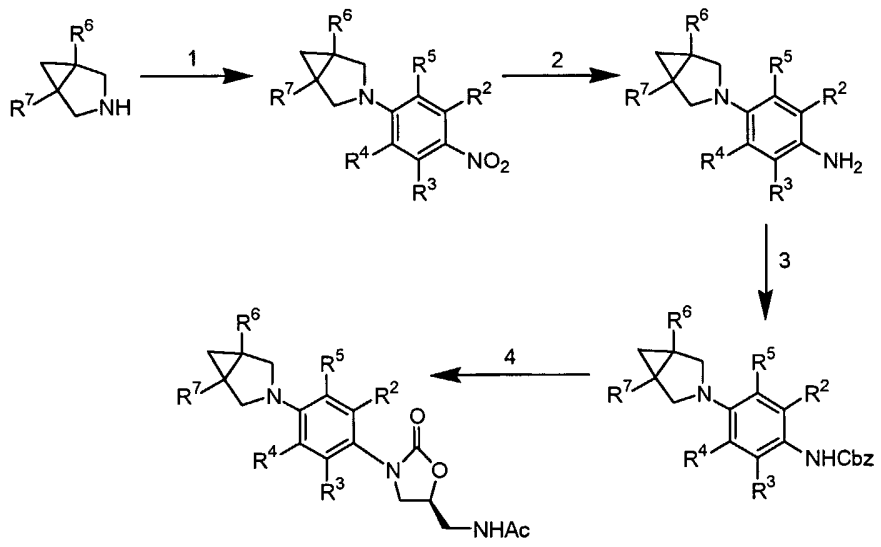
Step **3** of Scheme V involves reaction of the activated alcohol of step **2** with a nucleophilic nitrogen source to produce an azidomethyl substituent at C-5 of the oxazolidinone ring. This transformation can be accomplished using procedures similar to those described in Scheme II. The azide produced in step **3** is then reduced to the amine in step **4**. This transformation can be accomplished using conditions similar to those described in Scheme II.

Step **5** of Scheme V involves acylation or thioacylation of the amine intermediate using known art. This transformation can be accomplished using conditions similar

to those described in Scheme II. Finally, the Boc group is removed under similar conditions as described in step **6** of Scheme IV.

Scheme VI describes the synthesis of aryloxazolidinone compounds appended to an unsubstituted azabicyclo[3.1.0]hexane ring. The starting material, 3-azabicyclo[3.1.0]hexane is known art and was prepared according to the known procedure (Kollmeyer, US patent 4,183,857).

Scheme VI



Step **1** of Scheme VI involves a nucleophilic aromatic substitution reaction of the starting material with a substituted fluoronitro aromatic compound such as 3,4-difluoronitrobenzene or 3,4,5-trifluoronitrobenzene. This reaction is conducted under similar conditions as described in Scheme I.

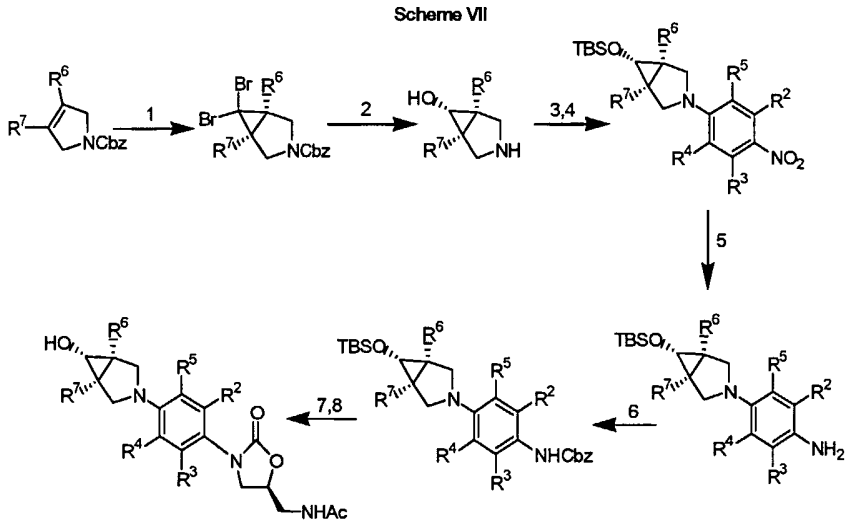
Step **2** of Scheme VI involves the reduction of the nitro substituent to an amino substituent. This reduction is accomplished under similar conditions as those described in Scheme I.

Step **3** of Scheme VI involves the introduction of benzyloxycarbonyl protection on the aniline formed in step **2**. This transformation is accomplished under similar conditions as those described in Scheme I.

Step **4** of Scheme VI illustrates the construction of the oxazolidinone group from the aryl carbamate prepared in step **3**. This transformation is accomplished under similar conditions as those described in Scheme I.

Scheme VII describes the synthesis of aryloxazolidinone compounds bearing a hydroxyl group on the appended azabicyclo[3.1.0]hexane ring. The starting material is commercially available and step **1** of Scheme VII involves the suprafacial addition of dibromocarbene to the olefin function of the starting material. This is known art and the dibromocarbenes can be generated from bromoform under phase transfer conditions (Markosza et. al. *Rocz. Chem.* 1976, vol. 50, p.2223). This reaction is preferably conducted in mixtures of aqueous base and a solvent such as dichloromethane in the presence of a phase-transfer catalyst such as an ammonium salt. The transformation is carried out at temperatures of around 0°C to 40°C.

Scheme VII



Step **2** of Scheme VII involves the conversion of the dibromocyclopropane ring to an *endo* cyclopropanol ring. This transformation is known art and was carried out according to the literature procedure (Danheiser et. al. J. Org. Chem. 1985, vol. 50, pp.2401-2403).

Step **3** of Scheme VII involves a nucleophilic aromatic substitution reaction of the starting material with a substituted fluoronitro aromatic compound such as 3,4-

difluoronitrobenzene or 3,4,5-trifluoronitrobenzene. This reaction is conducted under similar conditions as described in Scheme I.

Step **4** of Scheme VII involves the protection of the hydroxyl group of the cyclopropane ring as a trialkylsilyl ether. This standard organic transformation is carried out with a trialkylsilyl chloride or triflate in solvents such as dichloromethane or dimethylformamide and in the presence of a tertiary amine base such as triethylamine at a temperature of about –20°C to 40°C.

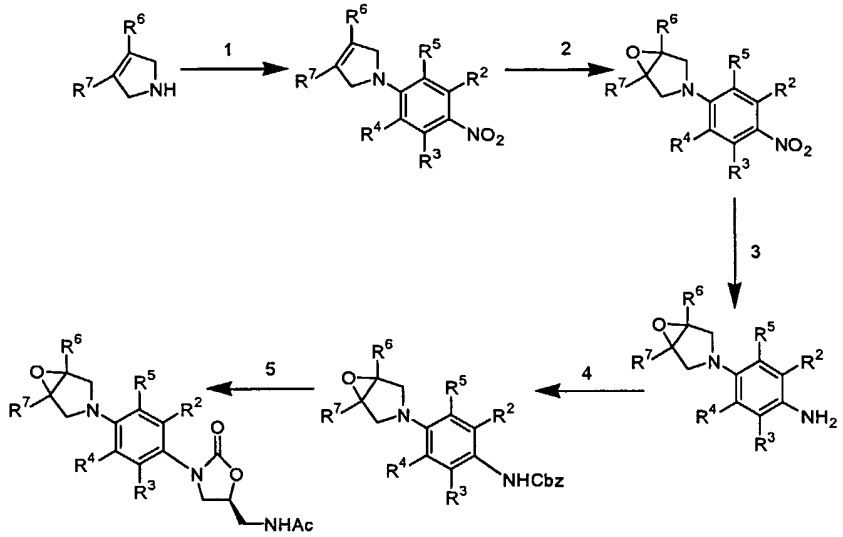
Step **5** of Scheme VII involves the reduction of the nitro substituent to an amino substituent. This reduction is accomplished under similar conditions as those described in Scheme I.

Step **6** of Scheme VII involves the introduction of benzyloxycarbonyl protection on the aniline formed in step **5**. This transformation is accomplished under similar conditions as those described in Scheme I.

Step **7** of Scheme VII illustrates the construction of the oxazolidinone group from the aryl carbamate prepared in step **6**. This transformation is accomplished under similar conditions as those described in Scheme I. Finally, in step **8** of Scheme VII the silyl ether is preferably removed by reaction with hydrofluoric acid in a solvent mixture of acetic acid, water, and tetrahydrofuran; however, other deprotection conditions can be employed.

Scheme VIII illustrates a general synthesis of aryloxazolidinone compounds bearing an 6-oxa-3-azabicyclo[3.1.0]hexyl ring. Step **1** of Scheme VIII involves a nucleophilic aromatic substitution reaction of the commercially available starting material, 3-pyrroline, with a substituted fluoronitro aromatic compound such as 3,4-difluoronitrobenzene or 3,4,5-trifluoronitrobenzene. This reaction is conducted under similar conditions as described in Scheme I.

Scheme VIII



Step **2** of Scheme VIII involves epoxidation of the *N*-arylpyrroline prepared in Step **1**. This reaction can be accomplished with an oxidant such as hydrogen peroxide in the presence of a base such as potassium bicarbonate (see Chaudhuri, N. K.; Ball, T. J. in J. Org. Chem. 1982, vol. 47, pp. 5196-5198). The reaction is conducted in the presence of acetonitrile, in alcohol solvents such as methanol and at temperatures of about 5°C to 40°C. An alternate 3-step synthesis of this intermediate involves (1) the oxidation of commercial benzyl 3-pyrroline-1-carboxylate with an oxidant such as 3-chloroperoxybenzoic acid in solvents such as dichloromethane, followed by (2) removal of the Cbz group (using the conditions of Step **1**, Scheme I) and (3) reaction of the product, 6-oxa-3-azabicyclo[3.1.0]hexane, with substituted fluoronitro aromatic compounds as described in Step **2**, Scheme I

Step **3** of Scheme VIII involves the reduction of the nitro substituent to an amino substituent. This reduction is accomplished under similar conditions as those described in Scheme I.

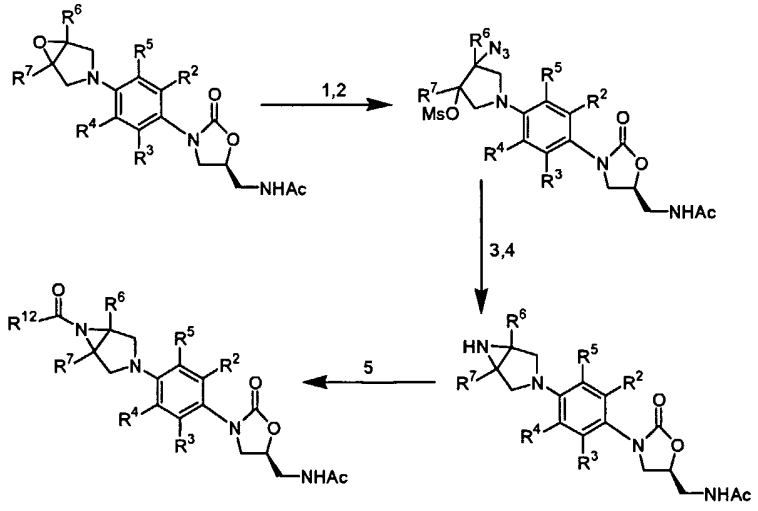
Step **4** of Scheme VII involves the introduction of benzyloxycarbonyl protection on the aniline formed in Step **3**. This transformation is accomplished under similar conditions as those described in Scheme I.

Step **5** of Scheme VIII illustrates the construction of the oxazolidinone group from the aryl carbamate prepared in Step **4**. This transformation is accomplished under similar conditions as those described in Scheme I.

Scheme IX illustrates the preparation of aryl oxazolidinone compounds bearing a 3,6-diazabicyclo[3.1.0]hexyl ring. The synthesis begins with the 6-oxa-3-azabicyclo[3.1.0]hexyl-substituted aryl oxazolidinone described in Scheme VIII. Step **1** of Scheme IX involves the nucleophilic addition of azide anion to the epoxide ring of the starting material. This is a standard organic reaction that will be familiar to those skilled in the art. The reaction is conducted in polar solvents such as acetone or dimethyl sulfoxide (optionally with added water) and at temperatures of about 50°C to 120°C.

In Step **2** of Scheme IX, the azido alcohol prepared in Step **1** is activated, for example, as a sulfonate ester such as a mesylate or tosylate. These reactions are well known to those skilled in the art and are preferably performed with reagents such as methanesulfonyl chloride or *p*-toluenesulfonyl chloride. The reactions are preferably carried out in organic solvents such as dichloromethane or tetrahydrofuran, and in the presence of acid-scavenging amines such as triethylamine or *N,N*-diisopropylethylamine a temperature of about 0°C to 40°C.

Scheme IX



In Step **3** of Scheme IX, the azide group is reduced to an amino functionality. This can be accomplished using the Staudinger reaction or one of the alternate reductions described for Step **4**, Scheme II. In Step **4** of Scheme IX, the amine from Step **3** is cyclized to an aziridine by treating the reaction mixture with aqueous potassium hydroxide or a similar base. This method for preparing aziridines is well-known to those skilled in the art and has been used previously to prepare the 3,6-diazabicyclo[3.1.0]hexyl ring system (see, e.g., International Publication WO 96/01262, published on 18 January 1996).

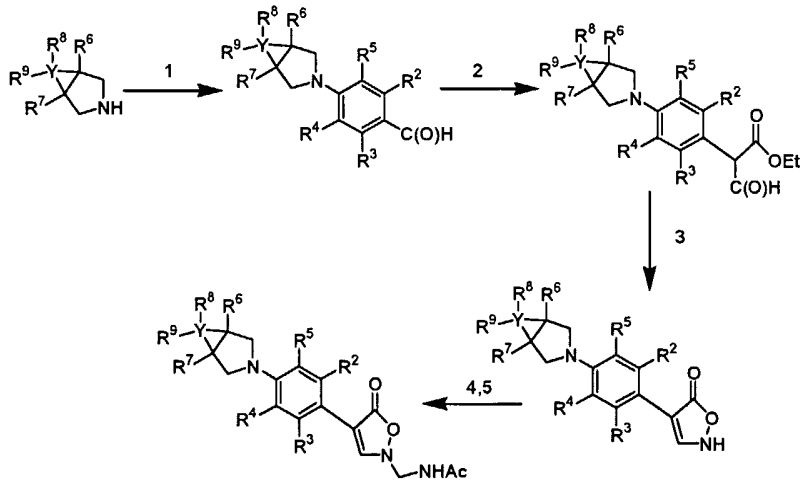
Step **5** of Scheme IX involves acylation of the aziridine described in Step **4** using known art. Hence, acylations can be performed by reaction of the amine with carboxylic acid anhydrides, esters or acid chlorides. These transformations are usually performed at temperatures between 0°C and 50°C in solvents such as dichloromethane, acetonitrile, tetrahydrofuran, dimethylformamide, methanol, or mixtures thereof. These reactions are preferably performed in the presence of acid-scavenging amines such as triethylamine, pyridine, or potassium carbonate. Alternatively, coupling reactions may be carried out between the aziridine (from Step **4**) and carboxylic acids using coupling regents such as DCC, HATU, or PyBop. These coupling reactions are known art and are typically conducted in solvents such as dichloromethane or dimethylformamide and in the presence of acid-scavenging amines such as triethylamine or *N,N*-diisopropylethylamine.

Schemes X-XII describe the synthesis of arylisoxazolinone and arylisoxazoline compounds bearing bicyclic rings of the type described in Schemes I-IX. It will be apparent to those skilled in the art that the following schemes describe *general* methods that may be employed using the bicyclic heterocycles described in Schemes I-IX to prepare claimed structures possessing either an isoxazolinone or isoxazoline ring in place of the oxazolidinone ring shown in the previous Schemes. A person skilled in the art will also recognize that some modifications of the synthetic protocol may be required if certain functional groups are incompatible with the methods described. In these cases, suitable protecting groups may be employed to protect these functional groups from participating in undesired

reactions, see "Protecting Groups" by Philip J. Kocienski (publisher: Georg Thieme Verlag: Stuttgart, 1994).

As shown in Scheme X, a bicyclic amine of the type described in Schemes I-IX can be reacted with a substituted fluorobenzaldehyde such as 4-fluorobenzaldehyde or 3,4-difluorobenzaldehyde to prepare the aryl aldehyde intermediate shown (Step **1**). Step **2** of Scheme X involves reaction of the fluorobenzaldehyde intermediate with ethyl diazoacetate (as described in Mahmood et al.,**1998** *J. Org. Chem.*, 63, pgs. 3333-3336) to provide the ester aldehyde intermediate shown. Addition of hydroxylamine, followed by warming to reflux in aqueous methanol, yields the arylisoxazolinone (Step **3**). This intermediate is then is converted to the corresponding methylacetamide (Step **4**) by reaction with N-(hydroxymethyl)acetamide acetate (prepared as described by Barnes et al in US Patent 5,284,863) in a polar aprotic solvent such as DMF. In an optional Step **5**, removal of a protecting group on amino, alcohol, or acid function of the bicyclic ring may be required. This deprotection is accomplished according to the methods described in Schemes I, IV, and VII.

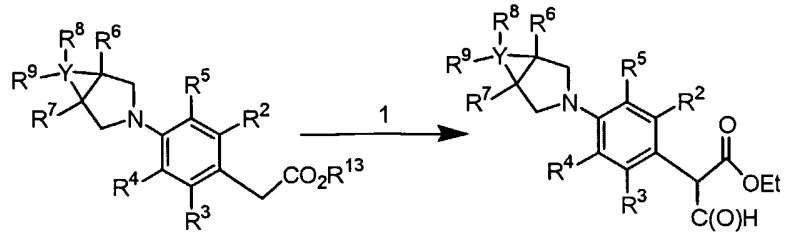
Scheme X



Scheme XI describes an alternate synthesis of the ester aldehyde intermediate of Scheme X. The starting aryl acetic ester is prepared from commercial starting materials and bicyclic heterocycles (described in Schemes I-IX) using known art (as outlined by Snyder and Zheng, International Publication WO 00/10566). Reaction of the aryl acetic ester with sodium hydride and ethyl formate then

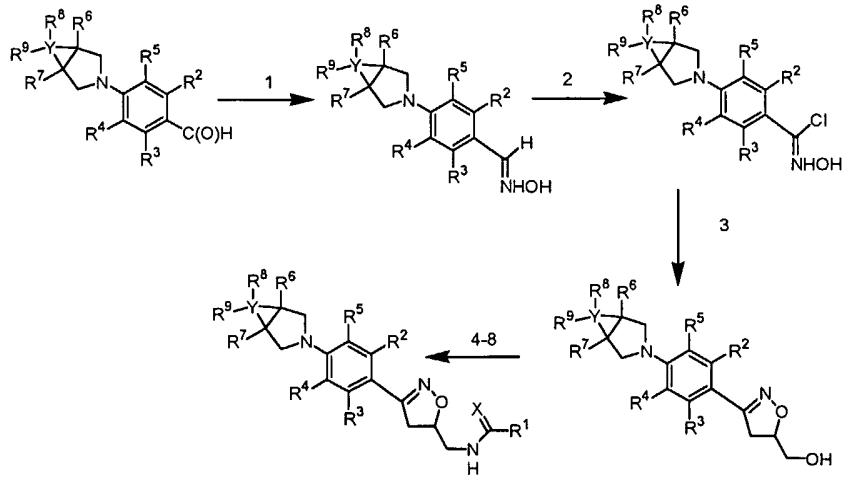
provides the ester aldehyde (Step **1**) that can be employed to prepare arylisoxazolinones using the procedures described in Steps **3-5** of Scheme X.

Scheme XI



Scheme XII describes a general method for preparing arylisoxazoline compounds bearing bicyclic heterocycles of the type described in Schemes I-IX. The starting materials for this Scheme are substituted benzaldehydes that can be prepared as described in Step **1** of Scheme X. In Step **1** of Scheme XII the substituted benzaldehyde is reacted with hydroxylamine hydrochloride in a polar protic solvent, such as methanol, in the presence of a base, such as pyridine, to afford the oxime.

Scheme XII

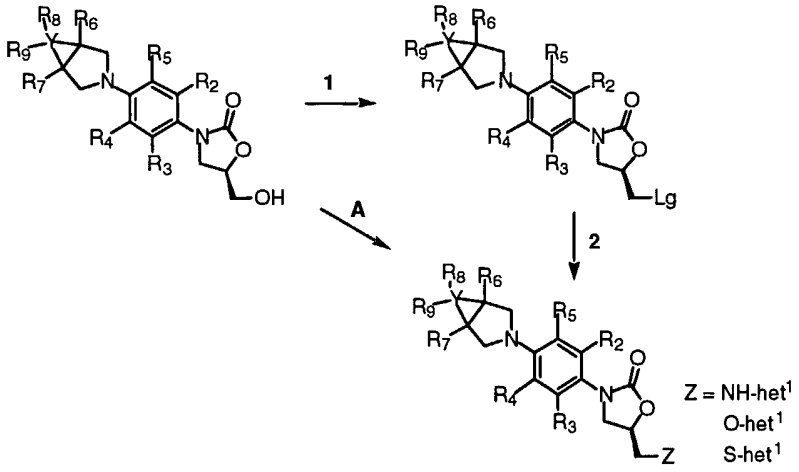


In Step **2** of Scheme XII, the oxime is oxidized with N-chlorosuccinamide (NCS) in an appropriate solvent, such as dichloromethane, to give the oximyl chloride. In Step **3**, the oximyl chloride is reacted with an allylic compound such as allyl alcohol or N-acetylallylamine, in the presence of a base such as triethylamine and in a solvent such as dichloromethane (DCM), to provide hydroxymethyl or

acetamidomethyl substituted isoxazolines (Step **3**). Alternatively, the oximyl chloride can be formed in situ and directly treated with the allylic compound. The hydroxymethyl analog shown can then be elaborated to substituted amide or thioamide analogs (Steps **4-7**) using the general methods of Scheme II. In an optional Step **8**, removal of a protecting group on amino, alcohol, or acid function of the bicyclic ring may be required. This deprotection is accomplished according to the methods described in Schemes I, IV, and VII.

Schemes XIII-XV below describe general methods for the preparation of compounds **I** in which Z = NHhet^1, Ohet^1, Shet^1, or het^2. The structures shown are those in which A = oxazolidinone; those skilled in the art will recognize that analogous procedures may be employed when A = isoxazolinone or isoxazoline. The synthesis of analogs in which Z = NHhet^1, Ohet^1, Shet^1 may be accomplished as shown in Scheme XIII. The starting materials for this procedure are hydroxymethyl compounds (described in previous schemes) and conversion of these intermediates to the final compounds is known art (see Gravestock, M. B., International Publications WO 99/64417 and WO 00/21960).

SCHEME XIII

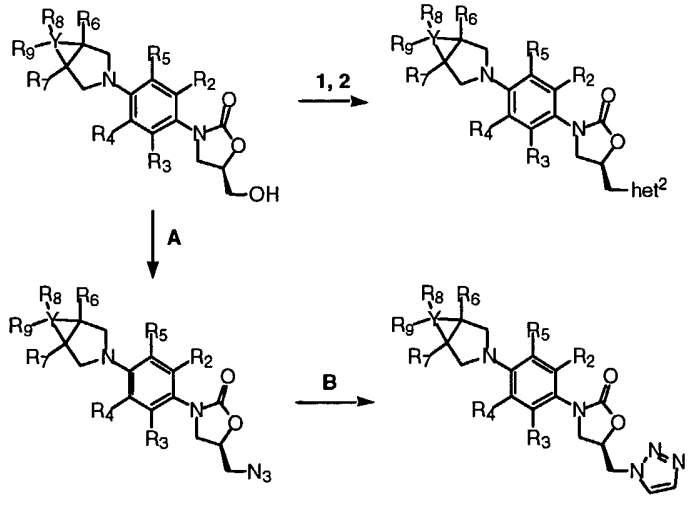


In Step **1** of Scheme XIII, the hydroxy group is converted to a displaceable group (Lg) such as alkyl or aryl sulfonate, bromide, or iodide. This activation may be accomplished according to procedure known to those skilled in the art, and as described for Step **2**, Scheme II. In Step **2** of Scheme XIII, the activated hydroxy compound is reacted with a compound of the formula HN(Pg)het^1, HOhet^1, HShet^1

or the corresponding metal alkoxide salts M-N(Pg)het[1], M-Ohet[1], M-Shet[1] where M is an alkali metal or another metal known to promote O-alkylation (e.g., silver) and "Pg" is a suitable protecting group. Alternatively, the hydroxymethyl starting material may be reacted directly with compounds of the formula HN(Pg)het[1], HOhet[1], HShet[1] (Step **A**) under Mitsunobu activation as described for Scheme II. As an optional final step, deprotection of various protecting groups may be required and the formation of pharmaceutically acceptable salts or *in vivo* hydrolysable esters may be desirable.

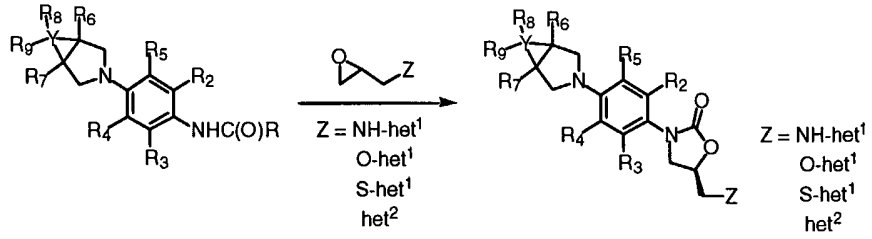
The synthesis of analogs in which Z = het[2] may be accomplished as shown in Scheme XIV. Preparation of these analogs from hydroxymethyl oxazolidinones is known art (see Gravestock, M. B., Betts, M. J., and Griffin, D. A., International Publications WO 01/81350). In Step **1**, the hydroxy group is converted to a displaceable group (Lg) such as alkyl or aryl sulfonate, bromide, or iodide using known art. In Step **2**, this intermediate is reacted with het[2]-H in the free base form or as the anion het[2]- formed from the free base. An alternative method for 1,2,3-triazoles involves conversion of the hydroxy group to the azide in Step **A** (as described for Scheme II) followed by cycloaddition with norbornadiene (Step **B**). As an optional final step, deprotection of various protecting groups may be required and the formation of pharmaceutically-acceptable salts or *in vivo* hydrolysable esters may be desirable.

SCHEME XIV



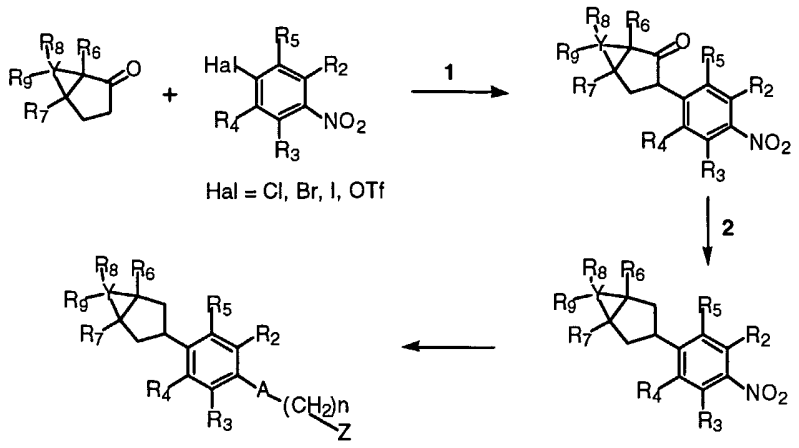
Scheme XV describes an alternative method for the preparation of the analogs described in Schemes XIII and XIV. This method is known art (see see Gravestock, M. B., International Publications WO 99/64417 and WO 00/21960; Gravestock, M. B., Betts, M. J., and Griffin, D. A., International Publications WO 01/81350). Reaction of carbamates (prepared as described in previous Schemes) with epoxides of the formula $CH_2(O)CHCH_2$-het^2, $CH_2(O)CHCH_2$-NHhet^1, $CH_2(O)CHCH_2$-Ohet^1, or $CH_2(O)CHCH_2$-Shet^1 provides the desired compounds. As an optional final step, deprotection of various protecting groups may be required and the formation of pharmaceutically-acceptable salts or *in vivo* hydrolysable esters may be desirable.

SCHEME XV



Scheme XVI describes a process for the preparation of compounds of formula **I** in which X = CH. The starting cyclopentanones may be prepared using known art (see for example Pedregal, C. et al. Tet. Lett. 1997, 38, pp. 2133-2136). Reaction of the cyclopentanone with substituted aryl chlorides or bromides using known Pd(0) chemistry (see for example Buchwald, S. L. et. al. J. Am. Chem. Soc. 2000, 122, pp. 1360-1370) then provides the aryl ketone intermediate (Step **1**). In Step **2**, the ketone group is removed using one of the known methods for this transformation (for a review see Reusch in *Reduction*, Augustine Ed.; Marcel Dekker:New York, 1968, pp. 171-211). The remaining steps involve conversion of the nitro function to a carbamate and subsequent installation of oxazolidinone, isoxazolinone or isoxazoline rings. These final steps are accomplished according to the procedures described in the previous schemes. As an optional final step, deprotection of various protecting groups may be required and the formation of pharmaceutically-acceptable salts or *in vivo* hydrolysable esters may be desirable.

SCHEME XVI



Utility and Testing

The compounds of the subject invention exhibit potent activities against a variety of organisms, including gram positive and gram negative bacteria. Accordingly, the compounds of the subject invention have broad antibacterial activity. Thus, the compounds of the present invention are useful antimicrobial agents and may be effective against a number of human and veterinary pathogens, including gram positive aerobic bacteria such as multiply-resistant staphylococci and streptococci, Gram negative organisms such as *H. influenzae* and *M. catarrahlis*, as well as anaerobic organisms such as bacteroides and clostridia species, and acid-fast organisms such as *Mycobacterium tuberculosis* and *Mycobacterium avium*. In addition the compounds of the present invention are effective against infections in any area of the body including but not limited to the eyes and the skin.

The *in vitro* activity of compounds of the subject invention may be assessed by standard testing procedures such as the determination of minimum inhibitory concentration (MIC) by agar dilution as described in "Approved Standard. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically," 3rd ed., published 1993 by the National Committee for Clinical Laboratory standards, Villanova, Pennsylvania, USA.

The *in vitro* MICs of test compounds may be determined by a standard agar dilution method. A stock drug solution of each analog is prepared in a preferred solvent, usually DMSO:H_2O (1:3). Serial 2-fold dilutions of each sample are made

using 1.0 ml aliquots of sterile distilled water. To each 1.0 ml aliquot of drug is added 9 ml of molten Mueller Hinton agar medium. The drug-supplemented agar is mixed, poured into 15 X 100 mm petri dishes, and allowed to solidify and dry prior to inoculation.

Vials of each of the test organisms are maintained frozen in the vapor phase of a liquid nitrogen freezer. Test cultures are grown overnight at 35°C on the medium appropriate for the organism. Colonies are harvested with a sterile swab, and cell suspensions are prepared in Trypticase Soy broth (TSB) to equal the turbidity of a 0.5 McFarland standard. A 1:20 dilution of each suspension is made in TSB. The plates containing the drug supplemented agar are inoculated with a 0.001 ml drop of the cell suspension using a Steers replicator, yielding approximately 10^4 to 10^5 cells per spot. The plates are incubated overnight at 35°C.

Following incubation the Minimum Inhibitory Concentration (MIC μg/ml), the lowest concentration of drug that inhibits visible growth of the organism, is read and recorded. For comparison, linezolid has an MIC of 4 μg/mL against S. aureus (UC9213), 1 μg/mL against S. pneumoniae (UC 9912) and 16 μg/mL against H. influenza (30063). The compounds synthesized in Examples 1 – 48 all had an MIC of 32 μg/mL or less against S. aureus (UC9213), 16 μg/mL or less against S. pneumoniae (UC 9912) and 64 μg/mL or less against H. influenza (30063), with the exception of the compounds in Examples 3, 13, 16, 17, 28 and 44-48 which had an MIC of >64 μg/mL against H. influenza (30063).

Administration and Pharmaceutical Formulations

In general, the compounds of the subject invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. The actual amount of the compound of the subject invention, i.e., the active ingredient, will depend on a number of factors, such as the severity of the disease, i.e., the infection, to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, and other factors.

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50} /ED_{50}. Compounds that exhibit large therapeutic indices are preferred.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range which includes the IC_{50} (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

When employed as pharmaceuticals, the compounds of the subject invention are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, or parenteral, rectal, transdermal, topical, subcutaneous, intravenous, intramuscular, and intranasal routes. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of the subject invention above associated with pharmaceutically acceptable carriers. In making the compositions of this invention, the active ingredient is usually mixed with an excipient, diluted by

an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methylcellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The quantity of active component, that is the compound according to the subject invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the potency of the particular compound and the desired concentration.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Preferably, the compound of the subject invention above is employed at no more than about 20 weight percent of the pharmaceutical composition, more preferably no more than about 15 weight percent, with the balance being pharmaceutically inert carrier(s).

The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically or therapeutically effective amount. It, will be understood, however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the severity of the bacterial infection being treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

In therapeutic use for treating, or combating, bacterial infections in warm-blooded animals, the compounds or pharmaceutical compositions thereof will be administered orally, topically, transdermally, and/or parenterally at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which will be antibacterially effective. Generally, such antibacterially or therapeutically effective amount of dosage of active component (i.e., an effective dosage) will be in the range of about 0. 1 to about 100, more preferably about 1.0 to about 50 mg/kg of body weight/day.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When

referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as corn oil, cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder

compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

The following formulation examples illustrate representative pharmaceutical compositions of the present invention.

Formulation Example 1

Hard gelatin capsules containing the following ingredients are prepared:

Ingredient	Quantity (mg/capsule)
Active Ingredient	30.0
Starch	305.0
Magnesium stearate	5.0

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

Formulation Example 2

A tablet formula is prepared using the ingredients below:

Ingredient	Quantity (mg/tablet)
Active Ingredient	25.0
Cellulose, microcrystalline	200.0
Colloidal silicon dioxide	10.0
Stearic acid	5.0

The components are blended and compressed to form tablets, each weighing 240 mg.

Formulation Example 3

A dry powder inhaler formulation is prepared containing the following components:

Ingredient	Weight %
Active Ingredient	5
Lactose	95

The active ingredient is mixed with the lactose and the mixture is added to a dry powder inhaling appliance

Formulation Example 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

Ingredient	Quantity (mg/tablet)
Active Ingredient	30.0 mg
Starch	45.0 mg
Microcrystalline cellulose	35.0 mg
Polyvinylpyrrolidone (as 10% solution in sterile water)	4.0 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1.0 mg
Total	120 mg

The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50°C to 60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

Formulation Example 5

Capsules, each containing 40 mg of medicament are made as follows:

Ingredient	Quantity (mg/capsule)
Active Ingredient	40.0 mg
Starch	109.0 mg
Magnesium stearate	1.0 mg
Total	150.0 mg

The active ingredient, starch and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

Formulation Example 6

Suppositories, each containing 25 mg of active ingredient are made as follows:

Ingredient	Amount
Active Ingredient	25 mg
Saturated fatty acid glycerides to	2,000 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

Formulation Example 7

Suspensions, each containing 50 mg of medicament per 5.0 mL dose are made as follows:

Ingredient	Amount
Active Ingredient	50.0 mg
Xanthan gum	4.0 mg
Sodium carboxymethyl cellulose (11%) Microcrystalline cellulose (89%)	50.0 mg
Sucrose	1.75 g
Sodium benzoate	10.0 mg
Flavor and Color	q.v.
Purified water to	5.0 mL

The active ingredient, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

Formulation Example 8

Ingredient	Quantity (mg/capsule)
Active Ingredient	15.0 mg
Starch	407.0 mg
Magnesium stearate	3.0 mg
Total	425.0 mg

The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 425.0 mg quantities.

Formulation Example 9

A subcutaneous formulation may be prepared as follows:

Ingredient	Quantity
Active Ingredient	5.0 mg
Corn Oil	1.0 mL

Formulation Example 10

A topical formulation may be prepared as follows:

Ingredient	Quantity
Active Ingredient	1-10 g
Emulsifying Wax	30 g
Liquid Paraffin	20 g
White Soft Paraffin	to 100 g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system used for the transport of biological factors to specific anatomical regions of the body is described in U.S. Patent 5,011,472, which is incorporated herein by reference in its entirety.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions that can transiently open the blood-brain barrier.

Other suitable formulations for use in the present invention can be found in *Remington's Pharmaceutical Sciences,* Mace Publishing Company, Philadelphia, PA, 17th ed. (1985).

As noted above, the compounds described herein are suitable for use in a variety of drug delivery systems described above. Additionally, in order to enhance the *in vivo* serum half-life of the administered compound, the compounds may be encapsulated, introduced into the lumen of liposomes, prepared as a colloid, or other conventional techniques may be employed which provide an extended serum half-life of the compounds. A variety of methods are available for preparing liposomes, as described in, e.g., Szoka, et al., U.S. Patent Nos. 4,235,871, 4,501,728 and 4,837,028 each of which is incorporated herein by reference.

As noted above, the compounds administered to a patient are in the form of pharmaceutical compositions described above. These compositions may be sterilized by conventional sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 and 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention.

EXAMPLES

In the discussion above and in the examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

bm	=	broad multiplet
BOC	=	*tert*-butoxycarbonyl
bd	=	broad doublet
bs	=	broad singlet
CDI	=	1,1 *O*–carbodiimidazole
d	=	doublet
dd	=	doublet of doublets
dq	=	doublet of quartets
dt	=	doublet of triplets
DMF	=	dimethylformamide
DMAP	=	dimethylaminopyridine
DMSO	=	dimethyl sulfoxide
eq.	=	equivalents
g	=	grams
h	=	hours
HPLC	=	high pressure liquid chromatography
HATU	=	N-[(dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-yl-methylene]-N-methylmethanaminium hexafluorophosphate N-oxide
LG	=	leaving group
m	=	multiplet
M	=	molar
M%	=	mole percent
max	=	maximum
meq	=	milliequivalent
mg	=	milligram
mL	=	milliliter
mm	=	millimeter
mmol	=	millimol
q	=	quartet
s	=	singlet
t or tr	=	triplet
TBS	=	tributylsilyl
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
TLC	=	thin layer chromatography
p-TLC	=	preparative thin layer chromatography
µL	=	microliter
N	=	normality
MeOH	=	methanol
DCM	=	dichloromethane
HCl	=	hydrochloric acid
ACN	=	acetonitrile

MS	=	mass spectrometry
rt	=	room temperature
EtOAc	=	ethyl acetate
EtO	=	ethoxy
Ac	=	acetate
NMP	=	1-methyl-2-pyrrolidinone
μL	=	microliter
J	=	coupling constant
NMR	=	Nuclear magnetic resonance
MHz	=	megahertz
Hz	=	hertz
m/z	=	mass to charge ratio
min	=	minutes
Boc	=	*tert*-butoxycarbonyl
CBZ	=	benzyloxycarbonyl
DCC	=	1,3-dicyclohexylcarbodiimide
PyBop	=	benzotriazole-1-yl-oxy-trispyrrolidinophosphonium hexafluorophosphate

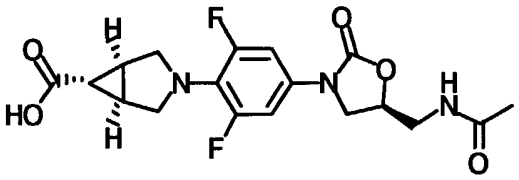
Additionally, the term "Aldrich" indicates that the compound or reagent used in the following procedures is commercially available from Aldrich Chemical Company, Inc., 1001 West Saint Paul Avenue, Milwaukee, WI 53233 USA; the term "Fluka" indicates that the compound or reagent is commercially available from Fluka Chemical Corp., 980 South 2nd Street, Ronkonkoma NY 11779 USA; the term "Lancaster" indicates that the compound or reagent is commercially available from Lancaster Synthesis, Inc., P.O. Box 100 Windham, NH 03087 USA; the term "Sigma" indicates that the compound or reagent is commercially available from Sigma, P.O. Box 14508, St. Louis MO 63178 USA; the term "Chemservice" indicates that the compound or reagent is commercially available from Chemservice Inc., Westchester, PA, USA; the term "Bachem" indicates that the compound or reagent is commercially available from Bachem Bioscience Inc., 3700 Horizon Drive, Renaissance at Gulph Mills, King of Prussia, PA 19406 USA; the term "Maybridge" indicates that the compound or reagent is commercially available from Maybridge Chemical Co. Trevillett, Tintagel, Cornwall PL34 OHW United Kingdom; and the term "TCI" indicates that the compound or reagent is commercially available from TCI America, 9211 North Harborgate St., Portland, Oregon, 97203, OR, USA; the term "Alfa" indicates that the compound or reagent is commercially available from Johnson Matthey Catalog Company, Inc. 30 Bond Street, Ward Hill, MA 01835-0747; and the term "Nova Biochem" indicates that

the compound or reagent is commercially available from NovaBiochem USA, 10933 North Torrey Pines Road, P.O. Box 12087, La Jolla CA 92039-2087.

In the examples below, all temperatures are in degrees Celsius (unless otherwise indicated) and the following general procedures were used to prepared the compounds as indicated.

Example 1.

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid



Trifluoroacetic acid (0.75 mL) was added to a solution of exo-(1R,5S)-3-{4-[(5S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2,6-difluoro-phenyl}-3-aza-bicyclo[3.1.0] hexane-6-carboxylic acid *tert*-butyl ester (0.129 g, 0.29 mmol) in 3 mL of dichloromethane. The solution was stirred for three hours and then concentrated to give the trifluoroacetic acid salt of exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid as a tan solid.

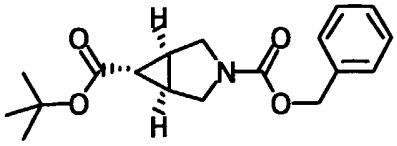
Yield 0.148 g (99%).

^{1}H NMR (300 MHz, DMSO): 1.65 (tr, J = 3 Hz, 1H), 1.82 (s, 3H), 2.03 (m, 2H), 3.37-3.69 (m, 7H), 4.05 (tr, J = 9 Hz, 1H), 4.71 (m, 1H), 7.23 (d, J = 12 Hz, 2H), 8.23 (tr, J = 6 Hz, 1H).

MS (m/z): $[M+H]^+ = 396$.

Intermediates for the preparation of Example 1 were synthesized as follows.

exo-(1R,5S)-3-benzyloxycarbonyl-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *t*-butyl ester

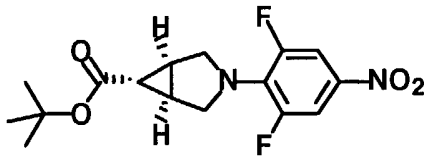


A solution of *tert*-butyl diazoacetate (2.9 mL, 21 mmol; Aldrich) in 10 mL of dichloromethane was added dropwise via syringe-pump over 3 days to a solution of benzyl 3-pyrroline-1-carboxylate (3.57 g, 17.6 mmol; Aldrich) in dichloromethane (70 mL). The green solution was then filtered through celite and concentrated. The crude material was subjected to column chromatography (0-20% ethyl acetate hexane). Unreacted benzyl 3-pyrroline-1-carboxylate elutes first, followed by the title compound and then by *endo* diastereomer.

Yield 1.39 g (25%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.42 (m, 1H), 1.44 (s, 9H), 2.03 (m, 2H), 3.49 (m, 2H), 3.73 (tr, J = 12 Hz, 2H), 5.10 (s, 2H), 7.30-7.40 (m, 5H).

II. exo-(1R,5S)-3-(2,6-Difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester

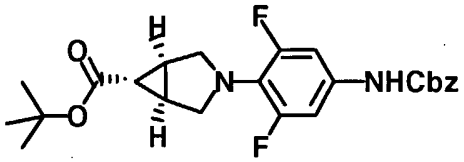


Palladium hydroxide (10% on carbon, 0.25 g) was added to a solution of exo-(1R,5S)-3-benzyloxycarbonyl-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *t*-butyl ester (0.800 g, 2.52 mmol) in 15 mL of methanol. The mixture was stirred under a hydrogen atmosphere for 1.5 h. The palladium was then removed by filtration through a pad of celite and the filtrate concentrated to give 0.423 g of exo-(1R,5S)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *t*-butyl ester.

Diisopropylethylamine (0.55 mL, 3.15 mmol) and 3,4,5-trifluoro-nitrobenzene (0.372 g, 2.1 mmol) were added to a solution of exo-(1R,5S)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *t*-butyl ester (0.423 g, 2.31 mmol) in 5 mL of DMF. The mixture was heated for 20 h at 50°C and then cooled to room temperature. The solution was diluted with ethyl acetate and washed with 0.5 M HCl, saturated $NaHCO_3$, brine, and dried ($MgSO_4$). The mixture was filtered and

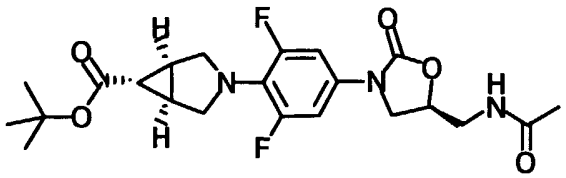
concentrated to provide exo-(1R,5S)-3-(2,6-difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester as a yellow solid.
Yield 0.791 g (92%).
^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.60 (m, 1 H), 2.13 (m, 2H), 3.77 (d, J = 11 Hz, 2H), 3.99 (d, J = 11 Hz, 2H), 7.72 (d, J = 9 Hz, 2H).

III. exo-(1R,5S)-3-(4-Benzyloxycarbonylamino-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.



Iron metal (0.39 g, 7.0 mmol) was added in five portions over 1 h to a refluxing solution of exo-(1R,5S)-3-(2,6-difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.79 g, 2.32 mmol) and ammonium chloride (1.25 g, 23.2 mmol) in 50 mL of 2:1 ethanol-H_2O. The rust colored mixture was refluxed for another 30 min and then cooled and filtered to remove iron oxide. 50 mL of H_2O was added to the filtrate and the mixture concentrated to remove ethanol. The resulting aqueous solution was extracted with three 25 mL portions of ethyl acetate and the combined organic phases washed with H_2O, brine, and dried ($MgSO_4$). Filtration and concentration gave the crude amine (0.59 g, 1.9 mmol) which was dissolved in 30 mL of dichloromethane. Pyridine (0.31 mL, 3.8 mmol) was added to the amine solution and after cooling to 0°C, benzyl chloroformate (0.32 mL, 2.2 mmol) was added. The mixture was stirred for 1 h at 0°C and for 30 min at room temperature. The reaction mixture was then diluted with dichloromethane and washed with H_2O, brine and then dried ($MgSO_4$). Concentration gave a yellow oil that was triturated with hexane to afford exo-(1R,5S)-3-(4-benzyloxycarbonylamino-2,6-difluoro-phenyl)-3-aza-bicyclo [3.1.0]hexane-6-carboxylic acid *tert*-butyl ester as a yellow solid.
Yield 0.71 g (69%).
^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.84 (m, 1H), 2.01 (m, 2H), 3.48 (s, 4H), 5.18 (s, 2H), 6.55 (s, 1 H), 6.91 (d, J = 11 Hz, 2H), 7.35-7.40 (m, 5 H).
MS (m/z): $[M+H]^+$ = 445.

IV. exo-(1R,5S)-3-{4-[(5S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2,6-difluoro-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.



Lithium butoxide solution (3.6 mmol of a 1.0 M THF solution, 3.6 mmol) was added to a cooled (0°C) solution of exo-(1R,5S)-3-(4-benzyloxycarbonyl-amino-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.53 g, 1.19 mmol) in DMF (0.8 mL) and MeOH (0.097 mL, 2.4 mmol). Solid (*S*)-acetic acid 2-acetylamino-1-chloromethyl-ethyl ester (0.457 g, 2.4 mmol) was then added and the solution allowed to warm to room temperature and stirred for 20 h. Saturated aqueous NH_4Cl (3 mL) was added, along with 15 mL of H_2O and 15 mL of brine. The solution was extracted with three portions of dichloromethane and the combined organic phases dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (0-2% MeOH-DCM) to provide pure exo-(1R,5S)-3-{4-[(5S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2,6-difluoro-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.

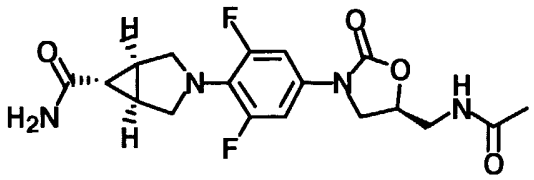
Yield 0.4 g (72 %).

^{1}H NMR (300 MHz, $CDCl_3$): 1.47 (s, 9 H), 1.81 (m, 1H), 2.01 (m, 2 H), 2.02 (s, 3H), 3.49-3.72 (m, 7 H), 3.97 (tr, J = 9 Hz, 1H), 4.75 (m, 1H), 6.10 (tr, J = 6 Hz, 1H), 7.03 (d, J = 11 Hz, 2H).

MS (m/z): $[M+H]^+ = 452$.

Example 2.

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxamide



Diisopropylethylamine (19 μL, 0.11 mmol) and HATU (21 mg, 0.055 mmol) were add to a solution of exo-(1R,5S)-3-{4-[(5S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2,6-difluoro-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid (14 mg of the TFA salt, 0.028 mmol; prepared as described for Example 1) in 0.7 mL of DMF. Ammonium chloride (3.0 mg, 0.055 mmol) was then added and the mixture stirred at room temperature for 5 hours. The reaction mixture was then concentrated and the crude product purified by preparative HPLC to provide exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxamide.

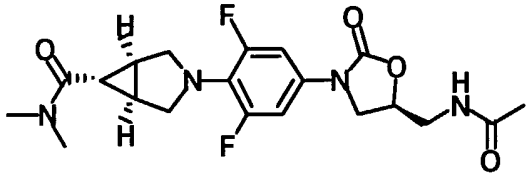
Yield 0.005 g (47%).

^{1}H NMR (300 MHz, DMSO): 1.76 (tr, J = 3 Hz, 1H), 1.82 (s, 3H), 1.87 (m, 2H), 3.37-3.70 (m, 7H), 4.06 (tr, J = 9 Hz, 1H), 4.71 (m, 1H), 6.81 (s, 1H), 7.23 (d, J = 12 Hz, 2H), 7.57 (s, 1H), 8.24 (tr, J = 6 Hz, 1H).

MS (m/z): $[M+H]^+ = 395$.

Example 3.

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N,N-dimethyl-3-azabicyclo[3.1.0]hexane-6-carboxamide



Diisopropylethylamine (23 μL, 0.13 mmol) and HATU (24 mg, 0.064 mmol) were add to a solution of exo-(1R,5S)-3-{4-[(5S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2,6-difluoro-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid (17 mg of the TFA salt, 0.033 mmol) in 0.8 mL of DMF. Dimethylamine (6.3 μl of a 40% aqueous soln, 0.049 mmol) was then added and the mixture stirred at room temperature for 4 hours. The reaction mixture was then concentrated and the crude product purified by preparative HPLC to provide exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N,N-dimethyl-3-azabicyclo[3.1.0]hexane-6-carboxamide.

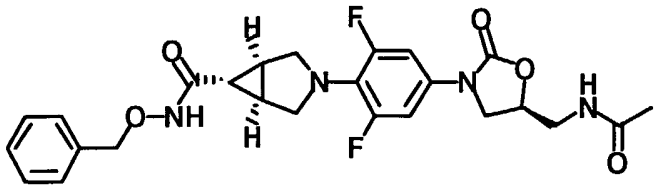
Yield 0.005 g (37%).

^{1}H NMR (300 MHz, DMSO): 1.82 (s, 3H), 1.94 (m, 2H), 1.97 (tr, J = 3Hz, 1H), 2.83 (s, 3H), 3.09 (s, 3H), 3.37-4.05 (m, 8H), 4.71 (m, 1H), 7.23 (d, J = 13 Hz, 2H), 8.23 (tr, J = 6 Hz, 1H).

MS (m/z): $[M+H]^+ = 423$.

Example 4.

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-(benzyloxy)-3-azabicyclo[3.1.0]hexane-6-carboxamide



Pyridine (0.014 mL, 0.17 mmol) and then pentafluorophenyltrifluoroacetate (0.015 mL, 0.086 mmol) were added to a solution of exo-(1R,5S)-3-{4-[(5S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2,6-difluoro-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid (0.022 g, 0.055 mmol) in 0.2 mL of DMF. The mixture was stirred at room temperature for 2 hours. The solution was then diluted with ethyl acetate and washed with dilute HCl, brine, and dried ($MgSO_4$), filtered and concentrated to give exo-(1R,5S)-3-{4-[(5S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2,6-difluoro-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid pentafluorophenyl ester (0.031 g, 0.055 mmol) that was dissolved in 0.3 mL of DMF. Diisopropylethylamine (0.014 mL, 0.083 mmol) and *O*-benzylhydroxylamine (7 μL, 0.066 mmol) were added to this solution. After 2 hours, the reaction mixture was diluted with ethyl acetate and washed with dilute HCl, brine, and dried ($MgSO_4$), filtered and concentrated. Purification by preparative TLC (5% MeOH-DCM) gave pure exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-(benzyloxy)-3-azabicyclo[3.1.0]hexane-6-carboxamide.

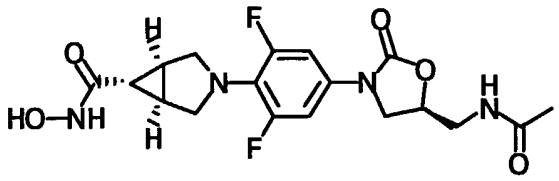
Yield 0.017 g (63%).

^{1}H NMR (300 MHz, DMSO): 1.64 (m, 1H), 1.82 (s, 3H), 1.95 (m, 2H), 3.33-3.45 (m, 6H), 3.67 (m, 1H), 4.05 (tr, J = 10 Hz, 1H), 4.71 (m, 1H), 4.79 (s, 2H), 7.23 (d, J = 12 Hz, 2H), 7.36-7.38 (m, 5H), 8.24 (tr, J = 5 Hz, 1H), 11.1 (s, 1H).

MS (m/z): $[M+H]^+ = 502$.

Example 5.

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-hydroxy-3-azabicyclo[3.1.0]hexane-6-carboxamide



10% Palladium on carbon (5 mg) was added to a solution of exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-(benzyloxy)-3-azabicyclo[3.1.0]hexane-6-carboxamide (0.013 g, 0.026 mmol) in 2 mL of ethanol. The mixture was stirred 2 hours under a hydrogen atmosphere and then filtered through celite. The filtrate was concentrated and the glassy solid obtained was lyophilized to give pure exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino) methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-hydroxy-3-azabicyclo [3.1.0]hexane-6-carboxamide as a white solid.

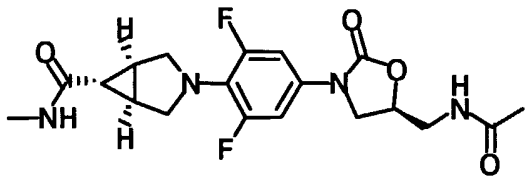
Yield 9 mg (84%).

^{1}H NMR (300 MHz, CD_3OD): 1.74 (tr, J = 3 Hz, 1H), 1.95 (s, 3H), 2.03 (m, 2H), 3.50-3.76 (m, 7H), 4.07 (tr, J = 9 Hz, 1H), 4.76 (m, 1H), 7.16 (d, J = 12 Hz, 2H).

MS (m/z): $[M+H]^+ = 411$.

Example 6.

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-methyl-3-azabicyclo[3.1.0]hexane-6-carboxamide



Lithium butoxide solution (1.16 mmol of a 1.0 M THF solution, 1.16 mmol) was added to a cooled (0°C) solution of exo-(1R,5S)-3-(4-benzyloxycarbonyl-amino-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid methylamide (0.116 g, 0.29 mmol) in DMF (0.20 mL) and MeOH (0.023 mL, 0.58 mmol). Solid (*S*)-acetic acid 2-acetylamino-1-chloromethyl-ethyl ester (0.112 g, 58 mmol)

was then added, and the solution allowed to warm to room temperature and stirred for 20 h. At this time the reaction was >80% complete by HPLC and the product had precipitated from solution. The mixture was treated with 0.5 mL of saturated NH_4Cl and then filtered. The solids were washed with plenty of water and then with ethyl acetate, and finally dried *in vacuo* to provide exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-methyl-3-azabicyclo[3.1.0]hexane-6-carboxamide as a tan solid.

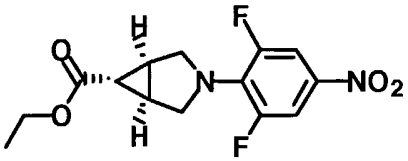
Yield 0.063 g (46% overall).

^{1}H NMR (300 MHz, DMSO): 1.74 (m, 1H), 1.82 (s, 3H), 1.88 (m, 2H), 2.57 (d, J = 5 Hz, 3H) , 3.16-3.41 (m, 4H), 3.66 (tr, J = 8 Hz, 1H), 4.06 (tr, J = 9 Hz, 1H), 4.71 (m, 1H), 7.23 (d, J = 12 Hz, 2H), 8.02 (q, J = 5 Hz, 1H), 8.23 (m, 1H).

MS (m/z): $[M+H]^+ = 409$.

Intermediates for the preparation of Example 6 were synthesized as follows.

exo-(1R,5S)-3-(2,6-Difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid ethyl ester



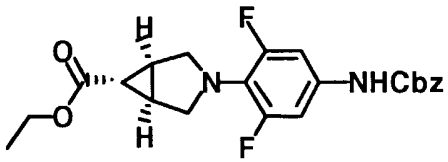
Palladium hydroxide (10% on carbon, 0.12 g) was added to a solution of exo-(1R,5S)-3-benzyloxycarbonyl-3-azabicyclo[3.1.0]hexane-6-carboxylic acid ethyl ester (0.25 g, 0.7 mmol; prepared as described in [Brighty, K. E., Castaldi, M. J. *Synlett*, **1996**, pp. 1097-1099]) in 2.5 mL of methanol. The mixture was stirred under a hydrogen atmosphere for 1.5 h. The palladium was then removed by filtration through a pad of celite and the filtrate concentrated to give 0.135 g of exo-(1R,5S)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid ethyl ester. Diisopropylethylamine (0.21 mL, 1.2 mmol) and trifluoronitrobenzene (0.139 g, 0.79 mmol) were added to a solution of exo-(1R,5S)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid ethyl ester (0.135 g, 0.87 mmol) in 1.7 mL of DMF. The mixture was heated for 3 days at 50°C and then cooled to room temperature. The solution was diluted with ethyl acetate and washed with 0.5 M HCl, saturated $NaHCO_3$,

brine, and dried ($MgSO_4$). The mixture was filtered and concentrated to give exo-(1R,5S)-3-(2,6-difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid ethyl ester as a yellow solid.

Yield 0.233 g (86%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.27 (tr, J = 7 Hz, 3H), 1.69 (tr, J = 3 Hz, 1H), 2.20 (m, 2H), 3.77 (d, J = 11 Hz, 2H), 3.99 (d tr, J = 11, 2 Hz, 2H), 4.14 (q, J = 7 Hz, 2H), 7.72 (d, J = 10 Hz, 2H).

II. exo-(1R,5S)-3-(4-Benzyloxycarbonylamino-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid ethyl ester.

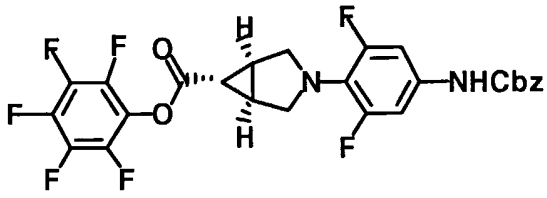


Iron metal (0.125 g, 2.21 mmol) was added in five portions over 1 h to a refluxing solution of exo-(1R,5S)-3-(2,6-difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid ethyl ester (0.230 g, 0.74 mmol) and ammonium chloride (0.395 g, 7.4 mmol) in 6 mL of 2:1 ethanol-H_2O. The rust colored mixture was refluxed for another 30 min and then cooled and filtered to remove iron oxide. 10 mL of H_2O was added to the filtrate and the mixture concentrated to remove ethanol. The resulting aqueous solution was extracted with three 15 mL portions of ethyl acetate and the combined organic phases washed with H_2O, brine, and dried ($MgSO_4$). Filtration and concentration gave the crude amine (0.186 g, 0.66 mmol) which was dissolved in 4 mL of dichloromethane. Pyridine (0.107 mL, 1.32 mmol) was added to the amine solution and after cooling to 0°C, benzyl chloroformate (0.108 mL, 0.76 mmol) was added. The mixture was stirred for 30 min at 0°C and for 30 min at room temperature. The reaction mixture was then diluted with dichloromethane and washed with H_2O, brine and then dried ($MgSO_4$). Concentration gave a yellow oil that was triturated with hexane to afford exo-(1R,5S)-3-(4-benzyloxycarbonylamino-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid ethyl ester as a yellow solid.

Yield 0.215 g (70%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.27 (tr, J = 7 Hz, 3H), 1.94 (tr, J = 3 Hz, 1H), 2.08 (m, 2H), 3.48 (m, 4H), 4.13 (q, J = 7 Hz, 2H), 5.18 (s, 2H), 5.57 (s, 1H), 6.91 (d, J = 11 Hz, 2H), 7.33-7.39 (m, 5H).

III. exo-(1R,5S)-3-(4-Benzyloxycarbonylamino-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid pentafluorophenyl ester.

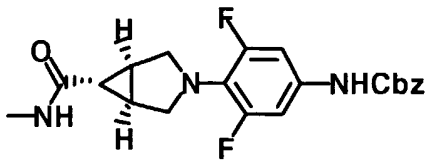


Sodium hydroxide (2.7 mL of a 1.0 M aqueous solution, 2.7 mmol) was added to a solution of exo-(1R,5S)-3-(4-benzyloxycarbonylamino-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid ethyl ester (0.140 g, 0.336 mmol) in 5 mL of THF. A catalytic quantity of benzyltriethylammonium chloride was then added and the mixture stirred for 3 days at room temperature. The reaction mixture was then treated with saturated $NaHCO_3$ and concentrated to remove THF. The resulting aqueous solution was acidified with 1M HCl and extracted with three portions of ethyl acetate. The combined organic extracts were then dried ($MgSO_4$), filtered and concentrated to give 0.113 g of exo-(1R,5S)-3-(4-benzyloxycarbonyl-amino-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid.

Pyridine (0.094 mL, 1.16 mmol) and then pentafluorophenyl trifluoroacetate (0.10 mL, 0.6 mmol) were added to a solution of exo-(1R,5S)-3-(4-benzyloxy-carbonylamino-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid (0.113 g, 0.29 mmol) in 1.2 mL of DMF. The mixture was stirred at room temperature for 2 hours. The solution was then diluted with ethyl acetate and washed with dilute HCl, brine, and dried ($MgSO_4$), filtered and concentrated to give exo-(1R,5S)-3-(4-benzyloxycarbonylamino-2,6-difluoro-phenyl)-3-aza-bicyclo [3.1.0]hexane-6-carboxylic acid pentafluorophenyl ester that was used without further purification.

Yield 0.161 g (86%).

IV. exo-(1R,5S)-3-(4-Benzyloxycarbonylamino-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid methylamide.



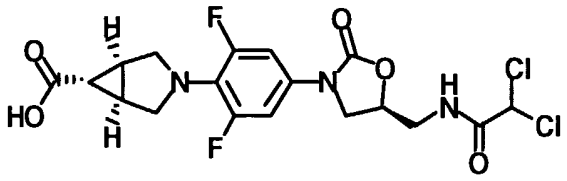
Methylamine (2mL of a 2.0 M solution in THF, 4.0 mmol) was added to a solution of exo-(1R,5S)-3-(4-benzyloxycarbonylamino-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid pentafluorophenyl ester (0.161 g, 0.29 mmol) in 1 mL of THF. The solution was stirred at room temperature for 2 h and concentrated. The resulting oil was taken into ethyl acetate and washed with 10% $NaHCO_3$, brine, and dried ($MgSO_4$), filtered and concentrated to provide crude exo-(1R,5S)-3-(4-benzyloxycarbonylamino-2,6-difluoro-phenyl)-3-aza-bicyclo [3.1.0]hexane-6-carboxylic acid methylamide that was used directly in the next step.

^{1}H NMR (300 MHz, $CDCl_3$): 1.66 (tr, J = 3 Hz, 1H), 2.05 (m, 2H), 2.81 (d, J = 5 Hz, 3H), 3.39-3.48 (m, 4H), 5.17 (s, 2H), 5.75 (br s, 1H), 6.93 (d, J = 11 Hz, 2H), 6.94 (br s, 1H), 7.33-7.40 (m, 5H).

MS (m/z): $[M+H]^+$ = 402.

Example 7.

exo-(1R,5S)-3-[4-((5S)-5-{[(dichloroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid



Exo-(1R,5S)-3-(4-{(5S)-[(2,2-dichloro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.22 g, 0.40 mmol) was dissolved in trifluoroacetic acid-dichloro-methane(5 mL, 1:4) and stirred for three hours at room temperature. The solution was then

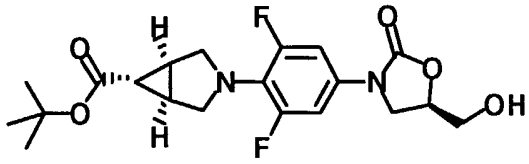
concentrated and the oil lyophilized from ACN-H_2O to provide exo-(1R,5S)-3-[4-((5S)-5-{[(dichloroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid.

Yield 0.185 g (89%).

^{1}H NMR (300 MHz, DMSO): 1.64 (tr, J = 3 Hz, 1H), 2.02 (m, 2H), 3.43 (m, 4H), 3.50 (m, 2H), 3.67 (dd, J = 9, 6 Hz, 1H), 4.09 (tr, J = 9 Hz, 1H), 4.78 (m, 1H), 6.47 (s, 1H), 7.21 (d, J = 12 Hz, 2H), 8.96 (tr, J = 5 Hz, 1H); MS (m/z): $[M+H]^+$ = 521.

Intermediates for the preparation of Example 7 were synthesized as follows.

exo-(1R,5S)-3-{2,6-Difluoro-4-[(5R)-hydroxymethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester



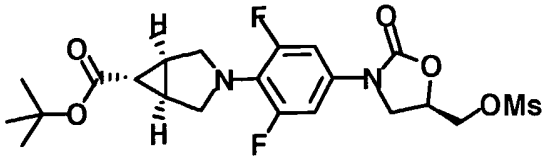
Lithium hexamethyldisilylamide (9.0 mL of a 1.0 M THF solution, 9.0 mmol) was added to a cooled (-78°C) solution of exo-(1R,5S)-3-(4-benzyloxy-carbonylamino-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (2.0 g, 4.5 mmol) in THF (10 mL). After stirring for 1.5 h, (*R*)-(-)-glycidyl butyrate (0.70 mL, 4.95 mmol) was added, and the reaction mixture allowed to warm to room temperature and stirred for 16 hours. The reaction was quenched with saturated NH_4Cl (50 mL) and extracted with ethyl acetate. The organic layers were washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (0-5% MeOH-DCM) provided pure exo-(1R,5S)-3-{2,6-difluoro-4-[(5R)-hydroxymethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.

Yield 1.6 g (87%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.45 (s, 9H), 1.82 (tr, J = 3 Hz, 1H), 2.02 (m, 2H), 3.48-3.56 (m, 4H), 3.72-4.02 (m, 4H), 4.73 (m, 1H), 7.07 (d, J = 12 Hz, 2H)

MS (m/z): $[M+H]^+$ = 411.

II. exo-(1R,5S)-3-{2,6-Difluoro-4-[(5R)-methanesulfonyloxymethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.

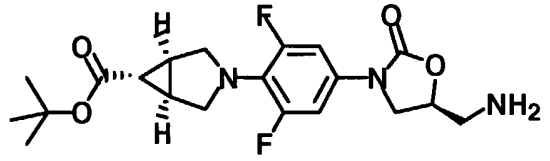


Triethylamine (0.5 mL, 5.5 mmol) and methanesulfonyl chloride (0.28 mL, 3.65 mmol) were added to a cooled (0°C) solution of exo-(1R,5S)-3-{2,6-difluoro-4-[(5R)-hydroxymethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (1.5 g, 3.65 mmol) in DCM (15 mL). After 30 min, the reaction mixture was warmed to room temperature and diluted with DCM (30 mL). The organic solution was washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated to provide exo-(1R,5S)-3-{2,6-difluoro-4-[(5R)-methane-sulfonyloxymethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.

Yield 1.7 g (99%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.81 (tr, J = 3 Hz, 1H), 2.03 (m, 2H), 3.11 (s, 3H), 3.50-3.58 (m, 4H), 3.86 (dd, J = 9, 6 Hz, 1H), 4.07 (tr, J = 9 Hz, 1H), 4.45 (dq, J = 12, 4 Hz, 2H), 4.91 (m, 1H), 7.05 (d, J = 11 Hz, 2H).

III. exo-(1R,5S)-3-{4-[(5S)-Aminomethyl-2-oxo-oxazolidin-3-yl]-2,6-difluoro-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester



Sodium azide (1.20 g, 18.3 mmol) was added to a solution of exo-(1R,5S)-3-{2,6-difluoro-4-[(5R)-methanesulfonyloxymethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (1.7 g, 3.5 mmol) in DMF (5 mL). The reaction mixture was heated at 70°C for 15 hours, cooled and diluted

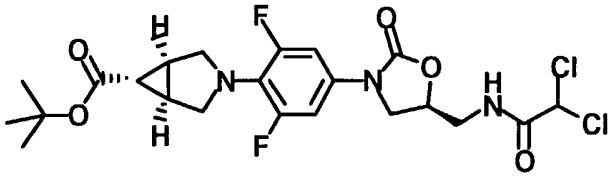
with ethyl acetate. The organic solution was washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated to provide the azide (1.5 g, 3.44 mmol). Triphenylphosphine (1.5 g, 3.8 mmol) was added to a solution of the crude azide in THF (11 mL). After 3 hours at room temperature, H_2O (0.36 mL) was added and the reaction mixture was heated at 40°C for 16 hours. The reaction mixture was then concentrated and the crude product purified by column chromatography (0-7% MeOH-DCM) to provide pure exo-(1R,5S)-3-{4-[(5S)-Aminomethyl-2-oxo-oxazolidin-3-yl]-2,6-difluoro-phenyl}-3-aza-bicyclo [3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.

Yield 1.20 g (86%).

^1H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.83 (tr, J = 3 Hz, 1H), 2.03 (m, 2H), 2.95 (dd, J = 14, 6 Hz, 1H), 3.12 (dd, J = 14, 4 Hz, 1H), 3.42-3.52 (m, 4H), 3.78 (dd, J = 9, 7 Hz, 1H), 3.95 (tr, J = 9 Hz, 1H), 4.66 (m, 1H), 7.08 (d, J = 10 Hz, 2H).

MS (m/z): $[M+H]^+ = 410$.

IV. exo-(1R,5S)-3-(4-{(5S)-[(2,2-Dichloro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester



Pyridine (0.20 mL, 2.4 mmol) and dichloroacetic anhydride (0.20 mL, 1.3 mmol) were added to a solution of exo-(1R,5S)-3-{4-[(5S)-aminomethyl-2-oxo-oxazolidin-3-yl]-2,6-difluoro-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.25 g, 0.61 mmol) in DMF (0.75 mL) at room temperature. The mixture was stirred for 16 h and then diluted with ethyl acetate and washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated. The crude product was purified by preparative TLC (7% MeOH-10% ACN-DCM) to provide exo-

(1R,5S)-3-(4-{(5S)-[(2,2-dichloro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.

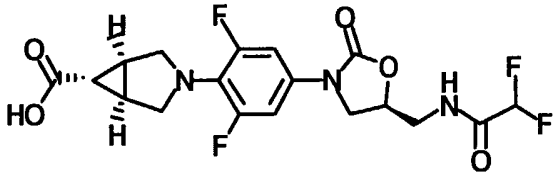
Yield 0.22 g (62%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.80 (tr, J = 3 Hz, 1H), 2.03 (m, 2H), 3.57 (m, 4H), 3.71-3.77 (m, 3H), 4.03 (tr, J = 9 Hz, 1H), 4.83 (m, 1H), 5.94 (s, 1H), 7.02 (d, J = 12 Hz, 2H), 7.06 (br s, 1H).

MS (m/z): $[M+H]^+$ = 521.

Example 8.

exo-(1R,5S)-3-[4-((5S)-5-{[(difluoroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid



Exo-(1R,5S)-3-(4-{(5S)-[(2,2-Difluoro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.21 g, 0.4 mmol) was dissolved in trifluoroacetic acid-dichloro-methane(5 mL, 1:4) and stirred for three hours at room temperature. The solution was then concentrated and the oil lyophilized from ACN-H_2O to provide exo-(1R,5S)-3-[4-((5S)-5-{[(difluoroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid.

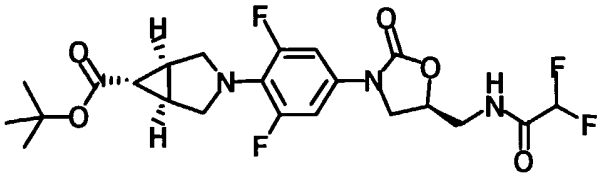
Yield 0.18 g (99%).

^{1}H NMR (300 MHz, DMSO): 1.64 (tr, J = 3 Hz, 1H), 2.03 (m, 2H), 3.39-3.52 (m, 2H), 3.43 (m, 4H), 3.71 (dd, J = 9, 6 Hz, 1H), 4.08 (tr, J = 9 Hz, 1H), 4.78 (m, 1H), 6.24 (tr, J = 54 Hz, 1H), 7.21 (d, J = 12 Hz, 2H), 9.15 (tr, J = 6 Hz, 1H).

MS (m/z): $[M+H]^+$ = 432.

Intermediate for the preparation of Example 8 was synthesized as follows.

exo-(1R,5S)-3-(4-{(5S)-[(2,2-Difluoro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.



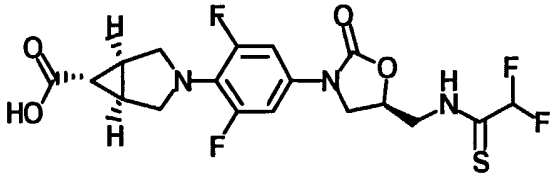
Pyridine (0.12 mL, 1.46 mmol) and difluoroacetic acid (0.05 mL, 0.8 mmol) were added to a solution of exo-(1R,5S)-3-{4-[(5S)-aminomethyl-2-oxo-oxazolidin-3-yl]-2,6-difluoro-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.30 g, 0.73 mmol) in DMF (3.0 mL). 1,3-Diisopropylcarbodiimide (0.125 mL, 0.8 mmol) was then added and the mixture stirred for 16 hours at room temperature. The mixture was diluted with ethyl acetate and washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (0-2% MeOH-DCM) to provide exo-(1R,5S)-3-(4-{(5S)-[(2,2-difluoro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester. Yield 0.22 g (60%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.80 (tr, J = 3 Hz, 1H), 2.03 (m, 2H), 3.44-3.57 (m, 4H), 3.61-3.70 (m, 2H), 3.82-3.89 (m, 1H), 4.03 (tr, J = 9 Hz, 1H), 4.80 (m, 1H), 5.93 (tr, J = 54 Hz, 1H), 6.9 (br s, 1H), 7.02 (d, J = 12 Hz, 2H).

MS (m/z): $[M+H]^+$ = 488.

Example 9.

exo-(1R,5S)-3-[4-((5S)-5-{[(2,2-difluoroethanethioyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid



Exo-(1R,5S)-3-(4-{(5S)-[(2,2-Difluoro-thioacetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.12 g, 0.24 mmol) was dissolved in trifluoroacetic acid – dichloro-methane (5 mL, 1:4) and stirred for two hours at room temperature. The solution was then concentrated and the oil lyophilized from ACN-H_2O to provide

exo-(1R,5S)-3-[4-((5S)-5-{[(2,2-difluoroethanethioyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid as the trifluoroacetic acid salt.

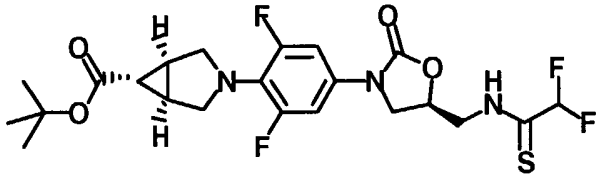
Yield 0.135 g (99%).

^{1}H NMR (300 MHz, DMSO): 1.64 (tr, J = 3 Hz, 1H), 2.03 (m, 2H), 3.44 (m, 4H), 3.76-3.81 (m, 1H), 3.94 (m, 2H), 4.12 (tr, J = 9 Hz, 1H), 5.00 (m, 1H), 6.48 (tr, J = 55 Hz, 1H), 7.22 (d, J = 12 Hz, 2H), 11.11 (tr, J = 5 Hz, 1H).

MS (m/z): $[M+H]^+$ = 448.

Intermediate for the preparation of Example 9 was synthesized as follows.

exo-(1R,5S)-3-(4-{(5S)-[(2,2-Difluoro-thioacetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.



Lawesson's reagent (0.14 g, 0.35 mmol) was added to a solution of exo-(1R,5S)-3-(4-{(5S)-[(2,2-difluoro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.17 g, 0.35 mmol) in dioxane (3.0 mL) and the mixture was heated at reflux for 2 hours. After cooling, the solution was concentrated and the crude material purified by column chromatography (0-2% MeOH-DCM) to afford exo-(1R,5S)-3-(4-{(5S)-[(2,2-difluoro-thioacetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.

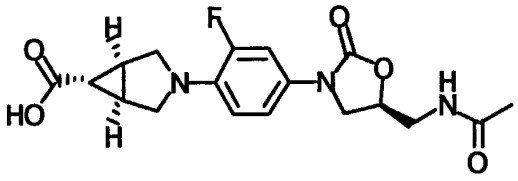
Yield 0.16 g (91%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.80 (tr, J = 3 Hz, 1H), 2.03 (m, 2H), 3.50-3.58 (m, 4H), 3.69 (m, 1H), 3.98-4.07 (m, 2H), 4.29 (m, 1H), 4.99 (m, 1H), 6.21 (tr, J = 56 Hz, 1H), 7.02 (d, J = 12 Hz, 2H), 8.63 (br s, 1H).

MS (m/z): $[M+H]^+$ = 505.

Example 10.

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid



Trifluoroacetic acid (0.75 mL) was added to a solution of exo-(1R,5S)-3-{4-[(5S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-3-aza-bicyclo[3.1.0] hexane-6-carboxylic acid *tert*-butyl ester (0.11 g, 0.25 mmol) in 3 mL of dichloromethane. The solution was stirred for three hours, concentrated, and lyophilized from H_2O-ACN to give exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino) methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid.

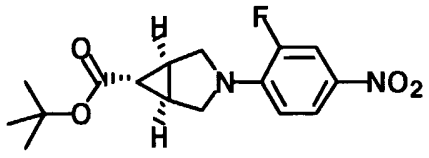
Yield 0.090 g (95%).

^{1}H NMR (300 MHz, DMSO): 1.58 (tr, J = 3 Hz, 1H), 1.81 (s, 3H), 2.09 (m, 2H), 3.23 (d, J = 9 Hz, 2H), 3.38 (tr, J = 5 Hz, 2H), 3.60-3.68 (m, 3H), 4.03 (tr, J = 9 Hz, 1H), 4.67 (m, 1H), 6.76 (tr, J = 10 Hz, 1H), 7.08 (dd, J = 9, 2 Hz, 1H), 7.38 (dd, J = 16, 2 Hz, 1H), 8.23 (tr, J = 6 Hz, 1H).

MS (m/z): $[M+H]^+ = 378$.

Intermediates for the preparation of Example 10 were synthesized as follows.

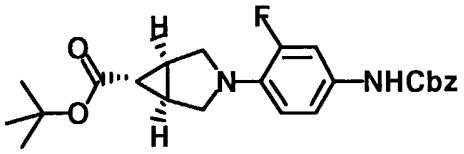
exo-(1R,5S)-3-(2-Fluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.



Diisopropylethylamine (2.3 mL, 13.2 mmol) and 3,4-difluoronitrobenzene (1.2 g, 10.8 mmol) were added to a solution of exo-(1R,5S)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid *t*-butyl ester (2.2 g, 12.0 mmol) in acetonitrile (20 mL). The mixture was heated at reflux for 4 hours and then cooled to room temperature.

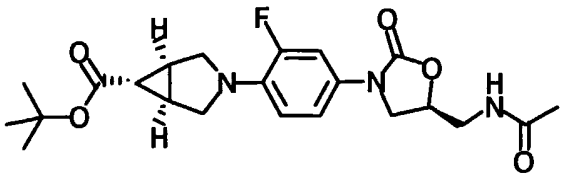
The solution was concentrated, diluted with ethyl acetate (75 mL) and washed with 0.1 M HCl, saturated $NaHCO_3$, brine, and dried ($MgSO_4$). The mixture was filtered and concentrated to give exo-(1R,5S)-3-(2-fluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester as a yellow solid. Yield 2.4 g (63%). ^1H NMR.

II. exo-(1R,5S)-3-(4-Benzyloxycarbonylamino-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.



Iron metal (1.25 g, 22.3 mmol) was added in five portions over 1 h to a refluxing solution of exo-(1R,5S)-3-(2-fluoro-4-nitro-phenyl)-3-aza-bicyclo [3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (2.4 g, 7.44 mmol) and ammonium chloride (4.0 g, 74.4 mmol) in 60 mL of 2:1 ethanol-H_2O. The rust colored mixture was refluxed for another 30 min and then cooled and filtered to remove iron oxide. 50 mL of H_2O was added to the filtrate and the mixture concentrated to remove ethanol. The resulting aqueous solution was extracted with three 35 mL portions of ethyl acetate and the combined organic phases washed with H_2O, brine, and dried ($MgSO_4$). Filtration and concentration gave the crude amine (2.2 g, 7.44 mmol) which was dissolved in 10 mL of dichloromethane. Pyridine (1.2 mL, 14.9 mmol) was added to the amine solution and after cooling to 0°C, benzyl chloroformate (1.2 mL, 8.2 mmol) was added. The mixture was stirred for 1 h at 0°C and for 30 min at room temperature. The reaction mixture was then diluted with dichloromethane (50 mL) and washed with H_2O, brine and then dried ($MgSO_4$). Concentration gave an oil that was purified by column chromatography (0-20% EtOAc-hexane) to afford exo-(1R,5S)-3-(4-benzyloxycarbonylamino-2-fluoro-phenyl)-3-aza bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester. Yield 2.2 g (69%). ^1H NMR.

III. exo-(1R,5S)-3-{4-[(5S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.



Lithium butoxide solution (2.1 mmol of a 1.0 M THF solution, 2.1 mmol) was added to a cooled (0°C) solution of exo-(1R,5S)-3-(4-benzyloxycarbonyl-amino-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.30 g, 0.7 mmol) in DMF (0.5 mL) and MeOH (0.057 mL, 1.4 mmol). Solid (*S*)-acetic acid 2-acetylamino-1-chloromethyl-ethyl ester (0.27 g, 1.4 mmol) was then added and the solution allowed to warm to room temperature and stirred for 20 h. Saturated aqueous ammonium chloride was added, the solution was extracted with three portions of ethyl acetate and the combined organic phases washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated. The crude product was purified by preparative TLC (5% MeOH-DCM) to provide pure exo-(1R,5S)-3-{4-[(5S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-3-aza-bicyclo [3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.

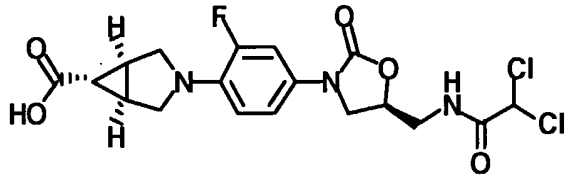
Yield 0.11 g (36%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.74 (tr, J = 3 Hz, 1H), 2.11 (m, 2H), 2.02 (s, 3H), 3.29 (d, J = 9 Hz, 2H), 3.54-3.78 (m, 5H), 3.99 (tr, J = 9 Hz, 1H), 4.74 (m, 1H), 5.93 (br s, 1H), 6.61 (tr, J = 9 Hz, 1H), 7.02 (d, J = 9 Hz, 1H), 7.30 (dd, J = 18, 2 Hz, 1H).

MS (m/z): $[M+H]^+ = 434$.

Example 11.

exo-(1R,5S)-3-[4-((5S)-5-{[(dichloroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid



Exo-(1R,5S)-3-(4-{(5S)-[(2,2-dichloro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.12 g, 0.24 mmol) was dissolved in trifluoroacetic acid – dichloro-methane(4 mL,

1:4) and stirred for three hours at room temperature. The solution was then concentrated and the oil lyophilized from ACN-H_2O to provide exo-(1R,5S)-3-[4-((5S)-5-{[(dichloroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid.

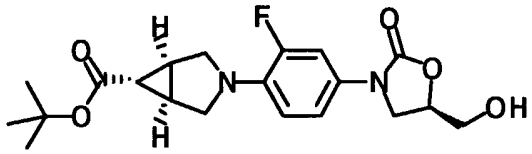
Yield 0.10 g (93%).

^{1}H NMR (300 MHz, DMSO): 1.58 (tr, J = 3 Hz, 1H), 2.09 (m, 2H), 3.23 (d, J = 9 Hz, 2H), 3.39-3.52 (m, 3H), 3.64 (d, J = 9 Hz, 2H), 4.07 (tr, J = 9 Hz, 1H), 4.75 (m, 1H), 6.48 (s, 1H), 6.76 (tr, J = 9 Hz, 1H), 7.07 (d, J = 9 Hz, 1H), 7.37 (dd, J= 14, 2 Hz, 1H), 8.95 (tr, J = 6 Hz, 1H).

MS (m/z): $[M+H]^+$ = 447.

Intermediates for the preparation of Example 11 were synthesized as follows.

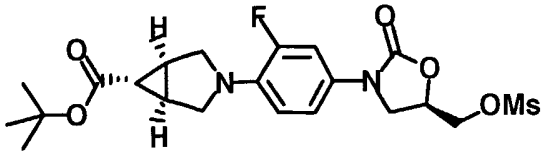
<u>exo-(1R,5S)-3-[2-Fluoro-4-[(5R)-hydroxymethyl-2-oxo-oxazolidin-3-yl]-phenyl]-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.</u>



Lithium hexamethyldisilylamide (7.0 mL of a 1.0 M THF solution, 7.0 mmol) was added to a cooled (-78°C) solution of exo-(1R,5S)-3-(4-benzyloxy-carbonylamino-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (1.5 g, 3.5 mmol) in THF (7 mL). After stirring 1.5 h, (*R*)-(-)-glycidyl butyrate (0.55 mL, 3.9 mmol) was added and the reaction mixture allowed to warm to room temperature and stirred for 15 hours. The reaction was quenched with satd NH_4Cl (50 mL) and extracted with ethyl acetate. The organic layers were washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (0-5% MeOH-DCM) provided pure exo-(1R,5S)-3-{2-fluoro-4-[(5R)-hydroxymethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo [3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.

Yield 1.2 g (87%). ^{1}H NMR.

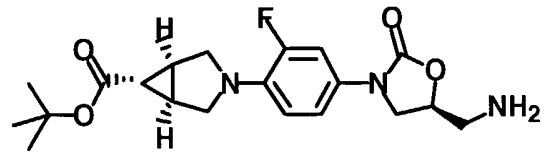
II. exo-(1R,5S)-3-[2-Fluoro-4-[(5R)-methanesulfonyloxymethyl-2-oxo-oxazolidin-3-yl]-phenyl]-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.



Triethylamine (0.64 mL, 4.6 mmol) and methanesulfonyl chloride (0.24 mL, 3.06 mmol) were added to a cooled (0°C) solution of exo-(1R,5S)-3-{2-fluoro-4-[(5R)-hydroxymethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (1.52 g, 3.06 mmol) in DCM (10 mL). After 30 min, the reaction mixture was warmed to room temperature and diluted with DCM (30 mL). The organic solution was washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated to provide exo-(1R,5S)-3-{2-fluoro-4-[(5R)-methanesulfonyloxymethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.

Yield 1.4 g (99%). ^{1}H NMR.

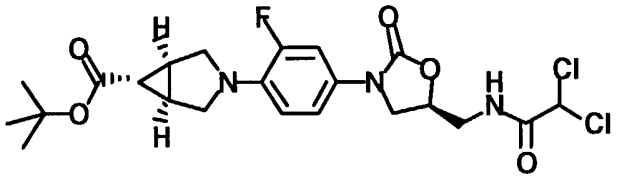
III. exo-(1R,5S)-3-{4-[(5S)-Aminomethyl-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester



Sodium azide (1.0 g, 15.3 mmol) was added to a solution of exo-(1R,5S)-3-[2-fluoro-4-((5R)-methanesulfonyloxymethyl-2-oxo-oxazolidin-3-yl)-phenyl]-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (1.40 g, 3.05 mmol) in DMF (4 mL). The reaction mixture was heated at 70°C for 15 hours, cooled and diluted with ethyl acetate. The organic solution was washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated to provide exo-(1R,5S)-3-{4-[(5S)-azidomethyl-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (1.0 g, 2.4 mmol). Triphenylphosphine (1.0 g, 2.4 mmol) was added to a solution of the crude azide in THF (8 mL). After 3 hours at room temperature, H_2O (0.24 mL) was added and the reaction mixture

was heated at 40°C for 16 hours. The reaction mixture was then concentrated and the crude product purified by column chromatography (0-7% MeOH-DCM) to provide pure exo-(1R,5S)-3-{4-[(5S)-aminomethyl-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester. Yield 0.75 g (80%). ^{1}H NMR.

IV. exo-(1R,5S)-3-(4-{(5S)-[(2,2-Dichloro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.



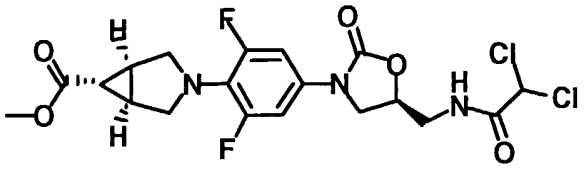
Pyridine (0.12 mL, 1.52 mmol) and dichloroacetic anhydride (0.116 mL, 0.77 mmol) were added to a solution of exo-(1R,5S)-3-[4-[(5S)-aminomethyl-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl]-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.15 g, 0.38 mmol) in DMF (1.0 mL) at room temperature. The mixture was stirred for 16 h and then diluted with ethyl acetate and washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated. The crude product was purified by preparative TLC (5% MeOH-10% ACN-DCM) to provide exo-(1R,5S)-3-(4-{(5S)-[(2,2-dichloro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester. Yield 0.12 g (63%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.74 (tr, J = 3 Hz, 1H), 2.11 (m, 2H), 2.29 (d, J = 9 Hz, 2H), 3.67-3.81 (m, 5H), 4.04 (tr, J = 9 Hz, 1H), 4.81 (m, 1H), 5.95 (s, 1H), 6.60 (tr, J = 9 Hz, 1H), 6.98 (dd, J = 9, 2 Hz, 1H), 7.16 (tr, J = 6 Hz, 1H), 7.27 (dd, J = 15, 2 Hz, 1H).

MS (m/z): $[M+H]^+ = 503$.

Example 12.

methyl exo-(1R,5S)-3-[4-((5S)-5-{[(dichloroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylate



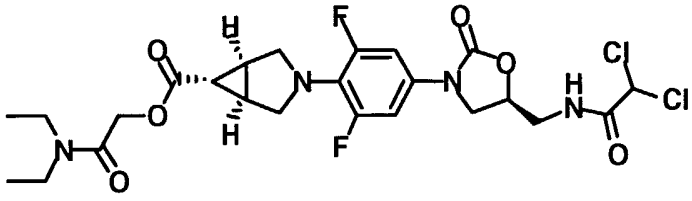
Trimethylsilyldiazomethane (2 mL of a 2 M solution in hexanes) was added slowly to a solution of exo-(1R,5S)-3-[4-((5S)-5-{[(dichloroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (0.10 g, 0.17 mmol) in MeOH (2 mL). After stirring at rt for 3 h, the reaction mixture was concentrated and dissolved in CH_2Cl_2. The organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (0-2% MeOH/DCM) to provide the title compound. Yield 65 mg (79%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.92 (tr, J = 3 Hz, 1H), 2.11 (m, 2H), 3.51-3.57 (m, 4H), 3.62-3.82 (m, 3H), 3.69 (s, 3H), 4.02 (tr, J = 9 Hz, 1H), 4.81-4.84 (m, 1H), 5.94 (s, 1H), 6.99 (m, 1H), 7.03 (d, J = 11 Hz, 2H).

MS (m/z): $[M+H]^+$ = 478.

Example 13.

2-(diethylamino)-2-oxoethyl exo-(1R,5S)-3-[4-((5S)-5-{[(dichloroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylate



2-Chloro, *N,N*-diethyl acetamide (0.03 mL, 0.22 mmol) was added to a solution of exo-(1R,5S)-3-[4-((5S)-5-{[(dichloroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (0.10 g, 0.22 mmol) in DMF(0.75 mL). Triethylamine (0.03 mL, 0.22 mmol) and sodium iodide (4 mg, 0.02 mmol) were added and the mixture was stirred at rt for 18 h. The reaction mixture was dissolved in water and extracted with EtOAc. The organic layers were washed with 1% sodium sulfite and sat. $NaHCO_3$, dried

($MgSO_4$) and concentrated. The residue was purified by PTLC (5% MeOH/DCM) to provide the title compound.

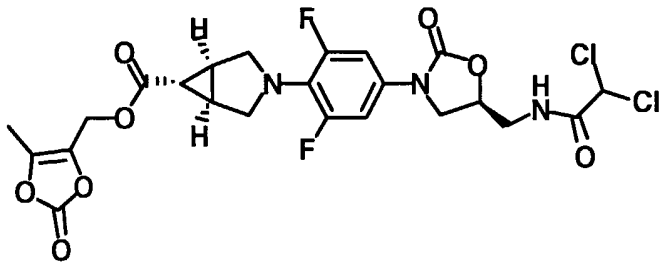
Yield 70 mg (55%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.17 (tr, J = 7 Hz, 3H), 1.24 (tr, J = 7 Hz, 3H), 2.08 (tr, J = 3 Hz, 1H), 2.20 (m, 2H), 3.25 (q, J = 7 Hz, 2H), 3.40 (q, J = 7 Hz, 2H), 3.51-3.59 (m, 4H), 3.67-3.79 (m, 3H), 4.02 (tr, J = 9 Hz, 1H), 4.73 (s, 2H), 4.80-4.84 (m, 1H), 5.96 (s, 1H), 7.02 (d, J = 11 Hz, 2H), 7.14 (br tr, 1H).

MS (m/z): $[M+H]^+$ = 577.

Example 14.

(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl exo-(1R,5S)-3-[4-((5S)-5-{[(dichloroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylate



4-Bromomethyl-5-methyl-[1,3]dioxol-2-one (62 mg, 0.32 mmol) and $KHCO_3$ (32 mg, 0.32 mmol) were added to a solution of exo-(1R,5S)-3-[4-((5S)-5-{[(dichloroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (0.15 g, 0.32 mmol) in DMF(1.5 mL) cooled at 0°C. The mixture was stirred at 0°C for 16 h. The mixture was dissolved in EtOAc and washed with 0.1 N HCl, water and sat. $NaHCO_3$. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by PTLC (5% MeOH/DCM) to provide the title compound.

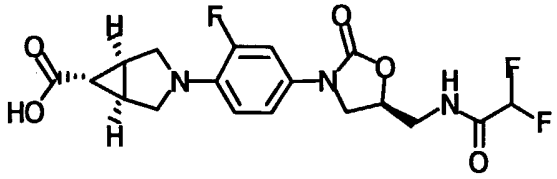
Yield 50 mg (33%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.97 (m, 1H), 2.15 (m, 2H), 2.18 (s, 3H), 3.55-3.78 (m, 7H), 4.03 (tr, J = 9 Hz, 1H), 4.82 (m, 1H), 4.85 (s, 2H), 5.94 (s, 1H), 6.98 (m, 1H), 7.04 (d, J = 12 Hz, 2H).

MS (m/z): $[M+H]^+$ = 576.

Example 15.

exo-(1R,5S)-3-[4-((5S)-5-{[(difluoroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid



Exo-(1R,5S)-3-(4-{(5S)-[(2,2-Difluoro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.15 g, 0.32 mmol) was dissolved in trifluoroacetic acid-dichloromethane(4 mL, 1:4) and stirred for three hours at room temperature. The solution was then concentrated and the oil lyophilized from ACN-H_2O to provide exo-(1R,5S)-3-[4-((5S)-5-{[(difluoroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid.

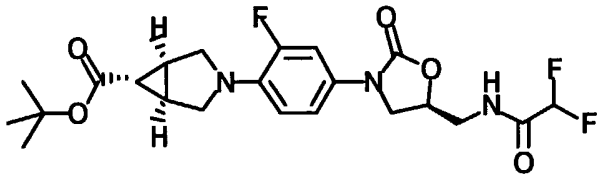
Yield 0.13 g (99%).

^{1}H NMR (300 MHz, DMSO): 1.58 (tr, J = 3 Hz, 1H), 2.10 (m, 2H), 3.23 (d, J = 9 Hz, 2H), 3.50 (tr, J = 6 Hz, 2H), 3.64-3.73 (m, 3H), 4.07 (tr, J = 9 Hz, 1H), 4.74 (m, 1H), 6.24 (tr, J = 54 Hz, 1H), 6.77 (tr, J = 9 Hz, 1H), 7.08 (dd, J = 9, 2 Hz, 1H), 7.37 (dd, J = 16, 2 Hz, 1H), 9.15 (br s, 1H).

MS (m/z): $[M+H]^+ = 414$.

Intermediate for the preparation of Example 15 was synthesized as follows.

exo-(1R,5S)-3-(4-{(5S)-[(2,2-Difluoro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester



Pyridine (0.083 mL, 1.02 mmol) and difluoroacetic acid (0.035 mL, 0.56 mmol) were added to a solution of exo-(1R,5S)-3-{4-[(5S)-aminomethyl-2-oxo-

oxazolidin-3-yl]-2-fluoro-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.29 g, 0.51 mmol) in DMF (2.0 mL). 1,3-Diisopropylcarbodiimide (0.088 mL, 0.56 mmol) was then added and the mixture stirred for 16 hours at room temperature. The mixture was diluted with ethyl acetate and washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (0-2% MeOH-10% ACN-DCM) to provide exo-(1R,5S)-3-(4-{(5S)-[(2,2-difluoro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.

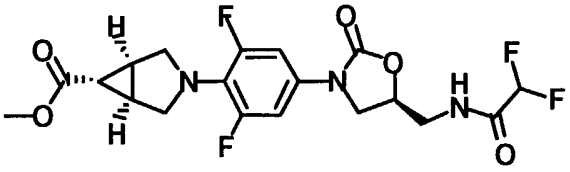
Yield 0.15 g (63%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.74 (tr, J = 3 Hz, 1H), 2.11 (m, 2H), 3.29 (d, J = 9 Hz, 2H), 3.56-3.90 (m, 5H), 4.06 (tr, J = 9 Hz, 1H), 4.78 (m, 1H), 5.93 (tr, J = 54 Hz, 1H), 6.61 (tr, J = 10 Hz, 1H), 6.82 (br s, 1H), 6.99 (dd, J = 9, 2 Hz, 1H), 7.28 (dd, J = 16, 2 Hz, 1H).

MS (m/z): $[M+H]^+ = 470$.

Example 16.

methyl exo-(1R,5S)-3-[4-((5S)-5-{[(difluoroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylate



Trimethylsilyldiazomethane (3 mL of a 2 M solution in hexanes) was added slowly to a solution of exo-(1R,5S)-3-[4-((5S)-5-{[(difluoroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (0.13 g, 0.23 mmol) in MeOH (3 mL). After stirring at rt for 3h, the reaction mixture was concentrated and dissolved in CH_2Cl_2. The organic layer was then washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (0-2% MeOH/DCM) to provide the title compound.

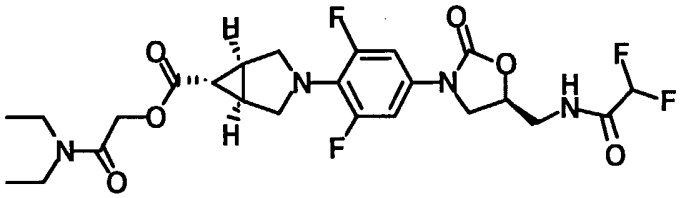
Yield 80 mg (75%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.92 (tr, J = 3 Hz, 1H), 2.11 (m, 2H), 3.55-3.67 (m, 6H), 3.69 (s, 3H), 3.81-3.89 (m, 1H), 4.04 (tr, J= 9 Hz, 1H), 4.80-4.83 (m, 1H), 5.93 (tr, J = 54 Hz, 1H), 6.82 (br tr, 1H), 7.03 (d, J = 11 Hz, 2H).

MS (m/z): $[M+H]^+$ = 446.

Example 17.

2-(diethylamino)-2-oxoethyl exo-(1R,5S)-3-[4-((5S)-5-{[(difluoroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylate



2-Chloro, *N,N*-diethyl acetamide (0.05 mL, 0.35 mmol) was added to a solution of exo-(1R,5S)-3-[4-((5S)-5-{[(difluoroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (0.15g, 0.27 mmol) in DMF (0.7 mL). Triethylamine (0.05 mL, 0.35 mmol) and sodium iodide (5 mg, 0.03 mmol) were added and the mixture was stirred at rt for 20 h. The reaction mixture was dissolved in water and extracted with EtOAc. The organic layers were washed with 1% sodium sulfite and sat. $NaHCO_3$, dried ($MgSO_4$) and concentrated. The residue was purified by pTLC (10% MeOH/DCM) to provide the title compound.

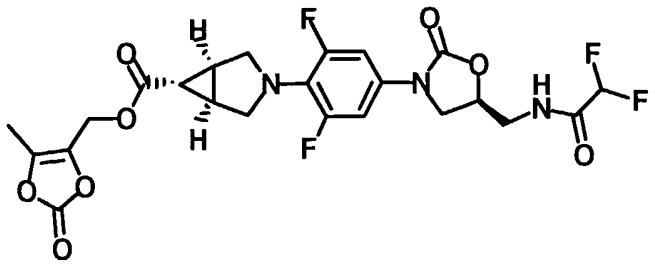
Yield 80 mg (54%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.14 (tr, J = 7 Hz, 3H), 1.28 (tr, J = 7 Hz, 3H), 2.09 (tr, J = 3 Hz, 1H), 2.21 (m, 2H), 3.26 (q, J = 7 Hz, 2H), 3.40 (q, J = 7 Hz, 2H), 3.51-3.87 (m, 7 H), 4.04 (tr, J = 9 Hz, 1H), 4.73 (s, 2H), 4.79-4.83 (m, 1H), 5.93 (tr, J = 54 Hz, 1H), 6.85 (br tr, 1H), 7.03 (d, J= 11 Hz, 2H).

MS (m/z): $[M+H]^+$ = 545.

Example 18.

(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl exo-(1R,5S)-3-[4-((5S)-5-{[(difluoroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylate



4-Bromomethyl-5-methyl-[1,3]dioxol-2-one (67 mg, 0.32 mmol) and $KHCO_3$ (35 mg, 0.32 mmol) were added to a solution of exo-(1R,5S)-3-[4-((5S)-5-{[(difluoroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2,6-difluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (0.15 g, 0.35 mmol) in DMF(1.5 mL) cooled at 0 °C. The mixture was stirred at 0°C for 18 h. The mixture was dissolved in EtOAc and washed with 0.1 N HCl, water and sat. $NaHCO_3$. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by pTLC (5% MeOH/DCM) and column chromatography (0-2.5% MeOH/DCM) to provide the title compound.

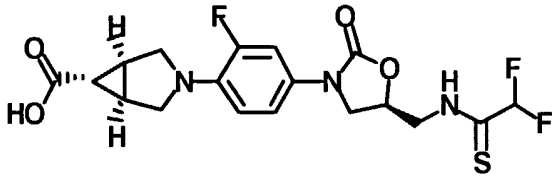
Yield 98 mg (52%).

^1H NMR (300 MHz, $CDCl_3$): 1.97 (tr, J = 3 Hz, 1H), 2.14 (m, 2H), 2.18 (s, 3H), 3.44-3.89 (m, 7 H), 4.04 (tr, J = 9 Hz, 1H), 4.78-4.83 (m, 1H), 4.85 (s, 2H), 5.93 (tr, J = 54 Hz, 1H), 6.81 (br tr, 1H), 7.04 (d, J = 12 Hz, 2H).

MS (m/z): $[M+H]^+$ = 544.

Example 19.

exo-(1R,5S)-3-[4-((5S)-5-{[(2,2-difluoroethanethioyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid



Exo-(1R,5S)-3-(4-{(5S)-[(2,2-Difluoro-thioacetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.06 g, 0.13 mmol) was dissolved in trifluoroacetic acid-dichloromethane (1.6 mL, 1:4) and stirred for two hours at room temperature. The solution was then concentrated and the oil lyophilized from ACN-H_2O to provide

exo-(1R,5S)-3-[4-((5S)-5-{[(2,2-difluoroethanethioyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)-2-fluorophenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid.

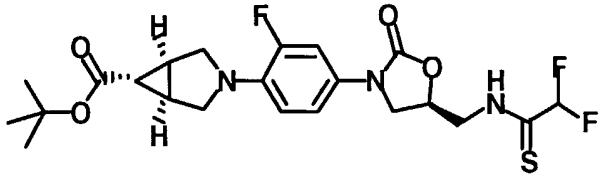
Yield 0.055 g (99%).

^{1}H NMR (300 MHz, DMSO): 1.58 (tr, J = 3 Hz, 1H), 2.10 (m, 2H), 3.24 (d, J = 9 Hz, 2H), 3.65 (d, J = 9 Hz, 2H), 3.75-3.96 (m, 3H), 4.11 (tr, J = 9 Hz, 1H), 4.97 (m, 1H), 6.49 (tr, J = 55 Hz, 1H), 6.77 (tr, J = 10 Hz, 1H), 7.09 (dd, J = 8, 2 Hz, 1H), 7.39 (dd, J = 14, 2 Hz, 1H), 11.12 (br s, 1H).

MS (m/z): $[M+H]^+$ = 430.

Intermediate for the preparation of Example 19 was synthesized as follows.

exo-(1R,5S)-3-(4-{(5S)-[(2,2-Difluoro-thioacetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.



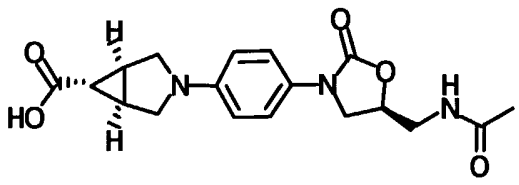
Lawesson's reagent (0.085 g, 0.21 mmol) was added to a solution of exo-(1R,5S)-3-(4-{(5S)-[(2,2-difluoro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.10 g, 0.21 mmol) in dioxane (2.5 mL) and the mixture was heated at reflux for 3 hours. After cooling, the solution was concentrated and the crude material purified by preparative TLC (2% MeOH-10% ACN-DCM) to afford exo-(1R,5S)-3-(4-{(5S)-[(2,2-difluoro-thioacetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.

Yield 0.06 g (59%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.74 (tr, J = 3 Hz, 1H), 2.12 (m, 2H), 3.30 (d, J = 9 Hz, 2H), 3.70-3.93 (m, 3H), 3.95-4.02 (m, 1H), 4.09 (tr, J = 9 Hz, 1H), 4.28-4.36 (m, 1H), 4.96 (m, 1H), 6.21 (tr, J = 56, 1H), 6.61 (tr, J = 9 Hz, 1H), 6.99 (dd, J = 9, 2 Hz, 1H), 7.27 (dd, J = 15, 3 Hz, 1H), 8.59 (br s, 1H).

Example 20.

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}phenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid



Exo-(1R,5S)-3-(4-{(5S)-[(Acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.060 g, 0.14 mmol) was dissolved in trifluoroacetic acid-dichloromethane(2 mL, 1:4) and stirred for three hours at room temperature. The solution was then concentrated and the oil lyophilized from ACN-H_2O to provide exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}phenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid.

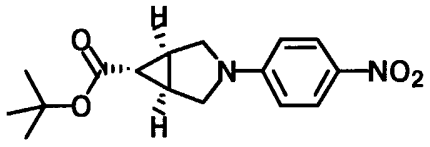
Yield 0.050 g (99%).

^{1}H NMR (300 MHz, DMSO): 1.45 (tr, J = 3 Hz, 1H), 1.82 (s, 3H), 2.15 (m, 2H), 3.17 (d, J = 9 Hz, 2H), 3.37 (m, 2H), 3.60 (m, 3H), 4.01 (tr, J = 9 Hz, 1H), 4.64 (m, 1H), 6.56 (d, J = 9 Hz, 2H), 7.28 (d, J = 9 Hz, 2H), 8.24 (tr, J = 6 Hz, 1H).

MS (m/z): $[M+H]^+$ = 360.

Intermediates for the preparation of Example 20 were synthesized as follows.

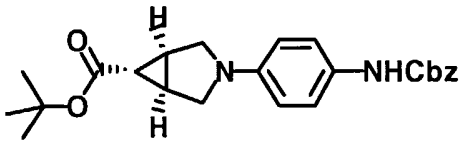
exo-(1R,5S)-3-(4-Nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.



Diisopropylethylamine (1.4 mL, 7.8 mmol) and 4-fluoronitrobenzene (0.75 mL, 7.09 mmol) were added to a solution of exo-(1R,5S)-3-azabicyclo[3.1.0] hexane-6-carboxylic acid *t*-butyl ester (1.3 g, 7.09 mmol; prepared as described for

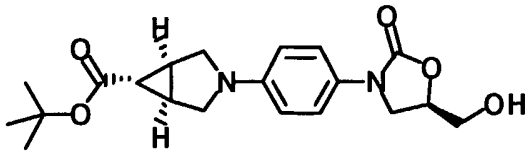
Example 1) in acetonitrile (15 mL). The mixture was heated at reflux for 20 hours and then cooled to room temperature. The solution was concentrated, diluted with ethyl acetate (60mL) and washed with 0.1 M HCl, saturated $NaHCO_3$, brine, and dried ($MgSO_4$). The mixture was filtered and concentrated to give exo-(1R,5S)-3-(4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester. Yield 2.1 g (99%). ^1H NMR.

II. exo-(1R,5S)-3-(4-Benzyloxycarbonylamino-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester



Iron metal (1.02 g, 18.2 mmol) was added in five portions over 1 h to a refluxing solution of exo-(1R,5S)-3-(4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (1.85 g, 6.08 mmol) and ammonium chloride (3.3 g, 60.8 mmol) in 45 mL of 2:1 ethanol-H_2O. The rust colored mixture was refluxed for another 30 min and then cooled and filtered to remove iron oxide. 50 mL of H_2O was added to the filtrate and the mixture concentrated to remove ethanol. The resulting aqueous solution was extracted with three 35 mL portions of ethyl acetate and the combined organic phases washed with H_2O, brine, and dried ($MgSO_4$). Filtration and concentration gave the crude amine (1.8 g, 6.08 mmol) which was dissolved in 7 mL of dichloromethane. Pyridine (1.0 mL, 12.2 mmol) was added to the amine solution and after cooling to 0°C, benzyl chloroformate (0.95 mL, 6.7 mmol) was added. The mixture was stirred for 1 h at 0°C and for 30 min at room temperature. The reaction mixture was then diluted with dichloromethane (50 mL) and washed with H_2O, brine and then dried ($MgSO_4$). Concentration gave an oil that was purified by column chromatography (0-20% EtOAc-hexane) to afford exo-(1R,5S)-3-(4-benzyloxycarbonylamino-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.
Yield 1.27 g (51%). ^1H NMR.

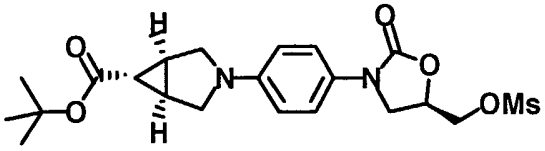
III. exo-(1R,5S)-3-{4-[(5R)-Hydroxymethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.



Lithium hexamethyldisilylamide (4.9 mL of a 1.0 M THF solution, 4.9 mmol) was added to a cooled (-78°C) solution of exo-(1R,5S)-3-(4-benzyloxycarbonylamino-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (1.0 g, 2.44 mmol) in THF (5 mL). After stirring 1.5 h, (*R*)-(-)-glycidyl butyrate (0.38 mL, 2.69 mmol) was added and the reaction mixture allowed to warm to room temperature and stirred for 16 hours. The reaction was quenched with satd NH_4Cl (50 mL) and extracted with ethyl acetate. The organic layers were washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (0-5% MeOH-DCM) provided pure exo-(1R,5S)-3-{4-[(5R)-hydroxymethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.

Yield 0.8 g (88%). ^1H NMR.

IV. exo-(1R,5S)-3-{4-[(5R)-Methanesulfonyloxymethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.

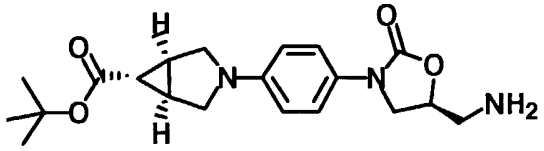


Triethylamine (0.45 mL, 3.2 mmol) and methanesulfonyl chloride (0.17 mL, 2.14 mmol) were added to a cooled (0°C) solution of exo-(1R,5S)-3-{4-[(5R)-hydroxymethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.80 g, 2.14 mmol) in DCM (7 mL). After 45 min, the reaction mixture was warmed to room temperature and diluted with DCM (40 mL). The organic solution was washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated to provide exo-(1R,5S)-3-{4-[(5R)-

methanesulfonyloxymethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.

Yield 1.0 g (99%). ^{1}H NMR.

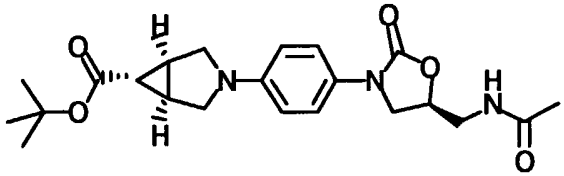
V. exo-(1R,5S)-3-[4-((5S)-Aminomethyl-2-oxo-oxazolidin-3-yl)-phenyl]-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester



Sodium azide (0.7 g, 10.7 mmol) was added to a solution of exo-(1R,5S)-3-{4-[(5R)-methanesulfonyloxymethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (1.0 g, 2.1 mmol) in DMF (3 mL). The reaction mixture was heated at 70°C for 16 hours, cooled and diluted with ethyl acetate. The organic solution was washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated to provide exo-(1R,5S)-3-{4-[(5S)-azidomethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.66 g, 1.65 mmol). Triphenylphosphine (0.66 g, 1.65 mmol) was added to a solution of the crude azide in THF (5 mL). After 3 hours at room temperature, H_2O (0.17 mL) was added and the reaction mixture was heated at 40°C for 16 hours. The reaction mixture was then concentrated and the crude product purified by column chromatography (0-6% MeOH-DCM) to provide pure exo-(1R,5S)-3-{4-[(5S)-aminomethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.

Yield 0.45 g (73%). ^{1}H NMR.

VI. exo-(1R,5S)-3-(4-{(5S)-[(Acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.



Pyridine (0.021 mL, 0.26 mmol) and acetic anhydride (0.014 mL, 0.15 mmol) were added to a solution of exo-(1R,5S)-3-{4-[(5S)-aminomethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.050 g, 0.13 mmol) in DMF (1.0 mL) at room temperature. The mixture was stirred for 16 h and then diluted with ethyl acetate and washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated. The crude product was purified by preparative TLC (5% MeOH-10% ACN-DCM) to provide exo-(1R,5S)-3-(4-{(5S)-[(acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.

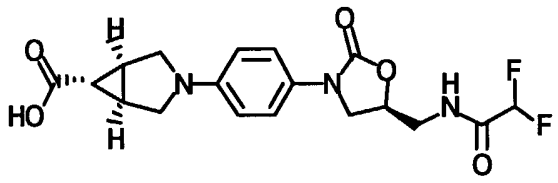
Yield 0.040 g (74%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (s, 9H), 1.58 (tr, J = 3 Hz, 1H), 2.02 (s, 3H), 2.18 (m, 2H), 3.28 (d, J = 9 Hz, 2H), 3.52-3.74 (m, 5H), 3.99 (tr, J = 9 Hz, 1H), 4.73 (m, 1H), 6.06 (br s, 1H), 6.50 (d, J = 9 Hz, 2H), 7.29 (d, J = 9 Hz, 2H).

MS (m/z): $[M+H]^+ = 416$.

Example 21.

exo-(1R,5S)-3-[4-((5S)-5-{[(difluoroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)phenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid



Exo-(1R,5S)-3-(4-{(5S)-[(2,2-Difluoro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.040 g, 0.09 mmol) was dissolved in trifluoroacetic acid-dichloromethane(1.2 mL, 1:4) and stirred for two hours at room temperature. The solution was then concentrated and the oil lyophilized from ACN-H_2O to provide exo-(1R,5S)-3-[4-((5S)-5-{[(difluoroacetyl)amino]methyl}-2-oxo-1,3-oxazolidin-3-yl)phenyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid.

Yield 0.030 g (86%).

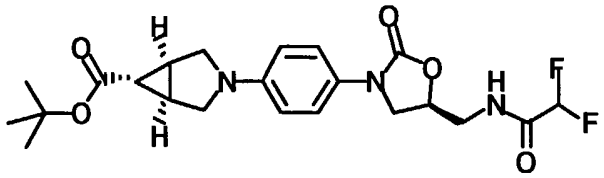
^{1}H NMR (300 MHz, DMSO): 1.45 (tr, J = 3 Hz, 1H), 2.15 (m, 2H), 3.17 (d, J = 9 Hz, 2H), 3.50 (m, 2H), 3.59 (d, J = 9 Hz, 2H), 3.68 (m, 1H), 4.05 (tr, J = 9 Hz,

1H), 4.72 (m, 1H), 6.24 (tr, J = 54 Hz, 1H), 6.56 (d, J = 9 Hz, 2H), 7.27 (d, J = 9 Hz, 2H), 9.15 (tr, J = 5 Hz, 1H).

MS (m/z): $[M+H]^+$ = 396.

Intermediate for the preparation of Example 21 was synthesized as follows.

exo-(1R,5S)-3-(4-{(5S)-[(2,2-Difluoro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.



Pyridine (0.095 mL, 1.18 mmol) and difluoroacetic acid (0.041 mL, 0.65 mmol) were added to a solution of exo-(1R,5S)-3-{4-[(5S)-aminomethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester (0.22 g, 0.59 mmol) in DMF (3.0 mL). 1,3-Diisopropylcarbodiimide (0.10 mL, 0.65 mmol) was then added and the mixture stirred for 16 hours at room temperature. The mixture was diluted with ethyl acetate and washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (0-2% MeOH-10% ACN-DCM) to provide exo-(1R,5S)-3-(4-{(5S)-[(2,2-difluoro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylic acid *tert*-butyl ester.

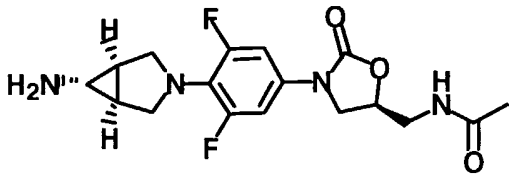
Yield 0.15 g (56%).

^{1}H NMR (300 MHz, $CDCl_3$): 1.45 (s, 9H), 1.54 (tr, J = 3 Hz, 1H), 2.18 (m, 2H), 3.29 (d, J = 8 Hz, 2H), 3.59-3.88 (m, 5H), 4.07 (tr, J = 9 Hz, 1H), 4.78 (m, 1H), 5.93 (tr, J = 54 Hz, 1H), 6.52 (d, J = 9 Hz, 2H), 6.89 (br s, 1H), 7.27 (d, J = 9 Hz, 2H).

MS (m/z): $[M+H]^+$ = 452.

Example 22.

N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide



A 4.0M solution of HCl in dioxane (1.5 mL) was added to *tert*-butyl exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylcarbamate (0.066 g, 0.142) in 1.5 mL of dioxane. The reaction mixture was stirred at room temperature for 2 hours and then concentrated. The resulting solid was lyophilized from acetonitrile-water to provide N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide as the hydrochloride salt.

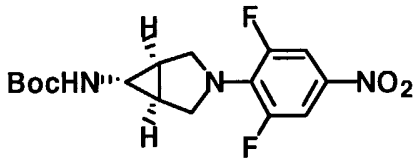
Yield 0.054 g (95%).

^{1}H NMR (300 MHz, $CDCl_3$-CD_3OD): 1.85 (s, 3H), 1.89 (br s, 2H), 2.60 (br s, 1H), 3.21-3.42 (m, 6H), 3.58 (tr, J = 6 Hz, 1H), 3.87 (tr, J = 3Hz, 1H), 4.62 (m, 1H), 6.93 (d, = 11 Hz, 2H).

MS (m/z): $[M+H]^+$ = 367.

Intermediates for the preparation of Example 22 were synthesized as follows.

I.[exo-(1R,5S)-3-(2,6-Difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester.

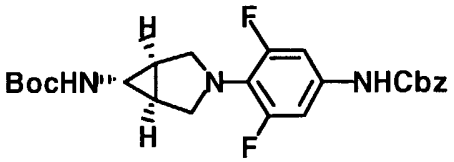


Diisopropylethylamine (0.17 mL, 0.96 mmol) and 3,4,5-trifluoronitrobenzene (0.113 g, 0.64 mmol) were added to a solution exo-(1R,5S)-6-*tert*-butoxycarbonylamine-3-azabicyclo[3.1.0]hexane (0.14 g, 0.7 mmol; prepared as described in [Brighty, K. E., Castaldi, M. J. *Synlett*, **1996**, 1097-1099]) in acetonitrile (3 mL). The mixture was heated for 3 h at reflux and then cooled to room temperature. The solution was concentrated, diluted with ethyl acetate and

washed with 0.5 M HCl, saturated $NaHCO_3$, brine, and dried (Na_2SO_4). The mixture was filtered and concentrated to give [exo-(1R,5S)-3-(2,6-difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester as a yellow solid.

Yield 0.210 g (93%). ^{1}H NMR.

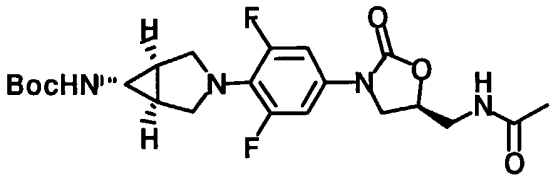
II. [exo-(1R,5S)-3-(4-Benzyloxycarbonylamino-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester.



Iron metal (0.047 g, 0.84 mmol) was added in five portions over 1 h to a refluxing solution of [exo-(1R,5S)-3-(2,6-difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester (0.10 g, 0.28 mmol) and ammonium chloride (0.148 g, 2.8 mmol) in 2.5 mL of 2:1 ethanol-H_2O. The rust colored mixture was refluxed for another 30 min and then cooled and filtered to remove iron oxide. H_2O was added to the filtrate and the mixture concentrated to remove ethanol. The resulting aqueous solution was extracted with three 15 mL portions of ethyl acetate and the combined organic phases washed with H_2O, brine, and dried ($MgSO_4$). Filtration and concentration gave the crude amine (0.091 g, 0.28 mmol) which was dissolved in 1.5 mL of dichloromethane. Pyridine (0.046 mL, 0.57 mmol) was added to the amine solution and after cooling to 0°C, benzyl chloroformate (0.046 mL, 0.32 mmol) was added. The mixture was stirred for 30 min at 0°C and for 30 min at room temperature. The reaction mixture was then diluted with dichloromethane and washed with H_2O, brine and then dried ($MgSO_4$). Concentration gave a yellow oil that was triturated with hexane to afford [exo-(1R,5S)-3-(4-benzyloxycarbonylamino-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester as a yellow solid.

Yield 0.100 g (77%). ^{1}H NMR.

III. *tert*-butyl exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylcarbamate



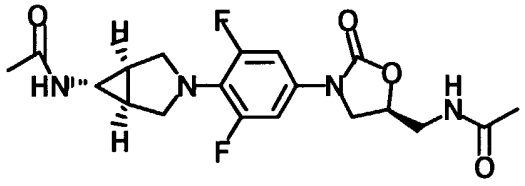
Lithium butoxide solution (0.61 mL of a 1.0 M THF solution, 0.61 mmol) was added to a cooled (0°C) solution of [exo-(1R,5S)-3-(4-benzyloxycarbonyl-amino-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester (0.093 g, 0.203 mmol) in DMF (0.14 mL) and MeOH (0.016 mL, 0.406 mmol). Solid (*S*)-acetic acid 2-acetylamino-1-chloromethyl-ethyl ester (0.078 g, 0.406 mmol) was then added and the solution allowed to warm to room temperature and stirred for 20 h. Saturated aq. ammonium chloride (0.5 mL) was added, along with 4 mL of H_2O and 3 mL of brine. The solution was extracted with three portions of dichloromethane and the combined organic phases dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (0-2% MeOH-DCM) to provide *tert*-butyl exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylcarbamate.

Yield 0.066 g (70%). ^{1}H NMR.

MS (m/z): $[M+H]^+ = 467$.

Example 23.

N-[((5S)-3-{4-[exo-(1R,5S)-6-(acetylamino)-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide



Triethylamine (0.012 mL, 0.086) and acetic anhydride (2.8 μL, 0.029 mmol) were added to a solution of N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo [3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide hydrochloride (0.010 g, 0.025 mmol) in DMF (0.2 mL), The reaction mixture was stirred for 3 hours at room temperature and then diluted with ethyl acetate (10

mL). This solution was washed with 2.5% aqueous $NaHCO_3$, brine, and dried (Na_2SO_4). The mixture was filtered and concentrated and the crude product purified by preparative TLC (5% MeOH-DCM) to afford N-[((5S)-3-{4-[exo-(1R,5S)-6-(acetylamino)-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide.

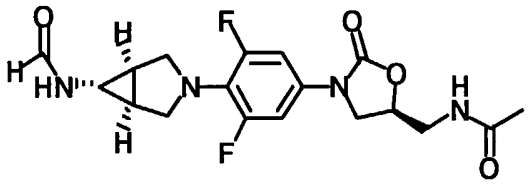
Yield 6 mg (60%).

^{1}H NMR (300 MHz, $CDCl_3$-CD_3OD): 1.59 (m, 2 H), 1.87 (s, 3H), 1.93 (s, 3H), 2.76 (m, 1H), 3.19-3.67 (m, 7H), 3.92 (tr, J = 9 Hz, 1H), 4.68 (m, 1H), 6.94 (dq, J = 10, 2 Hz, 2H).

MS (m/z): $[M+H]^+$ = 409.

Example 24.

N-[((5S)-3-{3,5-difluoro-4-[exo-(1R,5S)-6-(formylamino)-3-azabicyclo[3.1.0]hex-3-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide



A solution of N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide hydrochloride (0.010 g, 0.025 mmol) in formic acid (0.5 mL) and acetic anhydride (0.25 mL) was stirred at room temperature for three days in a sealed vial. The solution was concentrated and purified by preparative HPLC to afford N-[((5S)-3-{3,5-difluoro-4-[exo-(1R,5S)-6-(formylamino)-3-azabicyclo[3.1.0]hex-3-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide.

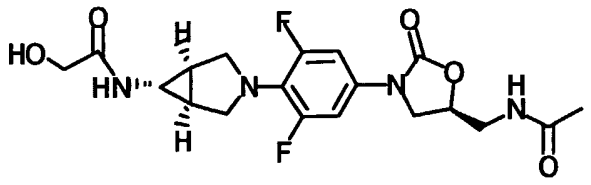
Yield 6 mg (61%).

^{1}H NMR (300 MHz, DMSO): 1.67 (m, 2H), 1.82 (s, 3H), 2.76 (m, 1H), 3.35-4.02 (m, 7H), 4.06 (tr, J = 9 Hz, 1H), 4.71 (m, 1H), 7.23 (d, J = 9 Hz, 2H), 7.98 (s, 1H), 8.17 (d, J = 3 Hz, 1H), 8.24 (tr, J = 6 Hz, 1H).

MS (m/z): $[M+H]^+$ = 395.

Example 25.

N-[exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-2-hydroxyacetamide



A mixture of acetoxyacetic acid (0.033 g, 0.28 mmol), diisopropylethylamine (0.131 mL, 0.75 mmol), and HATU (0.105 g, 0.28 mmol) in DMF (0.1 mL) was stirred for 15 minutes and then added to a solution of N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide hydrochloride (0.10 g, 0.25 mmol) in DMF (0.1 mL). After stirring for 1 hour, the solution was diluted with 15 mL of ethyl acetate and washed with 10% citric acid, H_2O, brine, and dried ($MgSO_4$), filtered and concentrated to an oil (0.08 g, 0.17 mmol). The crude acetate was dissolved in methanol (1 mL) and treated with 0.1M LiOH in methanol (1 mL). After stirring for 30 minutes the solution was concentrated and the residue purified by preparative TLC (6% MeOH-DCM) to provide N-[exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-yl]-2-hydroxyacetamide.

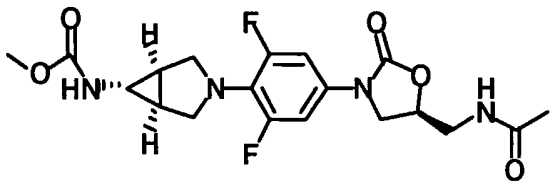
Yield 0.010 g (9%).

^{1}H NMR (300 MHz, DMSO): 1.76 (m, 2H), 1.82 (s, 3H), 2.79 (m, 1H), 3.33-3.42 (m, 6H), 3.68 (m, 1H), 3.78 (d, J = 6 Hz, 2H), 4.06 (tr, J = 9 Hz, 1H), 4.71 (m, 1H), 5.40 (tr, J = 6 Hz, 1H), 7.23 (d, J = 9 Hz, 2H), 7.83 (d, J = 5 Hz, 1H), 8.23 (br tr, 1H).

MS (m/z): $[M+H]^+ = 425$.

Example 26.

Methyl exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylcarbamate



Triethylamine (9 μL, 0.064) and methyl chloroformate (1.7 μL, 0.022 mmol) were added to a solution of N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo [3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide hydrochloride (6.3 mg, 0.016 mmol) in DMF (0.2 mL). After stirring 2 hours at room temperature, the solution was diluted with ethyl acetate (10 mL) and 2.5% $NaHCO_3$ (5 mL). The layers were separated and the aqueous solution extracted with two portions of ethyl acetate. The combined organic phases were washed with brine and dried ($MgSO_4$). The mixture was filtered and concentrated and the crude product purified by preparative TLC (5% MeOH-DCM) to afford methyl exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylcarbamate.

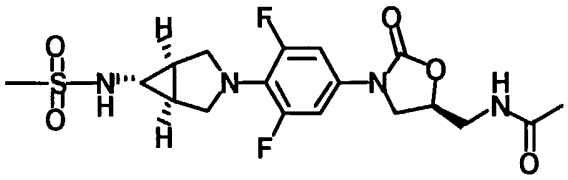
Yield 3.3 mg (50%).

^1H NMR (300 MHz, $CDCl_3$): 1.69 (br s, 2H), 2.02 (s, 3H), 2.75 (br s, 1H), 3.49 (s, 3H), 3.56-3.71 (m, 7 H), 3.96 (tr, J = 9 Hz, 1H), 4.76 (m, 1H), 4.78 (br s, 1H), 6.07 (tr, J = 6 Hz, 1H), 7.02 (d, J = 12 Hz, 2H).

MS (m/z): $[M+H]^+ = 425$.

Example 27.

N-{[(5S)-3-(3,5-difluoro-4-{exo-(1R,5S)-6-[(methylsulfonyl)amino]-3-azabicyclo[3.1.0]hex-3-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide



Triethylamine (8 μL, 0.057) and methanesulfonyl chloride (2.2 μL, 0.029 mmol) were added to a solution of N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide hydrochloride (7.6 mg, 0.019 mmol) in DMF (0.2 mL). After stirring 2 hours at room temperature, the solution was diluted with ethyl acetate (10 mL) and 2.5% $NaHCO_3$ (5 mL). The layers were separated and the aqueous solution extracted with two portions of ethyl acetate. The combined organic phases were washed with brine and dried ($MgSO_4$). The mixture was filtered and concentrated and the crude product purified by preparative TLC (5% MeOH-

DCM) to afford N-{[(5S)-3-(3,5-difluoro-4-{exo-(1R,5S)-6-[(methylsulfonyl)amino]-3-azabicyclo[3.1.0]hex-3-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide.

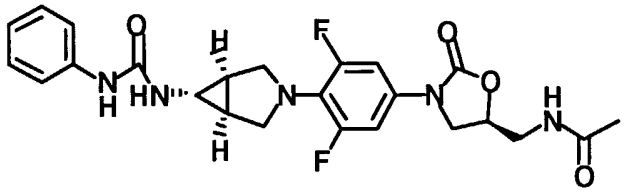
Yield 5.8 mg (70%).

^{1}H NMR (300 MHz, $CDCl_3$-CD_3OD): 1.84 (br s, 2H), 1.95 (s, 3H), 2.64 (br s, 1H), 2.98 (s, 3H), 3.42-3.55 (m, 6H), 3.64 (m, 1H), 3.93 (tr, J = 9 Hz, 1H), 4.70 (m, 1H), 6.98 (d, J = 11 Hz, 2H).

MS (m/z): $[M+H]^+$ = 445.

Example 28.

N-{[(5S)-3-(4-{exo-(1R,5S)-6-[(anilinocarbonyl)amino]-3-azabicyclo[3.1.0]hex-3-yl}-3,5-difluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide



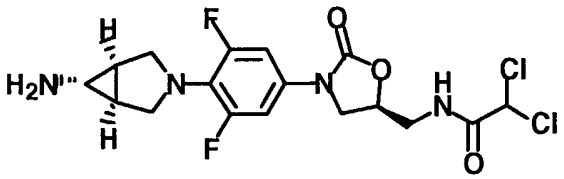
Triethylamine (6.0 μL, 0.042) and phenyl isocyanate (3.3 μL, 0.029 mmol) were added to a solution of N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide hydrochloride (8.6 mg, 0.021 mmol) in dichloromethane (0.1 mL) and NMP (0.1 mL). After stirring 2 hours at room temperature, the solution was diluted with ethyl acetate (10 mL) and 2.5% $NaHCO_3$ (5 mL). The layers were separated and the aqueous solution extracted with two portions of ethyl acetate. The combined organic phases were washed with brine and dried ($MgSO_4$). The mixture was filtered and concentrated and the crude product purified by preparative TLC (5% MeOH-DCM) to afford N-{[(5S)-3-(4-{exo-(1R,5S)-6-[(anilinocarbonyl)amino]-3-azabicyclo[3.1.0]hex-3-yl}-3,5-difluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide.

Yield 8.0 mg (80%).

^{1}H NMR (300 MHz, $CDCl_3$-CD_3OD): 1.72 (br s, 2H), 1.96 (s, 3H), 2.73 (br s, 1H), 3.51-3.67 (m, 7H), 3.93 (tr, J = 9 Hz, 1H), 4.70 (m, 1H), 7.00 (d, J = 12 Hz, 2H), 7.21-7.32 (m, 5H); MS (m/z): $[M+H]^+$ = 486.

Example 29.

N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2,2-dichloroacetamide



A 4M solution of HCl in dioxane (4 mL) was added to a solution of [exo-(1R,5S)-3-(4-{(5S)-[(2,2-dichloro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester (0.27g, 0.50 mmol) in dioxane (4 mL). The reaction mixture was stirred for 3 hours and the solvent was removed *in vacuo*. The residue was dissolved in H_2O (5 mL) and washed with two portions of dichloromethane. The layers were separated and the aqueous layer was frozen and lyophilized to afford the pure N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2,2-dichloroacetamide as a hydrochloride salt.

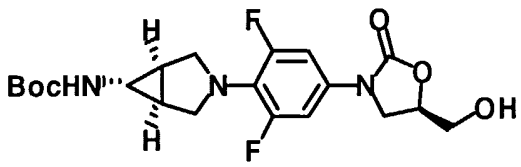
Yield 0.22 g (94%).

^{1}H NMR (300 MHz, DMSO): 1.95 (m, 2H), 2.58 (m, 1H), 3.36 (m, 4H), 3.51 (tr, J = 6 Hz, 2H), 3.65-3.70 (m, 1H), 4.09 (tr, J = 9 Hz, 1H), 4.79 (m, 1H), 6.49 (s, 1H), 7.22 (d, J = 12 Hz, 2H), 8.18 (m, 2H), 9.01 (br tr, 1H).

MS (m/z): $[M+H]^+ = 435$.

Intermediates for the preparation of Example 29 were synthesized as follows.

{exo-(1R,5S)-3-[2,6-Difluoro-4-[(5R)-hydroxymethyl-2-oxo-oxazolidin-3-yl]-phenyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid *tert*-butyl ester.

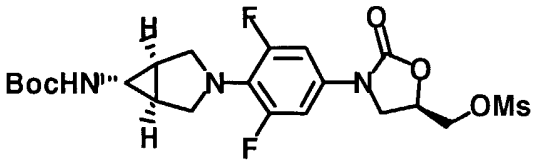


Lithium hexamethyldisilylamide (2.5 mL of a 1.0 M THF solution, 2.5 mmol) was added to a cooled (-78°C) solution of [exo-(1R,5S)-3-(4-benzyloxycarbonylamino-

2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester (0.57 g, 1.24 mmol) in THF (2.5 mL). After stirring 1.5 h, (*R*)-(-)-glycidyl butyrate (0.193 mL, 1.36 mmol) was added and the reaction mixture allowed to warm to room temperature and stirred for 16 hours. The reaction was quenched with satd NH_4Cl (50 mL) and extracted with ethyl acetate. The organic layers were washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (0-5% MeOH-DCM) provided pure {exo-(1R,5S)-3-[2,6-difluoro-4-[(5R)-hydroxymethyl-2-oxo-oxazolidin-3-yl]-phenyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid *tert*-butyl ester.

Yield 0.43 g (81%). ^1H NMR.

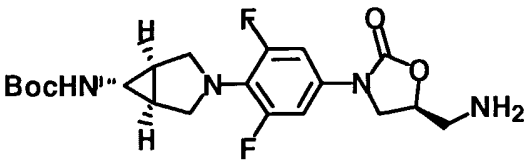
II. Methanesulfonic acid (5R)-3-[4-(exo-(1R,5S)-6-*tert*-butoxycarbonylamino-3-aza-bicyclo[3.1.0]hex-3-yl)-3,5-difluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl ester.



Triethylamine (0.28 mL, 2.02 mmol) and methanesulfonyl chloride (0.078 mL, 1.01 mmol) were added to a cooled (0°C) solution of {exo-(1R,5S)-3-[2,6-difluoro-4-[(5R)-hydroxymethyl-2-oxo-oxazolidin-3-yl]-phenyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid *tert*-butyl ester (0.43 g, 1.01 mmol) in DCM (5 mL). After 30 min, the reaction mixture was warmed to room temperature and diluted with DCM (20 mL). The organic solution was washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated to provide crude methanesulfonic acid (5R)-3-[4-exo-(1R,5S)-6-*tert*-butoxycarbonylamino-3-aza-bicyclo[3.1.0]hex-3-yl)-3,5-difluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl ester.

Yield 0.50 g (99%).

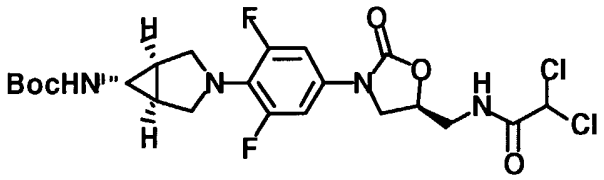
III. {exo-(1R,5S)-3-[4-[(5S)-Aminomethyl-2-oxo-oxazolidin-3-yl]-2,6-difluoro-phenyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid *tert*-butyl ester.



Sodium azide (0.328 g, 5.05 mmol) was added to a solution of methanesulfonic acid (5R)-3-[4-exo-(1R,5S)-6-*tert*-butoxycarbonylamino-3-aza-bicyclo[3.1.0]hex-3-yl)-3,5-difluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl ester (0.50 g, 1.01 mmol) in DMF (5 mL). The reaction mixture was heated at 70°C for 15 hours, cooled and diluted with ethyl acetate. The organic solution was washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated to provide the azide. Triphenylphosphine (0.618 g, 2.36 mmol) was added to a solution of the crude azide in THF (5 mL). After 3 hours at room temperature, H_2O (0.3 mL) was added and the reaction mixture was heated at 40°C for 16 hours. The reaction mixture was then concentrated and the crude product purified by column chromatography (0-5% MeOH-DCM) to provide {exo-(1R,5S)-3-[4-[(5S)-aminomethyl-2-oxo-oxazolidin-3-yl]-2,6-difluoro-phenyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid *tert*-butyl ester.

Yield 0.24 g (56% over 3 steps). ^1H NMR.

IV. [exo-(1R,5S)-3-(4-{(5S)-[(2,2-Dichloro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester



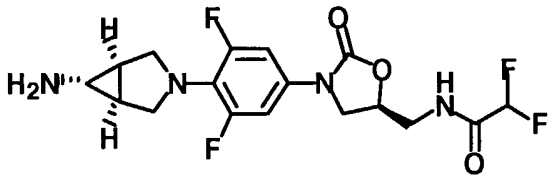
Dichloroacetic anhydride (0.20 mL, 1.36 mmol) and pyridine (0.22 mL, 2.72 mmol) were added to a solution of {exo-(1R,5S)-3-[4-[(5S)-aminomethyl-2-oxo-oxazolidin-3-yl]-2,6-difluoro-phenyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid *tert*-butyl ester (0.29 g, 0.68 mmol) in DMF (5 mL). The mixture was stirred for 15 hours at room temperature. The reaction mixture was then poured into ethyl acetate and washed with 5% citric acid, H_2O and brine. The organic layer is dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (0-3

% MeOH-DCM) provided [exo-(1R,5S)-3-(4-{(5S)-[(2,2-dichloro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester.

Yield 0.27 g (74%). ^{1}H NMR.

Example 30.

N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2,2-difluoroacetamide



A 4M solution of HCl in dioxane (4 mL) was added to a solution of [exo-(1R,5S)-3-(4-{(5S)-[(2,2-difluoro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester (0.34 g, 0.68 mmol) in dioxane (4 mL). The reaction mixture was stirred for 3 hours and the solvent was removed *in vacuo* and lyophilized from H_2O and ACN to afford N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2,2-difluoroacetamide hydrochloride.

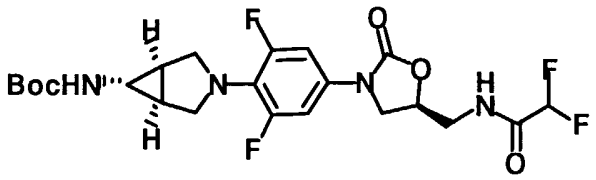
Yield 0.27 g (91%).

^{1}H NMR (300 MHz, DMSO): 1.91 (m, 2H), 2.48 (m, 1H), 3.28 (m, 4H), 3.43 (m, 2H), 3.65 (m, 1H), 4.02 (tr, J = 9 Hz, 1H), 4.71 (m, 1H), 6.18 (tr, J = 54 Hz, 1H), 7.15 (d, J = 12 Hz, 2H), 8.31 (d, J = 4 Hz, 2H), 9.14 (tr, J = 5 Hz, 1H).

MS (m/z): $[M+H]^+$ = 403.

Intermediate for preparation of Example 30 was synthesized as follows.

[exo-(1R,5S)-3-(4-{(5S)-[(2,2-Difluoro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester.

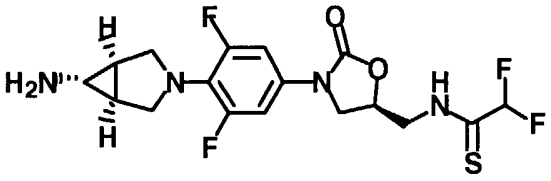


Ethyl difluoroacetate (0.50 mL, 5.0 mmol) and triethylamine (0.278 mL, 2.1 mmol) were added to a solution of {exo-(1R,5S)-3-[4-[(5S)-aminomethyl-2-oxo-oxazolidin-3-yl]-2,6-difluoro-phenyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid *tert*-butyl ester (0.30 g, 0.70 mmol) in MeOH (3 mL). The solution was stirred for 15 hours at room temperature and then concentrated. Purification by column chromatography (0-2% MeOH-DCM) provided [exo-(1R,5S)-3-(4-{(5S)-[(2,2-difluoro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester.

Yield 0.35 g (99%). ^{1}H NMR.

Example 31.

N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2,2-difluoroethanethioamide



A 4M solution of HCl in dioxane (3.8 mL) was added to a solution of [exo-(1R,5S)-3-(4-{(5S)-[(2,2-difluoro-thioacetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester (0.200 g, 0.386 mmol) in dioxane (3.8 mL). The reaction was stirred for 3 hours and the solvent was removed *in vacuo*. The residue was lyophilized from H$_2$O-ACN to afford N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2,2-difluoroethanethioamide hydrochloride.

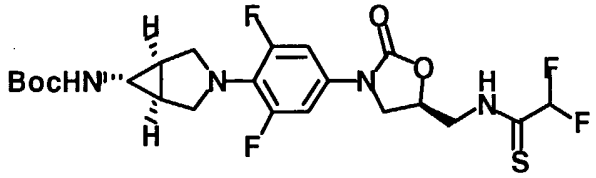
Yield 0.150 g (93%).

^{1}H NMR (300 MHz, DMSO): 1.97 (m, 2H), 2.58 (m, 1H), 3.65 (m, 4H), 3.82 (m, 1H), 3.95 (m, 2H), 4.14 (tr, J = 9 Hz, 1H), 5.02 (m, 1H), 6.51 (tr, J = 56 Hz, 1H), 7.24 (d, J = 12 Hz, 2H), 8.26 (br s, 2H), 11.18 (br tr, 1H).

MS (m/z): $[M+H]^+ = 419$.

Intermediate for preparation of Example 31 was synthesized as follows.

[exo-(1R,5S)-3-(4-{(5S)-[(2,2-Difluoro-thioacetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester.

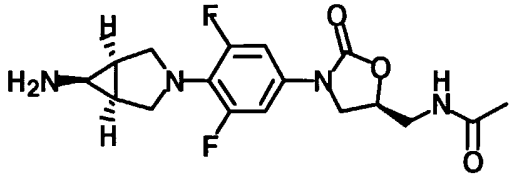


Difluoro-thioacetic acid *O*-(3,3-diphenyl-propyl) ester (0.172 g, 0.56 mmol) was added to a solution of {exo-(1R,5S)-3-[4-[(5S)-aminomethyl-2-oxo-oxazolidin-3-yl]-2,6-difluoro-phenyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid *tert*-butyl ester (0.24 g, 0.56 mmol) in DMF (0.5 mL) and ACN (2 mL). The solution was stirred for 24 hours at room temperature and then concentrated. Purification by column chromatography (0-5% MeOH-DCM) followed by trituration with 1:1 H_2O-ACN afforded [exo-(1R,5S)-3-(4-{(5S)-[(2,2-difluoro-thioacetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester.

Yield 0.20 g (69%). ^{1}H NMR.

Example 32.

N-[((5S)-3-{4-[endo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide



A 4.0M solution of HCl in dioxane (2.0 mL) was added to *tert*-butyl endo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylcarbamate (0.100 g, 0.215) in 2.0 mL of dioxane. The reaction mixture was stirred at room temperature for 2 hours and then concentrated to give N-[((5S)-3-{4-[endo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3,5-difluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide

as the hydrochloride salt.

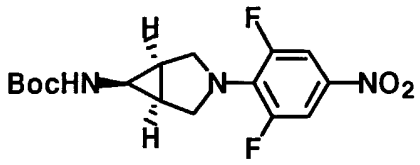
Yield 0.086 g (99%).

^{1}H NMR (300 MHz, DMSO): 1.82 (s, 3H), 1.90 (d, J = 8 Hz, 2H), 2.73 (tr, J = 8 Hz, 1H), 3.28-3.61 (m, 7H), 4.08 (tr, J = 9 Hz, 1H), 4.74 (m, 1H), 7.29 (d, J = 12 Hz, 2H), 7.96 (br s, 2H), 8.26 (tr, J = 6 Hz, 1H).

MS (m/z): $[M+H]^+$ = 367.

Intermediates for preparation of Example 32 were synthesized as follows.

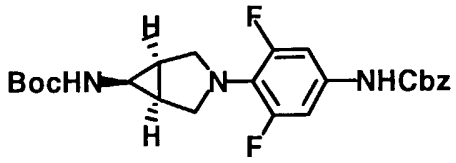
[endo-(1R,5S)-3-(2,6-Difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester.



Diisopropylethylamine (0.125 mL, 0.72 mmol) and 3,4,5-trifluoronitrobenzene (0.084 g, 0.48 mmol) were added to a solution endo-(1R,5S)-6-*tert*-butoxycarbonylamine-3-azabicyclo[3.1.0]hexane (0.105 g, 0.53 mmol; prepared as described in [Brighty, K. E., Castaldi, M. J. *Synlett*, **1996**, 1097-1099]) in DMF (1.5 mL). The mixture was heated for 16 h at 50°C and then cooled to room temperature. The solution was diluted with ethyl acetate and washed with 0.5 M HCl, saturated $NaHCO_3$, brine, and dried (Na_2SO_4). The mixture was filtered and concentrated to give [endo-(1R,5S)-3-(2,6-difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester as a yellow solid.

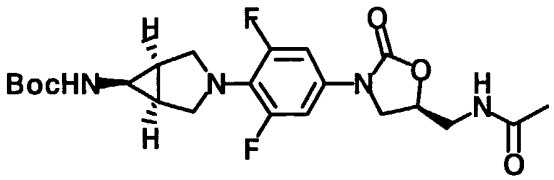
Yield 0.159 g (85%). ^{1}H NMR.

II. [endo-(1R,5S)-3-(4-Benzyloxycarbonylamino-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester.



Iron metal (0.074 g, 1.32 mmol) was added in five portions over 1 h to a refluxing solution of [endo-(1R,5S)-3-(2,6-difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester (0.159 g, 0.44 mmol) and ammonium chloride (0.238 g, 4.4 mmol) in 3.5 mL of 2:1 ethanol-H_2O. The rust colored mixture was refluxed for another 30 min and then cooled and filtered to remove iron oxide. H_2O was added to the filtrate and the mixture concentrated to remove ethanol. The resulting aqueous solution was extracted with three 20 mL portions of ethyl acetate and the combined organic phases washed with H_2O, brine, and dried ($MgSO_4$). Filtration and concentration gave the crude amine (0.130 g, 0.40 mmol) which was dissolved in 2.5 mL of dichloromethane. Pyridine (0.065 mL, 0.80 mmol) was added to the amine solution and after cooling to 0°C, benzyl chloroformate (0.066 mL, 0.46 mmol) was added. The mixture was stirred for 30 min at 0°C and for 30 min at room temperature. The reaction mixture was then diluted with dichloromethane and washed with H_2O, brine and then dried ($MgSO_4$). Concentration gave a yellow oil that was triturated with hexane to afford [endo-(1R,5S)-3-(4-benzyloxycarbonylamino-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester as a yellow solid. Yield 0.175 g (87%). ^1H NMR.

III. *tert*-butyl endo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylcarbamate



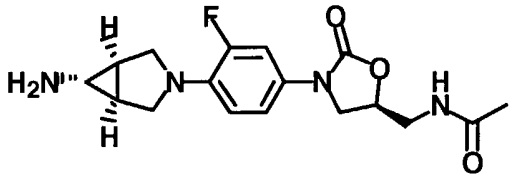
Lithium t-butoxide solution (1.53 mL of a 1.0 M THF solution, 1.53 mmol) was added to a cooled (ca. 0°C) solution of [endo-(1R,5S)-3-(4-benzyloxycarbonylamino-2,6-difluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester (0.175 g, 0.38 mmol) in DMF (0.25 mL) and MeOH (0.031 mL, 0.76 mmol). Solid (*S*)-acetic acid 2-acetylamino-1-chloromethyl-ethyl ester (0.147 g, 0.76 mmol) was then added, and the solution allowed to warm to room temperature and stirred for 20 h. Saturated aqueous ammonium chloride (0.5 mL) was added, along with 4 mL of H_2O and 3 mL of brine. The solution was extracted with three portions of dichloromethane and the combined organic phases dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (0-3% MeOH-DCM) to provide *tert*-butyl endo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylcarbamate.

Yield 0.102 g (58%). ^{1}H NMR.

MS (m/z): $[M+H]^+ = 467$.

Example 33.

N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide



A 4.0M solution of HCl in dioxane (1.0 mL) was added to *tert*-butyl exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylcarbamate (0.046 g, 0.103) in 1.0 mL of dioxane. The reaction mixture was stirred at room temperature for 2 hours and then concentrated to provide N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide as the hydrochloride salt.

Yield 0.039 g (99%).

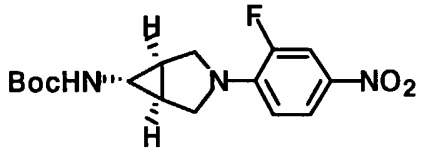
^{1}H NMR (300 MHz, DMSO): 1.82 (s, 3H), 2.02 (br s, 2H), 2.58 (br s, 1H), 3.20 (d, J = 9 Hz, 2H), 3.34-3.69 (m, 5 H), 4.05 (tr, J = 9 Hz, 1H), 4.68 (m, 1H), 6.79

(tr, J = 9 Hz, 1H), 7.10 (dd, J = 9, 2 Hz, 1H), 7.40 (dd, J = 16, 2 Hz, 1H), 8.20 (br s, 2H), 8.25 (tr, J = 6 Hz, 1H).

MS (m/z): $[M+H]^+ = 349$.

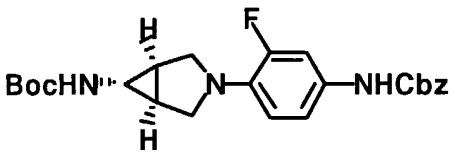
Intermediates for preparation of Example 33 were synthesized as follows.

[exo-(1R,5S)-3-(2-Fluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester.



Diisopropylethylamine (0.19 mL, 1.095 mmol) and 3,4-difluoronitrobenzene (0.105 g, 0.66 mmol) were added to a solution exo-(1R,5S)-6-*tert*-butoxycarbonylamine-3-azabicyclo[3.1.0]hexane (0.144 g, 073 mmol;) in DMF (2 mL). The mixture was heated for 18 h at 50°C and then cooled to room temperature. The solution was diluted with ethyl acetate and washed with 0.5 M HCl, saturated $NaHCO_3$, brine, and dried ($MgSO_4$). The mixture was filtered and concentrated to give [exo-(1R,5S)-3-(2-fluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester as a yellow solid. Yield 0.208 g (84%). ^{1}H NMR.

II. [exo-(1R,5S)-3-(4-Benzyloxycarbonylamino-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester.

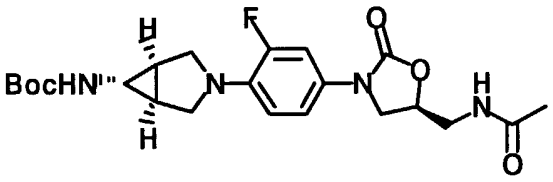


Iron metal (0.102 g, 1.82 mmol) was added in five portions over 1 h to a refluxing solution of [exo-(1R,5S)-3-(2-fluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester (0.205 g, 0.608 mmol) and ammonium chloride (0.367 g, 6.8 mmol) in 4.5 mL of 2:1 ethanol-H_2O. The rust colored mixture was

refluxed for another 30 min and then cooled and filtered to remove iron oxide. H_2O was added to the filtrate and the mixture concentrated to remove ethanol. The resulting aqueous solution was extracted with three 20 mL portions of ethyl acetate and the combined organic phases washed with H_2O, brine, and dried ($MgSO_4$). Filtration and concentration gave the crude amine (0.171 g, 0.55 mmol) which was dissolved in 3.0 mL of dichloromethane. Pyridine (0.089 mL, 1.1 mmol) was added to the amine solution and after cooling to 0°C, benzyl chloroformate (0.090 mL, 0.63 mmol) was added. The mixture was stirred for 30 min at 0°C and for 30 min at room temperature. The reaction mixture was then diluted with dichloromethane and washed with H_2O, brine and then dried ($MgSO_4$). Concentration gave a yellow oil that was triturated with hexane to afford [exo-(1R,5S)-3-(4-benzyloxycarbonylamino-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester as a yellow solid.

Yield 0.230 g (86%). ^1H NMR.

III. *tert*-butyl exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylcarbamate



Lithium butoxide solution (1.15 mL of a 1.0 M THF solution, 1.15 mmol) was added to a cooled (0°C) solution of [exo-(1R,5S)-3-(4-benzyloxycarbonyl-amino-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester (0.170 g, 0.385 mmol) in DMF (0.35 mL) and MeOH (0.031 mL, 0.771 mmol). Solid (*S*)-acetic acid 2-acetylamino-1-chloromethyl-ethyl ester (0.149 g, 0.771 mmol) was then added and the solution allowed to warm to room temperature and stirred for 20 h. Saturated aqueous ammonium chloride (0.8 mL) was added, along with 7 mL of H_2O and 6 mL of brine. The solution was extracted with three portions of dichloromethane and the combined organic phases dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (0-3% MeOH-DCM) to provide *tert*-butyl exo-(1R,5S)-3-(4-

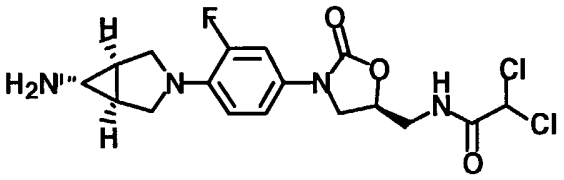
{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)-3-azabicyclo[3.1.0]hex-6-ylcarbamate.

Yield 0.115 g (66%). ^{1}H NMR

MS (m/z): $[M+H]^+ = 449$.

Example 34.

N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2,2-dichloroacetamide



A 4M solution of HCl in dioxane (3 mL) was added to a solution of [exo-(1R,5S)-3-(4-{(5S)-[(2,2-dichloro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester (0.08 g, 0.15 mmol) in dioxane (4 mL). The reaction mixture was stirred for 3 hours and the solvent was removed *in vacuo*. The residue was dissolved in H_2O (5 mL) and washed with two portions of dichloromethane. The layers were separated and the aqueous layer was lyophilized to afford the pure N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2,2-dichloroacetamide as a hydrochloride salt.

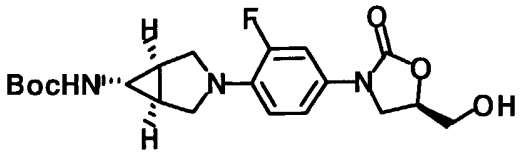
Yield 0.042 g (62%).

^{1}H NMR (300 MHz, CD_3OD): 2.04 (m, 2H), 2.70 (s, 1H), 3.24 (d, J = 9 Hz, 2H), 3.59-3.81 (m, 5H), 4.11 (tr, J = 9 Hz, 1H), 4.81 (m 1H), 6.26 (s, 1H), 6.79 (tr, J = 9 Hz, 1H), 7.08 (dd, J = 9, 2 Hz, 1H), 7.39 (dd, J = 16, 3 Hz, 1H).

MS (m/z): $[M+H]^+ = 418$.

Intermediates for preparation of Example 34 were synthesized as follows.

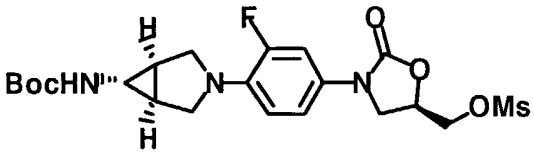
{exo-(1R,5S)-3-[2-Fluoro-4-[(5R)-hydroxymethyl-2-oxo-oxazolidin-3-yl]-phenyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid *tert*-butyl ester.



Lithium hexamethyldisilylamide (6.0 mL of a 1.0 M THF solution, 6.0 mmol) was added to a cooled (-78°C) solution of exo-(1R,5S)-3-(4-benzyloxycarbonylamino-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester (1.33 g, 3.0 mmol) in THF (20 mL). After stirring 1.5 h, (*R*)-(-)-glycidyl butyrate (0.467 mL, 3.3 mmol) was added and the reaction mixture allowed to warm to room temperature and stirred for 16 hours. The reaction was quenched with satd NH_4Cl (50 mL) and extracted with ethyl acetate. The organic layers were washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography (0-5% MeOH-DCM) provided pure {exo-(1R,5S)-3-[2-fluoro-4-[(5R)-hydroxymethyl-2-oxo-oxazolidin-3-yl)-phenyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid *tert*-butyl ester.

Yield 0.70 g (57%). ^1H NMR.

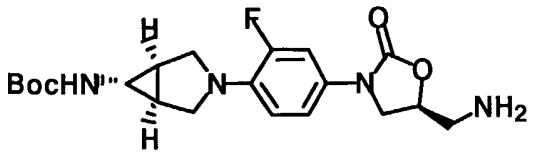
II. Methanesulfonic acid (5R)-3-[4-(exo-(1R,5S)-6-*tert*-butoxycarbonylamino-3-aza-bicyclo[3.1.0]hex-3-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl ester.



Triethylamine (0.354 mL, 2.55 mmol) and methanesulfonyl chloride (0.197 mL, 2.55 mmol) were added to a cooled (0°C) solution of {exo-(1R,5S)-3-[2-fluoro-4-[(5R)-hydroxymethyl-2-oxo-oxazolidin-3-yl]-phenyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid *tert*-butyl ester (0.70 g, 1.7 mmol) in DCM (10 mL). After 30 min, the reaction mixture was warmed to room temperature and diluted with DCM (20 mL). The organic solution was washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated to provide crude methanesulfonic acid (5R)-3-[4-(exo-(1R,5S)-6-*tert*-butoxycarbonylamino-3-aza-bicyclo[3.1.0]hex-3-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl ester.

Yield 0.82 g (99%).

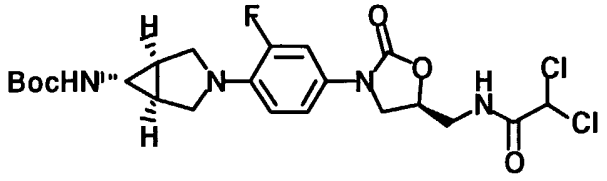
III. {exo-(1R,5S)-3-[4-[(5S)-Aminomethyl-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid *tert*-butyl ester.



Sodium azide (0.552 g, 8.5 mmol) was added to a solution of methanesulfonic acid 3-[4-(exo-(1R,5S)-6-*tert*-butoxycarbonylamino-3-aza-bicyclo[3.1.0]hex-3-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-(5R)-ylmethyl ester (0.82 g, 1.7 mmol) in DMF (10 mL). The reaction mixture was heated at 70°C for 15 hours, cooled and diluted with ethyl acetate. The organic solution was washed with H_2O, brine, and dried ($MgSO_4$), filtered and concentrated to provide the azide. Triphenylphosphine (0.89 g, 3.4 mmol) was added to a solution of the crude azide in THF (5 mL). After 3 hours at room temperature, H_2O (1.0 mL) was added and the reaction mixture was heated at 40°C for 16 hours. The reaction mixture was then concentrated and the crude product purified by column chromatography (0-5% MeOH-DCM) to provide {exo-(1R,5S)-3-[4-[(5S)-aminomethyl-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid *tert*-butyl ester.

Yield 0.40 g (58% over 3 steps). ^1H NMR.

IV. [exo-(1R,5S)-3-(4-{(5S)-[(2,2-Dichloro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester.



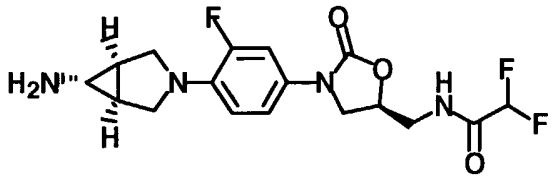
Ethyl dichloroacetate (0.052 mL, 0.48 mmol) and triethylamine (0.063 mL, 0.48 mmol) were added to a solution of {exo-(1R,5S)-3-[4-((5S)-aminomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid *tert*-butyl ester (0.10 g, 0.24 mmol) in DMF (2 mL). The mixture was stirred for 15

hours at room temperature and then additional ethyl dichloroacetate (0.52 mL, 4.8 mmol) was added. The reaction mixture was stirred 24 hours and then concentrated and purified by column chromatography (0-3 % MeOH-DCM) and preparative TLC (7% MeOH-DCM) to afford [exo-(1R,5S)-3-(4-{(5S)-[(2,2-dichloro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester.

Yield 0.08 g (31%). ^{1}H NMR.

Example 35.

N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2,2-difluoroacetamide



A 4M solution of HCl in dioxane (1 mL) was added to a solution of [exo-(1R,5S)-3-(4-{(5S)-[(2,2-difluoro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester (0.03 g, 0.06 mmol) in dioxane (1 mL). The reaction mixture was stirred for 3 hours and the solvent was removed *in vacuo*. The residue was dissolved in H_2O and washed with two portions of dichloromethane. The aqueous phase was then lyophilized to afford N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2,2-difluoroacetamide as a hydrochloride salt.

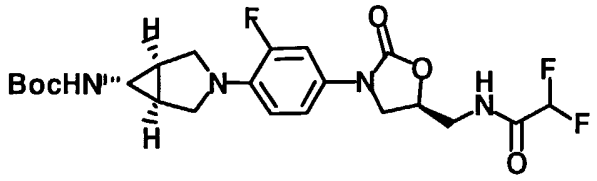
Yield 0.016 g (63%).

^{1}H NMR (300 MHz, CD_3OD): 2.04 (m, 2H), 2.69 (m, 1H), 3.25 (d, J = 9 Hz, 2H), 3.62-3.81 (m, 5H), 4.11 (tr, J = 9 Hz, 1H), 4.84 (m, 1H), 6.05 (tr, J = 54 Hz, 1H), 6.79 (tr, J = 9 Hz, 1H), 7.09 (dd, J = 9, 2 Hz, 1H), 7.38 (dd, J = 16, 2 Hz, 1H).

MS (m/z): $[M+H]^+$ = 385.

Intermediate for preparation of Example 35 was synthesized as follows.

[exo-(1R,5S)-3-(4-{(5S)-[(2,2-Difluoro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester.

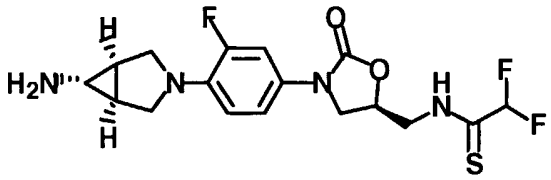


Ethyl difluoroacetate (0.50 mL, 5.0 mmol) and triethylamine (0.066 mL, 0.5 mmol) were added to a solution of {exo-(1R,5S)-3-[4-[(5S)-aminomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-3-aza-bicyclo[3.1.0]hex-6-yl}-carbamic acid *tert*-butyl ester (0.14 g, 0.34 mmol) in MeOH (3 mL). The solution was stirred for 15 hours at room temperature and then concentrated. Purification by column chromatography (0-2% MeOH-DCM) provided [exo-(1R,5S)-3-(4-{(5S)-[(2,2-difluoro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester.

Yield 0.120 g (70%). ^{1}H NMR.

Example 36.

N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2,2-difluoroethanethioamide



A 4M solution of HCl in dioxane (1.0 mL) was added to a solution of [exo-(1R,5S)-3-(4-{(5S)-[(2,2-difluoro-thioacetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester (0.099 g, 0.198 mmol) in dioxane (1.0 mL). The reaction was stirred for 3 hours and the solvent was removed *in vacuo*. The residue was lyophilized from H_2O-ACN to afford N-[((5S)-3-{4-[exo-(1R,5S)-6-amino-3-azabicyclo[3.1.0]hex-3-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2,2-difluoroethanethioamide

as a hydrochloride salt.

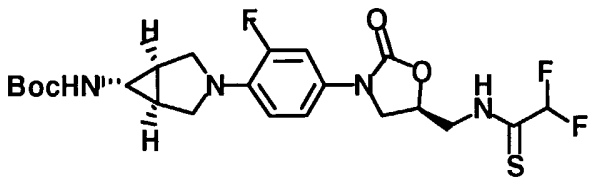
Yield 0.078 g (90%).

^{1}H NMR (300 MHz, DMSO): 2.05 (m, 2H), 2.56 (m, 1H), 3.21 (d, J = 9 Hz, 2H), 3.78-3.98 (m, 5H), 4.11 (tr, J = 9 Hz, 1H), 5.00 (m, 1H), 6.51 (tr, J = 55 Hz, 1H), 6.80 (tr, J = 9 Hz, 1H), 7.11 (dd, J = 9, 2 Hz, 1H), 7.40 (dd, J = 16, 2 Hz, 1H), 8.38 (d, J = 4 Hz, 2H), 11.2 (br tr, 1H).

MS (m/z): $[M+H]^+$ = 401.

Intermediate for preparation of Example 36 was synthesized as follows.

[exo-(1R,5S)-3-(4-{(5S)-[(2,2-Difluoro-thioacetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester.

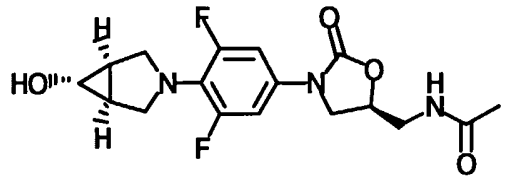


Lawesson's reagent (0.075 g, 0.18 mmol) was added to a solution of [exo-(1R,5S)-3-(4-{(5S)-[(2,2-difluoro-acetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester (0.10 g, 0.20 mmol) in dioxane (1.8 mL) and stirred for 3 hours at 95°C. The solution was cooled to room temperature and concentrated. Purification by column chromatography (0-2% MeOH-DCM) afforded [exo-(1R,5S)-3-(4-{(5S)-[(2,2-difluoro-thioacetylamino)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-carbamic acid *tert*-butyl ester.

Yield 0.099 g (96%). ^{1}H NMR.

Example 37.

N-[((5S)-3-{3,5-difluoro-4-[exo-(1R,5S)-6-hydroxy-3-azabicyclo[3.1.0]hex-3-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide



Hydrogen fluoride (2.0 μL of a 48% solution) was added to a solution of *N*-(3-{4-[exo-(1R,5S)-6-(*tert*-butyl-dimethyl-silanyloxy)-3-aza-bicyclo[3.1.0]hex-3-yl]-3,5-difluoro-phenyl}-2-oxo-oxazolidin-(5S)-ylmethyl)-acetamide(0.027 g, 0.056 mmol) in 4 mL of acetic acid-THF-H_2O (2:1:1). The reaction mixture was stirred for 4 hours at room temperature and then the THF was removed *in vacuo*. The aqueous solution was diluted with 2.5% $NaHCO_3$ and extracted with three portions of ethyl acetate. The combined organic phases were washed with brine, and dried ($MgSO_4$), filtered and concentrated. The product was triturated with hexane to provide pure N-[((5S)-3-{3,5-difluoro-4-[exo-(1R,5S)-6-hydroxy-3-azabicyclo[3.1.0]hex-3-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide as a white solid.

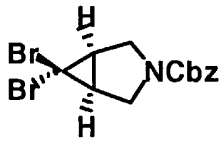
Yield 0.017 g (85%).

^1H NMR (300 MHz, CD_3OD): 1.62 (s, 2H), 1.95 (s, 3H), 3.43-3.54 (m, 7H), 3.72 (m, 1H), 4.06 (tr, J = 9 Hz, 1H), 4.76 (m, 1H), 7.13 (d, J = 12 Hz, 2H).

MS (m/z): $[M+H]^+ = 368$.

Intermediates for preparation of Example 37 were synthesized as follows.

6,6-Dibromo-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester.

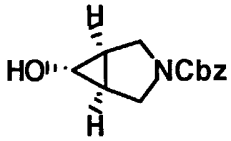


A solution of bromoform (0.94 mL, 10.8 mmol) in 5 mL of dichloromethane was added over 1.5 hours to a stirred solution of benzyl 3-pyrroline-1-carboxylate (1.77 mL, 9.8 mmol) and benzyltriethylammonium chloride (0.055 g, 0.025 mmol) in 1:1 dichloromethane-50% aqueous NaOH (60 mL). The black solution was stirred for 18 hours at room temperature and then diluted with dichloromethane and H_2O. The layers were separated and the organic phase washed with satd NH_4Cl, brine, and dried ($MgSO_4$), filtered and concentrated. The crude product was purified by

column chromatography (0-20% ethyl acetate-hexane) to afford 6,6-dibromo-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester.

Yield 1.83 g (50%). ^{1}H NMR.

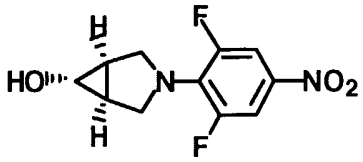
II. exo-(1R,5S)-6-Hydroxy-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester.



n-BuLi (1.64 mL of a 1.6M solution, 2.62 mmol) was added dropwise over 1 hour to a cooled (–95°C) solution of 6,6-dibromo-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester (0.85 g, 2.28 mmol) in THF (20 mL). After 10 minutes, a solution of catechol borane (4.56 mL of a 1.0M solution, 4.56 mmol) was added dropwise over 30 minutes. The reaction mixture was allowed to warm slowly to room temperature and then heated at 50°C for 16 h. After cooling to 0°C, the reaction mixture was treated with 50% H_2O_2 (0.53 mL, 9.12 mmol) and 2.5M NaOH (2.7 mL, 6.84 mmol) and stirred for 18 hours. The reaction was quenched by addition of satd $Na_2S_2O_3$ and 2.5% $NaHCO_3$. The aqueous solution was concentrated to remove THF and then extracted with three portions of ethyl acetate. Combined organic phases were washed with satd $Na_2S_2O_3$, brine, and dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (20-50% ethyl acetate-hexane) to afford exo-(1R,5S)-6-hydroxy-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester.

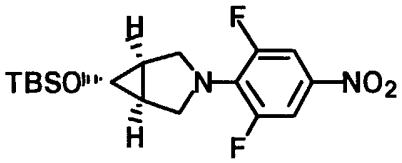
Yield 0.076 g (15%). ^{1}H NMR.

III. exo-(1R,5S)-3-(2,6-Difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexan-6-ol.



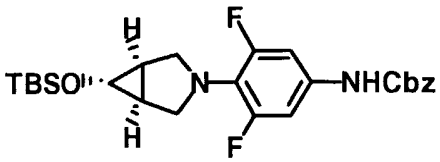
Palladium hydroxide (0.030 g, 10% on carbon) was added to a solution of exo-(1R,5S)-6-hydroxy-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester (0.071 g, 0.3 mmol) in methanol (2mL). The mixture was stirred under a hydrogen atmosphere for 3 hours and then filtered through a pad of celite and concentrated to give exo-(1R,5S)-3-aza-bicyclo[3.1.0]hexan-6-ol as a solid film. The amine was dissolved in DMF (0.75 mL) and treated with diisopropylethylamine (0.078 mL, 0.45 mmol) and 3,4,5-trifluoronitrobenzene (0.048 g, 0.27 mmol). The mixture was heated for 12 h at 50°C, diluted with ethyl acetate and washed with 0.5 M HCl, saturated $NaHCO_3$, brine, and dried ($MgSO_4$). The mixture was filtered and concentrated to give exo-(1R,5S)-3-(2,6-difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexan-6-ol.
Yield 0.070 g (91%). ^1H NMR.

IV. exo-(1R,5S)-6-(*tert*-Butyl-dimethyl-silanyloxy)-3-(2,6-difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane.



Imidazole (0.033 g, 0.49 mmol) and *tert*-butyldimethylsilyl chloride (0.065 g, 0.43 mmol) were added to a solution of (exo-(1R,5S)-3-(2,6-difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexan-6-ol (0.070 g, 0.27 mmol) in dichloromethane (3.0 mL). After 3 hours, satd $NaHCO_3$ was added and the layers separated. The aqueous phase was extracted with more dichloromethane and the combined organic phases washed with 0.3 M HCl, saturated $NaHCO_3$, brine, and dried ($MgSO_4$). The mixture was filtered and concentrated to give exo-(1R,5S)-6-(*tert*-butyl-dimethyl-silanyloxy)-3-(2,6-difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane.
Yield 0.088 g (88%). ^1H NMR.

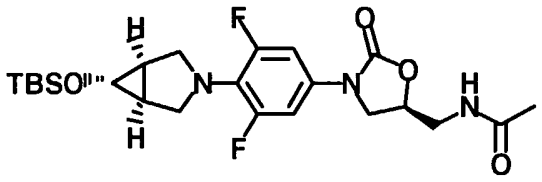
V. {4-[exo-(1R,5S)-6-(*tert*-Butyl-dimethyl-silanyloxy)-3-aza-bicyclo[3.1.0]hex-3-yl]-3,5-difluoro-phenyl}-carbamic acid benzyl ester.



Iron metal (0.039 g, 0.713 mmol) was added in five portions over 1 h to a refluxing solution of exo-(1R,5S)-6-(*tert*-butyl-dimethyl-silanyloxy)-3-(2,6-difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane (0.088 g, 0.24 mmol) and ammonium chloride (0.129 g, 2.38 mmol) in 2.5 mL of 2:1 ethanol-H_2O. The rust colored mixture was refluxed for another 30 min and then cooled and filtered to remove iron oxide. H_2O was added to the filtrate and the mixture concentrated to remove ethanol. The resulting aqueous solution was extracted with three 15 mL portions of ethyl acetate and the combined organic phases washed with H_2O, brine, and dried ($MgSO_4$). Filtration and concentration gave the crude amine (0.078 g, 0.23 mmol) which was dissolved in 1.5 mL of dichloromethane. Pyridine (0.037 mL, 0.46 mmol) was added to the amine solution and after cooling to 0°C, benzyl chloroformate (0.037 mL, 0.26 mmol) was added. The mixture was stirred for 30 min at 0°C and for 30 min at room temperature. The reaction mixture was then diluted with dichloromethane and washed with H_2O, brine and then dried ($MgSO_4$). Concentration gave an oil that was triturated with hexane and purified by column chromatography (0-10% ethyl acetate-hexane) to afford {4-[exo-(1R,5S)--6-(*tert*-butyl-dimethyl-silanyloxy)-3-aza-bicyclo[3.1.0]hex-3-yl]-3,5-difluoro-phenyl}-carbamic acid benzyl ester.

Yield 0.078 g (70%). ^1H NMR.

VI. *N*-((5S)-3-{4-[exo-(1R,5S)-6-(*tert*-Butyl-dimethyl-silanyloxy)-3-aza-bicyclo[3.1.0]hex-3-yl]-3,5-difluoro-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide.

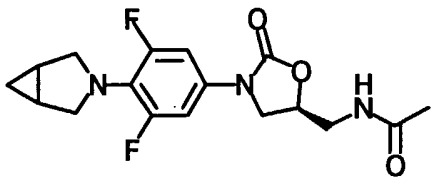


Lithium butoxide solution (0.53 mL of a 1.0 M THF solution, 0.53 mmol) was added to a cooled (0°C) solution of {4-[exo-(1R,5S)-6-(*tert*-butyl-dimethyl-silanyloxy)-3-aza-bicyclo[3.1.0]hex-3-yl]-3,5-difluoro-phenyl}-carbamic acid benzyl ester (0.077 g, 0.16 mmol) in DMF (0.1 mL) and MeOH (0.013 mL, 0.32 mmol). Solid (*S*)-acetic acid 2-acetylamino-1-chloromethyl-ethyl ester (0.062 g, 0.32 mmol) was then added and the solution allowed to warm to room temperature and stirred for 20 h. Saturated aqueous ammonium chloride (0.5 mL) was added, along with 4 mL of H_2O and 3 mL of brine. The solution was extracted with three portions of dichloromethane and the combined organic phases dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (0-2% MeOH-DCM) to provide *N*-((5S)-3-{4-[exo-(1R,5S)-6-(*tert*-butyl-dimethyl-silanyloxy)-3-aza-bicyclo[3.1.0]hex-3-yl]-3,5-difluoro-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide.

Yield 0.056 g (73%). ^{1}H NMR.

Example 38.

N-({(5S)-3-[4-(3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide



Lithium butoxide solution (1.6 mL of a 1.0 M THF solution, 1.6 mmol) was added to a cooled (0°C) solution of [4-(3-aza-bicyclo[3.1.0]hex-3-yl)-3,5-difluoro-phenyl]-carbamic acid benzyl ester (0.180 g, 0.52 mmol) in DMF (0.35 mL) and MeOH (0.042 mL, 1.05 mmol). Solid (*S*)-acetic acid 2-acetylamino-1-chloromethyl-ethyl ester (0.203 g, 1.05 mmol) was then added and the solution allowed to warm to room temperature and stirred for 20 h. Saturated aqueous ammonium chloride (0.8 mL) was added, along with 7 mL of H_2O and 6 mL of brine. The solution was extracted with three portions of dichloromethane and the combined organic phases dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (0-2% MeOH-DCM) to provide

N-({(5S)-3-[4-(3-azabicyclo[3.1.0]hex-3-yl)-3,5-difluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide.

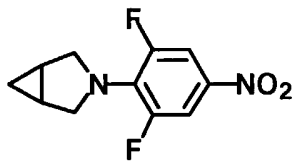
Yield 0.127 g (70%).

^{1}H NMR (300 MHz, $CDCl_3$): 0.53 (m, 2H), 1.47 (m, 2H), 2.02 (s, 3H), 3.48 (m, 4H), 3.50-3.74 (m, 3H), 3.96 (tr, J = 9 Hz, 1H), 4.74 (m, 1H), 5.98 (tr, J = 5 Hz, 1H), 7.00 (d, J = 12 Hz, 2H).

MS (m/z): $[M+H]^+ = 352$.

Intermediates for preparation of Example 38 were synthesized as follows.

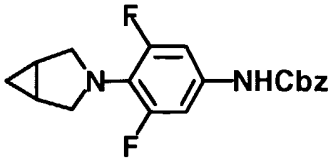
3-(2,6-Difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane.



Diisopropylethylamine (0.39 mL, 2.25 mmol) and 3,4,5-trifluoronitrobenzene (0.143 g, 0.81 mmol) were added to a solution 3-aza-bicyclo[3.1.0]hexane (prepared by the general procedure of Brighty, K. E., Castaldi, M. J. *Synlett*, **1996**, 1097-1099; 0.106 g of the HCl salt, 0.9 mmol) in DMF (2 mL). The mixture was heated for three days at 45°C and then cooled to room temperature. The solution was diluted with ethyl acetate and washed with 0.5 M HCl, saturated $NaHCO_3$, brine, and dried ($MgSO_4$). The mixture was filtered and concentrated to give 3-(2,6-difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane as a yellow solid.

Yield 0.177 g (82%). ^{1}H NMR.

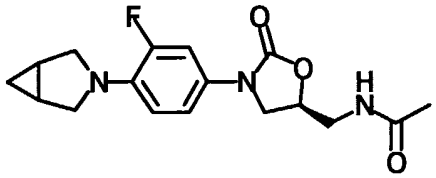
II. [4-(3-Aza-bicyclo[3.1.0]hex-3-yl)-3,5-difluoro-phenyl]-carbamic acid benzyl ester.



Iron metal (0.120 g, 2.15 mmol) was added in five portions over 1 h to a refluxing solution of 3-(2,6-difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane (0.172 g, 0.72 mmol) and ammonium chloride (0.385 g, 7.2 mmol) in 6.0 mL of 2:1 ethanol-H_2O. The rust colored mixture was refluxed for another 30 min and then cooled and filtered to remove iron oxide. H_2O was added to the filtrate and the mixture concentrated to remove ethanol. The resulting aqueous solution was extracted with three 20 mL portions of ethyl acetate and the combined organic phases washed with H_2O, brine, and dried ($MgSO_4$). Filtration and concentration gave the crude amine (0.145 g, 0.69 mmol) which was dissolved in 5.0 mL of dichloromethane. Pyridine (0.111 mL, 1.38 mmol) was added to the amine solution and after cooling to 0°C, benzyl chloroformate (0.113 mL, 0.79 mmol) was added. The mixture was stirred for 30 min at 0°C and for 30 min at room temperature. The reaction mixture was then diluted with dichloromethane and washed with H_2O, brine and then dried ($MgSO_4$). Concentration gave a yellow oil that was triturated with hexane to afford [4-(3-aza-bicyclo[3.1.0]hex-3-yl)-3,5-difluoro-phenyl]-carbamic acid benzyl ester as a yellow solid.
Yield 0.195 g (79%). ^1H NMR.

Example 39.

N-({(5S)-3-[4-(3-azabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide



Lithium butoxide solution (2.5 mL of a 1.0 M THF solution, 2.5 mmol) was added to a cooled (0°C) solution of [4-(3-aza-bicyclo[3.1.0]hex-3-yl)-3-fluoro-phenyl]-carbamic acid benzyl ester (0.267 g, 0.82 mmol) in DMF (0.6 mL) and MeOH (0.060 mL, 1.64 mmol). Solid (*S*)-acetic acid 2-acetylamino-1-chloromethyl-ethyl ester (0.316 g, 1.64 mmol) was then added and the solution allowed to warm to room temperature and stirred for 20 h. Saturated aqueous ammonium chloride (1.0 mL) was added, along with 9 mL of H_2O and 8 mL of brine. The solution was extracted with three portions of dichloromethane and the combined organic phases

dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (0-3% MeOH-DCM) to provide N-({(5S)-3-[4-(3-azabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide.

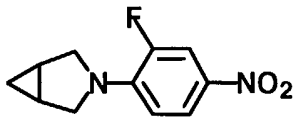
Yield 0.169 g (62%).

^{1}H NMR (300 MHz, $CDCl_3$): 0.49 (m, 1H), 0.61 (m, 1H), 1.56 (m, 2H), 2.01 (s, 3H), 3.22 (d, J = 9 Hz, 2H), 3.56-3.68 (m, 5 H), 3.97 (tr, J = 9 Hz, 1H), 4.75 (m, 1H), 6.46 (tr, J = 6 Hz, 1H), 6.59 (tr, J = 9 Hz, 1H), 6.96 (dd, J = 9, 3 Hz, 1H), 7.27 (dd, J = 15, 2 Hz, 1H).

MS (m/z): $[M+H]^+ = 334$.

Intermediates for preparation of Example 39 were synthesized as follows.

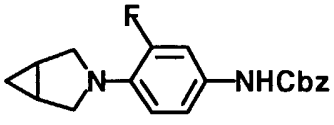
3-(2-Fluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane.



Diisopropylethylamine (0.56 mL, 3.2 mmol) and 3,4-difluoronitrobenzene (0.184 g, 1.16 mmol) were added to a solution 3-aza-bicyclo[3.1.0]hexane (0.152 g of HCl salt, 1.28 mmol; prepared as described in US Patent 4,183,857) in DMF (3.2 mL). The mixture was heated for three days at 45°C and then cooled to room temperature. The solution was diluted with ethyl acetate and washed with 0.5 M HCl, saturated $NaHCO_3$, brine, and dried ($MgSO_4$). The mixture was filtered and concentrated to give 3-(2-fluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane as a yellow solid.

Yield 0.233 g (82%). ^{1}H NMR.

II. [4-(3-Aza-bicyclo[3.1.0]hex-3-yl)-3-fluoro-phenyl]-carbamic acid benzyl ester

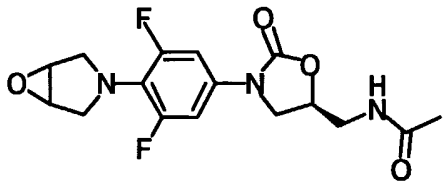


Iron metal (0.168 g, 3.15 mmol) was added in five portions over 1 h to a refluxing solution of 3-(2-fluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane (0.233 g, 1.05 mmol) and ammonium chloride (0.566 g, 10.5 mmol) in 7.5 mL of 2:1 ethanol-H_2O. The rust colored mixture was refluxed for another 30 min and then cooled and filtered to remove iron oxide. H_2O was added to the filtrate and the mixture concentrated to remove ethanol. The resulting aqueous solution was extracted with three 20 mL portions of ethyl acetate and the combined organic phases washed with H_2O, brine, and dried ($MgSO_4$). Filtration and concentration gave the crude amine (0.194 g, 0.99 mmol) which was dissolved in 8.0 mL of dichloromethane. Pyridine (0.160 mL, 2.0 mmol) was added to the amine solution and after cooling to 0°C, benzyl chloroformate (0.162 mL, 1.14 mmol) was added. The mixture was stirred for 30 min at 0°C and for 30 min at room temperature. The reaction mixture was then diluted with dichloromethane and washed with H_2O, brine and then dried ($MgSO_4$). Concentration gave a yellow oil that was triturated with hexane to afford [4-(3-aza-bicyclo[3.1.0]hex-3-yl)-3-fluoro-phenyl]-carbamic acid benzyl ester as a yellow solid.

Yield 0.299 g (87%). ^1H NMR.

Example 40.

N-({(5S)-3-[3,5-difluoro-4-(6-oxa-3-azabicyclo[3.1.0]hex-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide



Lithium butoxide solution (1.9 mL of a 1.0 M THF solution, 1.9 mmol) was added to a cooled (0°C) solution of [3,5-difluoro-4-(6-oxa-3-aza-bicyclo[3.1.0]hex-3-yl)-phenyl]-carbamic acid benzyl ester (0.22g, 0.64 mmol) in DMF (0.43 mL) and MeOH (0.05 mL, 1.2 mmol). Solid (*S*)-acetic acid 2-acetylamino-1-chloromethyl-ethyl ester (0.25 g, 1.27 mmol) was then added and the solution allowed to warm to room temperature and stirred for 16 h. The reaction mixture was quenched with sat. NH_4Cl and extracted with ethyl acetate. The organic layers were washed with

water, brine and dried ($MgSO_4$). The title compound was isolated by silica gel chromatography (0-3% MeOH / dichloromethane).

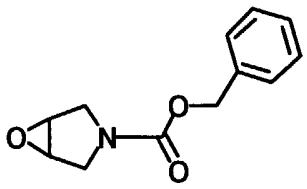
Yield 140 mg (62%).

^1H NMR (300 MHz, $CDCl_3$): 2.02 (s, 3H), 3.48-3.52 (d, J = 11 Hz, 2H), 3.62-3.67 (m, 2H), 3.69-3.74 (m, 3H), 3.80-3.84 (d, J = 11 Hz, 2H), 3.93-3.99 (t, J = 9 Hz, 1H), 4.72-4.79 (m, 1H), 6.49-6.51 (s, 1H), 7.00-7.04 (d, J = 11 Hz, 2H).

MS (m/z): $[M+H]^+ = 354.2$

Intermediates for preparation of Example 40 were synthesized as follows.

6-Oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester

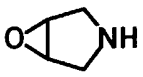


Benzyl-3-pyrroline-1-carboxylate (5 g, 24.6 mmol) and 3-chloroperoxybenzoic acid (8.5 g, 49.2 mmol) were dissolved in dichloromethane (250 mL) and stirred for 16 h at room temperature. The reaction mixture was washed with sat. $NaHCO_3$, brine and dried ($MgSO_4$). The title compound was isolated by silica gel chromatography (0-35% EtOAc-hexanes).

Yield 3.6 g (68%).

^1H NMR (300 MHz, $CDCl_3$): 3.34-3.40 (d, J = 11 Hz, 2H), 3.66 (s, 2H), 3.80-3.89 (t, J = 12 Hz, 2H), 5.10(s, 2H), 7.27-7.38 (m, 5H).

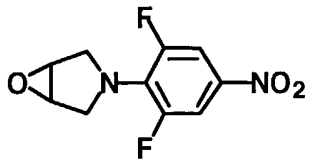
II. 6-Oxa-3-aza-bicyclo[3.1.0]hexane



20% Palladium hydroxide on carbon (1.3 g) was added to a solution of 6-Oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester (3.5 g, 16.0 mmol) dissolved in methanol (45 mL). The flask was charged with hydrogen gas and the

mixture was stirred at room temperature for 4 h. The reaction mixture was filtered through celite and the solvent removed to provide the title compound which was used without further purification.

III. 3-(2,6-Difluoro-4-nitro-phenyl)-6-oxa-3-aza-bicyclo[3.1.0]hexane

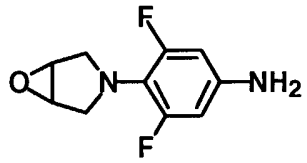


Trifluoronitrobenzene (1.04 g, 5.88 mmol) was added to a solution of 6-Oxa-3-aza-bicyclo[3.1.0]hexane (0.5 g, 5.88 mmol) dissolved in DMF (10.0 mL) and DIEA (1.5 mL, 8.82 mmol) and heated to 60°C for 16 h. The reaction mixture was cooled to room temperature, dissolved in EtOAc, and washed with 0.1 N HCl, water, brine and dried ($MgSO_4$). The title compound was isolated by silica gel chromatography (0-1.5% MeOH-DCM) as a yellow solid.

Yield 0.4 g (28%).

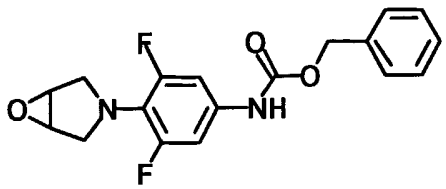
^1H NMR (300 MHz, $CDCl_3$): 3.75-3.82 (m, 4H), 4.16-21 (d, J = 14 Hz, 2H), 7.71-7.75 (d, J = 14 Hz, 2H).

IV. 3,5-Difluoro-4-(6-oxa-3-aza-bicyclo[3.1.0]hex-3-yl)-phenylamine



10 % Palladium on carbon (0.02 g) was added to 3-(2,6-difluoro-4-nitro-phenyl)-6-oxa-3-aza-bicyclo[3.1.0]hexane (0.2 g, 0.83 mmol) dissolved in ethyl acetate (8.0 mL). The flask was charged with hydrogen gas and the mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through celite and the solvent removed to get the title compound which was used directly in the next reaction.

V. [3,5-Difluoro-4-(6-oxa-3-aza-bicyclo[3.1.0]hex-3-yl)-phenyl]-carbamic acid benzyl ester



3,5-Difluoro-4-(6-oxa-3-aza-bicyclo[3.1.0]hex-3-yl)-phenylamine (0.14 g, 0.66 mmol) was dissolved in dichloromethane (1.0 mL) and pyridine (0.11 mL, 1.32 mmol) and stirred at 0°C. Benzyl chloroformate (0.1 mL, 0.72 mmol) was added and the mixture was stirred at 0°C for one hour. The reaction mixture was allowed to warm to room temperature, washed with water, brine and dried ($MgSO_4$). The title compound was isolated by silica gel chromatography (0-1% MeOH-DCM) as a pale yellow solid.

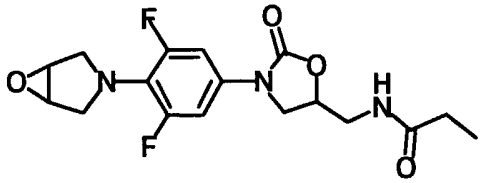
Yield 0.22 g (96%).

^1H NMR (300 MHz, $CDCl_3$): 3.42-3.46 (d, J = 11 Hz, 2H), 3.70 (s, 2H), 3.73-3.77 (d, J = 11 Hz, 2H), 5.15(s, 2H), 6.52 (s, 1H), 6.87-6.91 (d, J = 11 Hz, 2H), 7.33-7.37 (m, 5H).

MS (m/z): $[M+H]^+$ = 347.2.

Example 41.

N-({(5S)-3-[3,5-difluoro-4-(6-oxa-3-azabicyclo[3.1.0]hex-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanamide



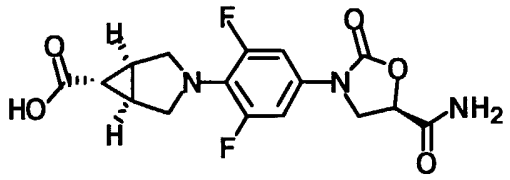
A solution of *N*-{3-[3,5-difluoro-4-(2,3-dihydropyrrol-3-yl)-phenyl]-2-oxo-oxazolidin-(5S)-ylmethyl}-propionamide (0.043 g, 0.12 mmol) in acetonitrile (2 mL) and MeOH (1 mL) was treated with $KHCO_3$ (0.043 g, 0.36 mmol) and 30% H_2O_2 (0.081 mL, 0.72 mmol). The mixture was stirred overnight and quenched by the addition of saturated aqueous $Na_2S_2O_3$. Most of organic solvent was removed under vacuum, and the resulting aqueous solution extracted with EtOAc. Combined organic phases were washed with brine and dried ($MgSO_4$). The crude product was purified by pTLC (5% MeOH-DCM) to afford the title compound.

Yield 0.015 g (34%). ^{1}H NMR

MS (m/z): $[M+H]^+ = 368$.

Example 42.

exo-(1R,5S)-3-{4-[(5R)-5-(Aminocarbonyl)-2-oxo-1,3-oxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid



A solution of *tert*-butyl exo-(1R,5S)-3-{4-[(5R)-5-(aminocarbonyl)-2-oxo-1,3-oxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylate (60 mg, 0.14 mmol) in TFA / dichloromethane (2.5 mL, 1:4) was stirred at rt for 1.5 h. The reaction mixture was concentrated and lyophilized from water-acetonitrile to provide the title compound as a TFA salt.

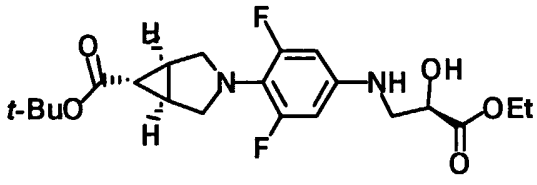
Yield 0.050 g (99%).

MS (m/z): $[M + H]^+ = 468.4$

^{1}H NMR (300 MHz, d6-DMSO): 1.63 (br s, 1H), 2.02 (br s, 2H), 3.4-3.6 (m, 4H), 3.92-3.98 (m, 1H), 4.20 (tr, $J = 9$ Hz, 1H), 4.98-5.03 (m, 1H), 7.27 (d, $J = 11$ Hz, 2H), 7.61 (s, 1H), 7.85 (s, 1H).

Intermediates for the preparation of Example 42 were synthesized as follows.

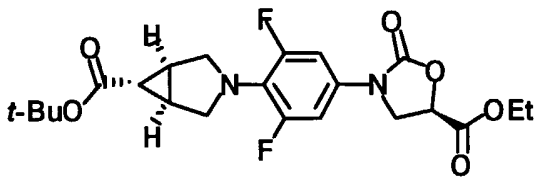
tert-Butyl exo-(1R,5S)-3-{4-[(2R)-2-ethoxycarbonyl-2-hydroxy-ethylamino]-2,6-difluoro-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylate



A solution of *tert*-butyl exo-(1R,5S)-3-(2,6-difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane-6-carboxylate (5 g, 14.7 mmol, prepared as described above for example 1) in EtOH/water (120 mL, 2 :1) was treated with NH_4Cl (5.85 g, 147 mmol) and refluxed at 95 °C. Iron powder (2.5 g, 44.1 mmol) was added in portions over one hour and the mixture refluxed for another hour. The reaction mixture was cooled and dissolved in water (50 mL), filtered and the filtrate extracted thrice with dichloromethane. The organic layers were washed with brine, dried ($MgSO_4$) and evaporated to provide the aniline intermediate, which was used without further purification. A mixture of the crude aniline (0.5 g, 1.61 mmol), ethyl-(2R)-epoxy propionate (0.28 g, 2.41 mmol) and lithium triflate (0.37 g, 2.41 mmol) was dissolved in acetonitrile (5.4 mL) and heated to 50-60 °C for 20 h. The reaction mixture was cooled and concentrated. The title compound was isolated by column chromatography (0–25 % EtOAc / hexanes).

Yield 0.29 g (42%). ^{1}H NMR.

II. *tert*-Butyl exo-(1R,5S)-3-{4-[(5R)-5-(ethoxycarbonyl)-2-oxo-1,3-oxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylate

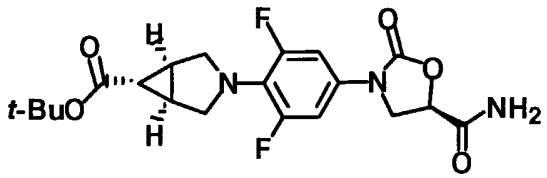


A solution of *tert*-butyl exo-(1R,5S)-3-{4-[(2R)-2-ethoxycarbonyl-2-hydroxy-ethylamino]-2,6-difluoro-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylate (0.29 g 0.68 mmol) in acetonitrile (7 mL) was treated with carbonyl diimidazole (0.22 g, 1.36 mmol) and stirred at rt for 60 h. The reaction mixture was concentrated, dissolved in EtOAc, washed with 3% citric acid, water and brine, and dried ($MgSO_4$). The title compound was isolated by column chromatography (0-25 % EtOAc / hexanes).

Yield 0.078 g (25%). ^{1}H NMR.

MS (m/z): $[M + H]^+ = 453.5$

III. *tert*-Butyl exo-(1R,5S)-3-{4-[(5R)-5-(aminocarbonyl)-2-oxo-1,3-oxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylate



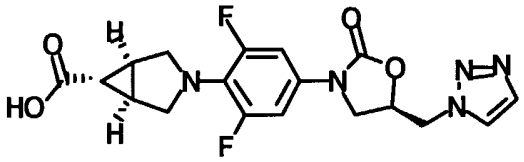
tert-Butyl exo-(1R,5S)-3-{4-[(5R)-5-(ethoxycarbonyl)-2-oxo-1,3-oxazolidin-3-yl]-2,6-difluorophenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylate (70 mg, 0.15 mmol) was taken into 2.0 M ammonia in MeOH (1.5 mL) and heated to 60 °C for 1.5 h. The reaction mixture was concentrated to provide the title compound which was used without further purification.

Yield 0.060 g (94%). ^{1}H NMR.

MS (m/z): $[M + H]^+ = 424.4$.

Example 43.

exo-(1R,5S)-3-{2,6-difluoro-4-[(5R)-2-oxo-5-(1H-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-3-yl]phenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylic acid



A solution of *tert*-butyl exo-(1R,5S)-3-{2,6-difluoro-4-[(5R)-2-oxo-5-(1H-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-3-yl]phenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylate (20 mg, 0.04 mmol) in TFA / dichloromethane (1.25 mL, 1:4) was stirred at rt for 1.5 h. The reaction mixture was then concentrated and the residue lyophilized to provide the title compound as the TFA salt.

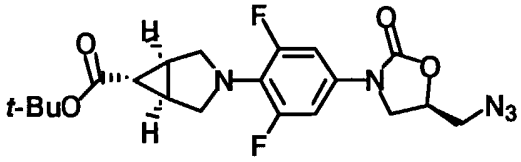
Yield 20 mg (>95%).

MS (m/z): $[M + H]^+ = 406.4$

^{1}H NMR (300 MHz, d6-DMSO): 1.63 (tr, J = 3 Hz, 1H), 2.02 (br s, 2H), 3.3-3.6 (m, 4H), 3.80-3.85 (m, 1H), 4.16 (tr, J = 9 Hz, 1H), 4.81 (m, 2H), 5.09-5.14 (m, 1H), 7.16 (d, J = 12 Hz, 2H), 7.75 (s, 1H), 8.15 (s, 1H).

Intermediates for the preparation of Example 43 were synthesized as follows.

tert-Butyl exo-(1R,5S)-3-{2,6-difluoro-4-[(5R)-5-(azidomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylate

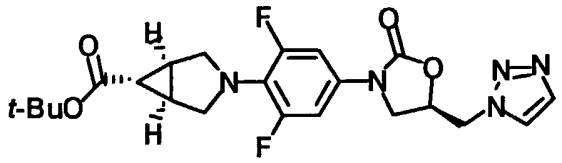


A solution of *tert*-butyl exo-(1R,5S)-3-{2,6-difluoro-4-[(5R)-hydroxymethyl-2-oxo-oxazolidin-3-yl]-phenyl}-3-aza-bicyclo[3.1.0]hexane-6-carboxylate (0.2 g, 0.49 mmol, prepared as described in Example 7) in dichloromethane (2 mL) was treated with triethylamine (0.1 mL, 0.74 mmol) and cooled to 0 °C. To this solution, methanesulfonyl chloride (0.04 mL, 0.49 mmol) was added and the mixture was stirred at 0 °C for 45 min. The reaction was allowed to warm up to rt and diluted with dichloromethane. The organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated to provide the mesylate intermediate. The crude mesylate was dissolved in DMF (2 mL), sodium azide (0.16 g, 2.45 mmol) was added and the mixture heated to 70 °C for 16 h. The reaction mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried ($MgSO_4$) and concentrated provide the title compound which was used without further purification.

Yield 0.20 g. ^{1}H NMR.

MS (m/z): $[M + Na]^+$ = 458.4

II. *tert*-butyl exo-(1R,5S)-3-{2,6-difluoro-4-[(5R)-2-oxo-5-(1H-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-3-yl]phenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylate



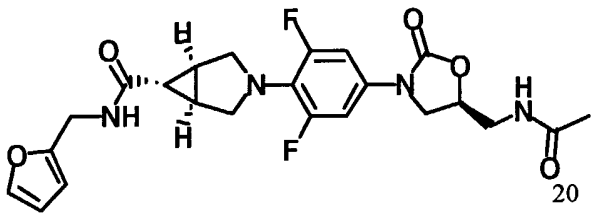
A solution of *tert*-butyl exo-(1R,5S)-3-{2,6-difluoro-4-[(5R)-5-(azidomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-3-azabicyclo[3.1.0]hexane-6-carboxylate (60 mg, 0.14 mmol) in dioxane (0.9 mL) was treated with bicyclo[2.2.1] hepta 2,5-diene (0.074 mL, 0.69 mmol) and refluxed for 24 h. The reaction mixture was concentrated and the residue purified by pTLC (5% MeOH / DCM) to provide the title compound.

Yield 20 mg (31%). ^{1}H NMR.

MS (m/z): $[M + Na]^+ = 484.5$

Example 44.

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-(2-furylmethyl)-3-azabicyclo[3.1.0]hexane-6-carboxamide



A solution of exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (0.8 g, 1.57 mmol, prepared as described in Example 1) in DMF (6 mL) and pyridine (0.51 mL, 6.28 mmol) was treated with pentafluorophenyl trifluoroacetate (0.54 mL, 3.14 mmol) and the mixture was stirred at rt for 2 h. The reaction mixture was dissolved in EtOAc and washed with 0.1 N HCl, water, and brine, dried over $MgSO_4$ and concentrated. The resulting pentafluorophenyl ester intermediate (0.075 g, 0.13 mmol) was dissolved in DMF (2 mL) and to this solution, furfurylamine (0.035 mL, 0.4 mmol) was added and the mixture stirred at rt for 16 h. The reaction mixture was dissolved in EtOAc and washed with water and brine, dried over $MgSO_4$ and concentrated. The title compound was isolated by pTLC (5% MeOH/DCM).

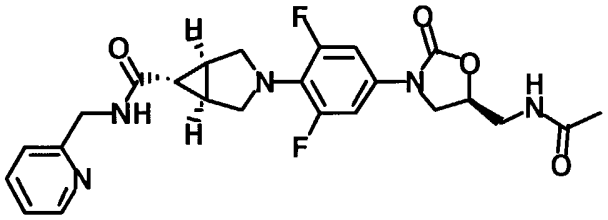
Yield 0.043 g (70%).

MS (m/z): $[M+H]^+ = 475.4$.

^{1}H NMR (300 MHz, d_6-DMSO): 1.81-1.84 (m, 4H) 1.90 (s, 2H), 3.35-3.41 (m, 6H), 3.62-3.68 (m, 1H), 4.01-4.07 (t, $J = 9$ Hz, 1H), 4.23-4.25 (d, $J = 9$ Hz, 3H), 4.67-4.72 (m, 1H), 6.21-6.23 (d, $J = 4$ Hz, 1H), 6.36-6.38 (d, $J = 4$ Hz, 1H), 7.19-7.23 (d, $J = 9$ Hz, 2H), 7.56 (s, 1H), 8.20-8.24 (t, $J = 4$ Hz, 1H), 8.53-8.57(t, $J = 4$ Hz, 1H).

Example 45.

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-(pyridin-2-ylmethyl)-3-azabicyclo[3.1.0]hexane-6-carboxamide



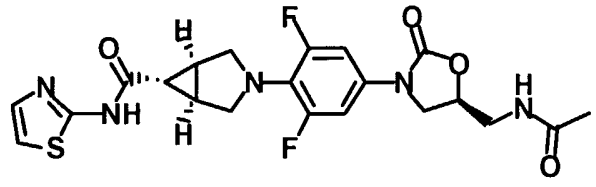
The title compound was prepared in 67% yield using the procedure described for Example 44, but using 2-(aminomethyl)pyridine in reaction with the pentafluorophenyl ester intermediate.

MS (m/z): $[M+H]^+ = 486.5$

^{1}H NMR (300 MHz, d_6-DMSO): 1.82 (br s, 2H), 1.90 (br s, 1H), 1.92 (s, 3H), 3.26-3.44 (m, 6H), 3.63-3.69 (m, 1H), 4.05 (tr, $J = 9$ Hz, 1H), 4.36 (m, 2H), 4.67-4.73 (m, 1H), 7.19-7.28 (m, 4H), 7.76 (dt, $J = 8$, 2 Hz, 1H), 8.22 (tr, $J = 6$ Hz, 1H), 8.48 (d, $J = 3$ Hz, 1H), 8.71 (tr, $J = 3$ Hz, 1H).

Example 46.

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-(1,3-thiazol-2-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide



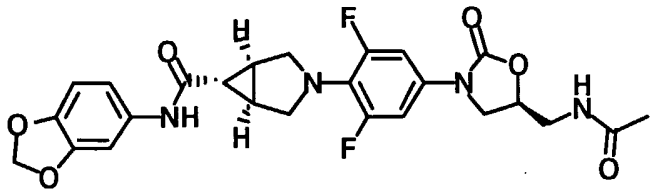
The title compound was prepared in 66% yield using the procedure described for Example 44, but using 2-aminothiazole in reaction with the pentafluorophenyl ester intermediate.

MS (m/z): $[M+H]^+ = 478.5$

^{1}H NMR (300 MHz, d_6-DMSO): 1.83 (s, 3H), 2.14 (br s, 2H), 2.25 (tr, J = 2 Hz, 1H), 3.40 (tr, J = 4 Hz, 2H), 3.50 (br s, 4H), 3.68 (dd, J = 7, 5 Hz, 1H), 4.07 (tr, J = 7 Hz, 1H), 4.72 (m, 1H), 7.18 (d, J = 3 Hz, 1H), 7.26 (d, J = 9 Hz, 2H), 7.44 (d, J = 3 Hz, 1H), 8.24 (tr, J = 6 Hz, 1H), 12.3 (s, 1H).

Example 47.

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-(1,3-benzodioxol-5-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide



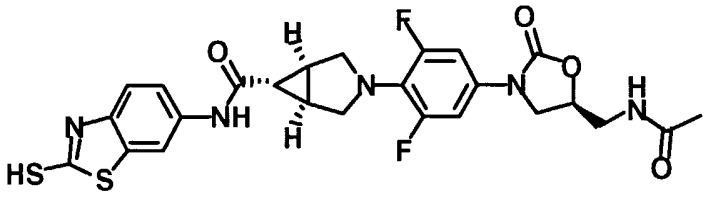
The title compound was prepared in 46% yield using the procedure described for Example 44, but using 3,4-(methylenedioxy)aniline in reaction with the pentafluorophenyl ester intermediate.

MS (m/z): $[M+H]^+ = 515.5$

^{1}H NMR (300 MHz, d_6-DMSO): 1.82 (s, 3H), 1.98 (m, 1H), 2.00 (br s, 2H), 3.29-3.47 (m, 6H), 3.67 (m, 1H), 4.06 (tr, J = 9 Hz, 1H), 4.71 (m, 1H), 5.95 (s, 2H), 6.81 (d, J = 8 Hz, 1H), 6.94 (dd, J = 8, 2 Hz, 1H), 7.24 (d, J = 12 Hz, 2H), 7.29 (d, J = 2 Hz, 1H), 8.23 (tr, J = 6 Hz, 1H), 10.1 (s, 1H).

Example 48.

exo-(1R,5S)-3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2,6-difluorophenyl)-N-(2-mercapto-1,3-benzothiazol-6-yl)-3-azabicyclo[3.1.0]hexane-6-carboxamide



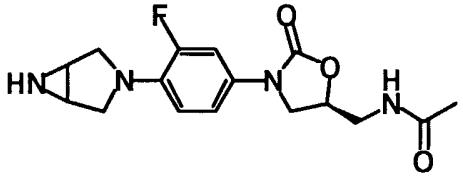
The title compound was prepared in 45% yield using the procedure described for Example 44, but using 6-amino-2-mercaptobenzothiazole in reaction with the pentafluorophenyl ester intermediate.

MS (m/z): $[M+H]^+ = 560.5$

^{1}H NMR (300 MHz, d_6-DMSO): 1.82 (s, 3H), 2.04 (br s, 3H), 3.29-3.48 (m, 6H), 3.66 (m, 1H), 4.06 (tr, $J = 9$ Hz, 1H), 4.70 (m, 1H), 7.22 (d, $J = 9$ Hz, 1H), 7.24 (d, $J = 12$ Hz, 2H), 7.47 (dd, $J = 9$, 2 Hz, 1H), 8.01 (d, $J = 2$ Hz, 1H), 8.23 (tr, $J =$ 6 Hz, 1H), 10.4 (s, 1H).

Example 49.

N-({(5S)-3-[4-(3,6-diazabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide



Triphenylphosphine (18 mg, 0.07 mmol) was added to a solution of N-({(5S)-3-[4-(3-azido-4-methansulfonyloxypyrrolidin-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (29 mg, 0.06 mmol) in THF (0.5 mL) and the solution stirred overnight. Water (100μL) was then added and the mixture heated to 40 °C for 2 h. The solution was diluted with more water and treated with aq KOH until pH 14 was attained. After 30 min the solution was diluted with water and extracted with ethyl acetate. The combined organic phases were washed with

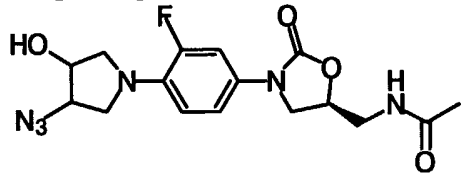
brine, dried ($MgSO_4$), filtered and concentrated. The crude product could be used in subsequent reactions, or purified by pTLC (5% MeOH-CH_2Cl_2) to provide the title compound.

^{1}H NMR (300 MHz, CD_3OD): 1.95 (s, 3H), 2.82 (br s, 2H), 3.29 (m, 2H), 3.53 (d, J = 5 Hz, 2H), 3.72-3.80 (m, 3H), 4.07 (tr, J = 9 Hz, 1H), 4.70-4.79 (m, 1H), 6.75 (tr, J = 9 Hz, 1H), 7.07 (d, J = 7 Hz, 1H), 7.36 (dd, J = 15, 2 Hz, 1H).

MS (m/z): $[M+H]^+$ = 335.2

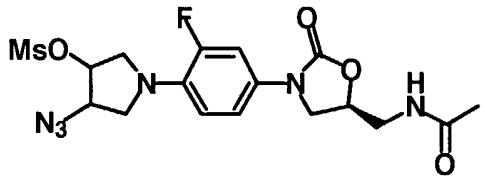
Intermediates for preparation of Example 49 were synthesized as follows.

N-({(5S)-3-[4-(3-azido-4-hydroxypyrrolidin-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide



Sodium azide (42 mg, 0.64 mmol) was added to a solution of N-({(5S)-3-[3-fluoro-4-(6-oxa-3-azabicyclo[3.1.0]hex-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (36 mg, 0.107 mmol, prepared using the general procedure described for Example 40) in 2:1 acetone-H_2O (1.0 mL) and the solution heated at 55 °C for 16 hours. The solution was cooled, concentrated to remove acetone, diluted with water and extracted with chloroform. Combined organic extracts were dried ($MgSO_4$), filtered and concentrated to provide the title compound. This material was used directly in the next reaction. MS (m/z): $[M+H]^+$ = 379

II. N-({(5S)-3-[4-(3-azido-4-methansulfonyloxypyrrolidin-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide

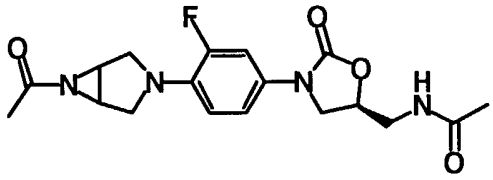


Methanesulfonyl chloride (8 μL, 0.10 mmol) was added to a solution of N-({(5S)-3-[4-(3-azido-4-hydroxypyrrolidin-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (30mg, 0.08 mmol) and triethylamine (16 μL, 0.12 mmol) in

dichloromethane (0.5 mL) at 0°C. After 1 h, the solution was diluted with more dichloromethane, washed with dilute $NaHCO_3$, brine and dried ($MgSO_4$), filtered and concentrated to give the title compound as an oil. This material was used directly in the next reaction.

Example 50.

N-({(5S)-3-[4-(6-acetyl-3,6-diazabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide



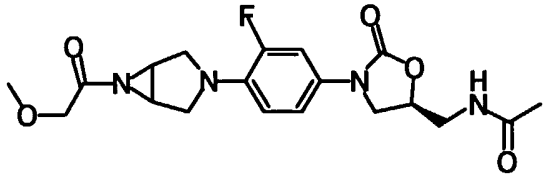
Acetic anhydride (3.5 μL, 0.05 mmol) was added to a cooled (0 °C) solution of N-({(5S)-3-[4-(3,6-diazabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (12 mg, 0.036 mmol) in triethylamine (10 μL, 0.072 mmol) and dichloromethane (0.7 mL). After 1 hour, the solution was diluted with dichloromethane, and washed with dilute $NaHCO_3$, brine, and dried ($MgSO_4$), filtered and concentrated. Purification by pTLC (4% MeOH-CH_2Cl_2) provided the title compound.

^{1}H NMR (300 MHz, CD_3OD): 1.95 (s, 3H), 2.07 (s, 3H), 3.09 (app d, J = 11 Hz, 2H), 3.34 (s, 2H), 3.53 (d, J = 5 Hz, 2H), 3.75 (dd, J = 9, 6 Hz, 1H), 3.96 (app d, J = 11 Hz, 2H), 4.07 (tr, J = 9 Hz, 1H), 4.73-4.80 (m, 1H), 6.84 (tr, J = 9 Hz, 1H), 7.09 (d, J = 9 Hz, 1H), 7.40 (dd, J = 15, 2 Hz, 1H).

MS (m/z): $[M+H]^+$ = 377.2

Example 51.

N-({(5S)-3-[4-(6-methoxyacetyl-3,6-diazabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide



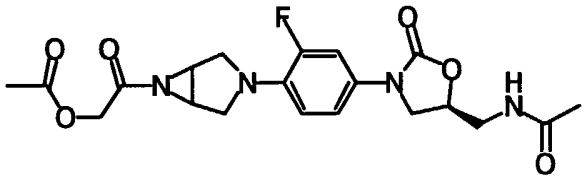
Methoxyacetyl chloride (6 μL, 0.067 mmol) was added to a cooled (0 °C) solution of N-({(5S)-3-[4-(3,6-diazabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (15 mg, 0.05 mmol) in triethylamine (14 μL, 0.10 mmol) and dichloromethane (1.0 mL). After 1 hour, the solution was diluted with dichloromethane, and washed with dilute $NaHCO_3$, brine, and dried ($MgSO_4$), filtered and concentrated. Purification by pTLC (5% MeOH-CH_2Cl_2) provided the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): 2.02 (s, 3H), 3.12 (d, J = 11 Hz, 2H), 3.36 (s, 2H), 3.45 (s, 3H), 3.60-3.73 (m, 3H), 3.99 (tr, J = 9 Hz, 1H), 4.03 (s, 2H), 4.04 (d, J = 11 Hz, 2H), 4.75 (m, 1H), 6.00 (br tr, 1H), 6.69 (tr, J = 9 Hz, 1H), 7.01 (d, J = 9 Hz, 1H), 7.36 (dd, J = 15, 2 Hz, 1H).

MS (m/z): $[M+H]^+$ = 407.5

Example 52.

2-[3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}2-fluorophenyl)-3,6-diazabicyclo[3.1.0]hex-6-yl]-2-oxoethyl acetate



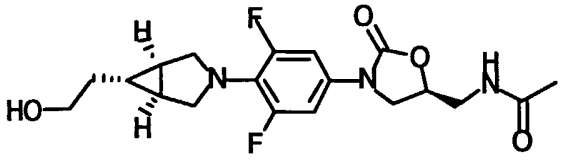
An excess (2-4 equiv) of acetoxyacetyl chloride was added to a vigorously stirred solution of N-({(5S)-3-[4-(3,6-diazabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (10 mg, 0.030 mmol) in water-aq. K_2CO_3 (3 mL). After 1 hour, the solution was diluted with water, the layers separated and the aqueous phase extracted with more ethyl acetate. Combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification by pTLC (5% MeOH-dichloromethane) provided the title compound.

^{1}H NMR (300 MHz, d6-DMSO): 1.83 (s, 3H), 2.09 (s, 3H), 3.14 (d, J = 11 Hz, 2H), 3.39 (m, 2H), 3.48 (s, 2H), 3.68 (dd, J = 9, 6 Hz, 1H), 3.82 (d, J = 10 Hz, 2H), 4.05 (tr, J = 9 Hz, 1H), 4.60 (s, 2H), 4.68 (m, 1H), 6.84 (tr, J = 9 Hz, 1H), 7.10 (d, J = 9 Hz, 1H), 7.39 (dd, J = 15, 2 Hz, 1H), 8.23 (tr, J = 6 Hz, 1H).

MS (m/z): $[M+H]^+$ = 435.3

Example 53.

N-((5S)-3-{3,5-Difluoro-4-[exo-(1R,5S)-6-(2-hydroxy-ethyl)-3-aza-bicyclo[3.1.0]hex-3-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide



A solution of (4-{6-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-3-aza-bicyclo[3.1.0]hex-3-yl}-3,5-difluoro-phenyl)-carbamic acid benzyl ester (1.0 g, 2.1 mmol) in DMF (1 ml) and MeOH (0.17 ml, 4.1 mmol) was cooled to 10 °C. To this mixture, LiOtBu (8.2 ml of a 1M solution, 8.2 mmol) was added slowly at 0 °C and then (*S*)-acetic acid 2-acetylamino-1-chloromethyl-ethyl ester (0.44 g, 2.3 mmol) was added and the mixture stirred at room temperature overnight. The mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (0-3% MeOH/EtOAc) to afford *N*-((5S)-3-{3,5-Difluoro-4-[exo-(1R,5S)-6-(2-{*tert*-Butyl-dimethyl-silanyloxy}-ethyl)-3-aza-bicyclo[3.1.0]hex-3-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide.

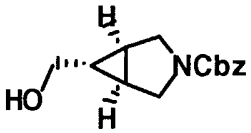
To a solution of *N*-((5S)-3-{3,5-Difluoro-4-[exo-(1R,5S)-6-(2-{*tert*-Butyl-dimethyl-silanyloxy}-ethyl)-3-aza-bicyclo[3.1.0]hex-3-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide (0.2 g, 0.39 mmol) in THF (3 ml) was added 3HF•Et_3N complex (0.19 g, 1.2 mmol) at room temperature. After 1 hour, additional 3HF•Et_3N (0.19 g) was added and the mixture was stirred for an additional hour. The solvent was then removed in vacuo, and the residue was dissolved in dichloromethane and washed with saturated $NaHCO_3$ solution (back-extracting thrice with dichloromethane), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (3-5% MeOH/dichloromethane) to afford the title compound.

^1H NMR (300 MHz, $CDCl_3$): 0.96-1.01 (m, 1H), 1.31 (s, 2H), 1.51-1.57 (m, 2H), 2.02 (s, 3H), 3.42-3.51 (m, 3H), 3.62-3.75 (m, 6H), 3.93-3.99 (t, J = 8.7 Hz, 1H), 4.73-4.77 (m, 1H), 6.05-6.09 (t, 1H), 6.99-7.03 (d, J = 11.1 Hz, 2H).

MS (m/z): $[M+H]^+$ = 396.1

Intermediates for preparation of Example 53 were synthesized as follows.

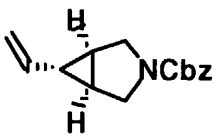
exo-(1R,5S)-6-hydroxymethyl-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester.



To a solution of exo-(1R,5S)-3-benzyloxycarbonyl-3-azabicyclo[3.1.0]hexane-6-carboxylic acid ethyl ester (2.0 g, 6.9 mmol) in 20:2:1 THF-MeOH-H_2O (23 mL) was added LiOH (0.83 g of the hydrate, 34.6 mmol) at room temperature and the mixture was stirred for 4 hours. The solvent was removed in vacuo the residue partitioned between water and diethyl ether. The ether extract was removed and the aqueous layer was treated with 1M HCl solution to pH < 4, and then extracted with Ethyl acetate thrice. The organic extracts were then dried ($MgSO_4$), filtered, and concentrated to afford the carboxylic acid which was used without further purification.

A solution of the acid (1.8 g, 6.8 mmol) in THF (100 ml) was treated with N-methylmorpholine (1 g, 10.2 mmol) and the mixture was cooled to –15 °C. Isobutyl chloroformate (1.39 g, 10.2 mmol) was added dropwise and the mixture was stirred for 3 hours. The solid formed was filtered off and the filtrate was added dropwise to a suspension of $NaBH_4$ (0.5 g 13.6 mmol) and H_2O (10 ml) over 20 min at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was then acidified with 1 M HCl solution to pH = 2 and extracted thrice with Ethyl acetate. The combined organic layer was washed with saturated Na_2CO_3, dried ($MgSO_4$), filtered, and concentrated. The title compound was obtained in 91% overall yield and was used in the next step without further purification.

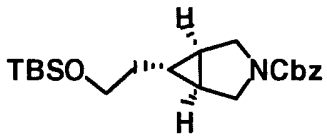
II. exo-(1R,5S)-6-vinyl-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester.



The Dess-Martin periodinane (3.2 g, 7.6 mmol) and $NaHCO_3$ (5.1 g, 60.7 mmol) were added to a solution of exo-(1R,5S)-6-hydroxymethyl-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester. (1.5 g, 6.1 mmol) in dichloromethane (50 ml). The mixture was stirred at room temperature for 3 hours. The reaction was quenched with aqueous $Na_2S_2O_3$ solution, extracted thrice with dichloromethane, and washed with brine. The organic layer was dried ($MgSO_4$), filtered, concentrated to afford the aldehyde which was used in the next step without further purification.

To a suspension of methyltriphenylphosphonium bromide (4.2 g, 11.4 mmol) in THF (5 ml) at 0 °C under N_2 atmosphere was added KHMDS (0.5 M in toluene, 22.8 ml, 11.4 mmol) dropwise. The mixture was allowed to stir at room temperature for 1 hour and then cooled to –78 °C. A solution of crude aldehyde (1.4 g, 5.7 mmol) in dry THF (20 ml) was added slowly and the mixture was warmed to –10 °C and stirred for 1 hour. The reaction was quenched with saturated NH_4Cl solution, extracted thrice with Ethyl acetate, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (10-20% EtOAc/hexanes) to afford the title compound.
^1H NMR (300 MHz, $CDCl_3$): 1.55-1.59 (m, 3H), 3.44-3.48 (m, 2H), 3.66-3.74 (m, 2H), 4.88-5-06 (m, 2H), 5.11 (s, 2H), 5.36-5.48 (m, 1H), 7.28-7.38 (m, 5H).

III. exo-(1R,5S)-6-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester.

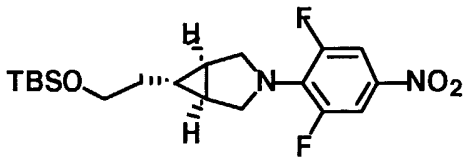


A solution of $BH_3 \cdot SMe_2$ complex (2 M in THF, 2.1 ml, 4.2 mmol) was added to a solution of exo-(1R,5S)-6-vinyl-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester (0.95 g, 4.2 mmol) in THF (10 ml) cooled at 0 °C and the mixture stirred for 30 minutes. The reaction was allowed to warm to room temperature and after 1 hour was re-cooled to 0 °C. The mixture was treated carefully with 3 N NaOH solution (3 ml) (Note: gas evolved), followed by H_2O_2 (30% solution, 4 ml). The resulting mixture was warmed to 65 °C for 2 hours. The reaction was

allowed to cool to room temperature and the solvent was removed in vacuo. Brine and Ethyl acetate were added, the layers separated and the aqueous layer acidified with 1 M HCl solution to pH = 5, extracted thrice with Ethyl acetate , dried ($MgSO_4$), filtered, and concentrated to afford the crude alcohol which was used in the next step without further purification.

To a cooled (0 °C) solution of the alcohol (0.95 g, 3.8 mmol) in dry DMF (10 ml) was added imidazole (0.65 g, 9.5 mmol) and *tert*-butyldimethylsilyl chloride (0.72 g, 4.8 mmol) and the mixture was stirred at room temperature overnight. Ethyl acetate was added and the solution washed with brine, 1 M HCl solution, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (10-20% Ethyl acetate/hexanes) to afford the title compound. ^1H NMR (300 MHz, $CDCl_3$): 0.04 (s, 6H), 0.89 (s, 9H), 1.26-1.30 (m, 3H), 1.43-1.49 (m, 2H), 3.38-3.43 (m, 2H), 3.58-3.66 (m, 4H), 5.10 (s, 2H), 7.31-7.35 (m, 5H).

IV. exo-(1R,5S)-6-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-3-(2,6-difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane.

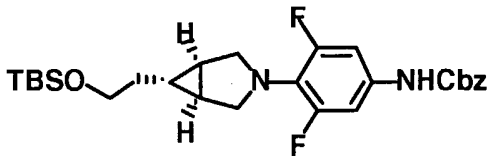


Palladium on carbon (10%, 0.2 g) was added to a solution of exo-(1R,5S)-6-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester (1.2 g, 3.3 mmol) dissolved in Ethyl acetate (15 mL) and MeOH (1 mL). The flask was charged with hydrogen gas and the mixture was stirred at room temperature overnight. The reaction mixture was then filtered through celite and the solvent was removed in vacuo to afford the amine, which was used in the next step without further purification.

Trifluoronitrobenzene (0.55 g, 3.1 mmol) was added to a solution of the crude amine (0.75 g, 3.1 mmol) in acetonitrile (10 ml) and diisopropylethylamine (3.2 g, 24.8 mmol) and the mixture was heated to reflux for 2 hours. The solvent was removed in vacuo and Ethyl acetate

was added. The Ethyl acetate layer was washed with 0.1N HCl solution and brine, saturated $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), and concentrated to afford the major product and some trace amount of desilylated by-product. The mixture was re-subjected to silylation with with *tert*-butyldimethylsilyl chloride (0.65 g) and imidazole (0.59 g) as described above to afford the title compound in 81% crude overall yield. This material was used in the next step without further purification.

V. (4-{exo-(1R,5S)-6-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-3-aza-bicyclo[3.1.0]hex-3-yl}-3,5-difluoro-phenyl)-carbamic acid benzyl ester.

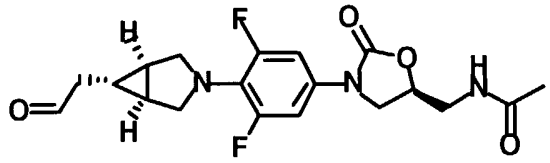


Solid NH_4Cl (1.3 g, 25 mmol) was added to a solution of exo-(1R,5S)-6-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-3-(2,6-difluoro-4-nitro-phenyl)-3-aza-bicyclo[3.1.0]hexane (1.0 g, 2.5 mmol) in 2:1 EtOH/H_2O (60 mL). The resulting mixture was heated to 95 °C and iron metal (0.42 g, 7.5 mmol) was added in portions over one hour. The mixture was cooled to room temperature and then extracted thrice with dichloromethane. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to afford the crude aniline in, which was used in the next step without further purification.

Pyridine (0.39 g, 4.9 mmol) was added to a solution of the crude amine (0.90 g, 2.4 mmol) in dichloromethane (10 ml) at 0 °C. Benzyl chloroformate (0.46 g, 2.7 mmol) was added dropwise and the reaction was stirred at 4 °C overnight. The solvent was removed in vacuo and the residue was purified by column chromatography (10-20% EtOAc/hexanes) to afford the title compound.
MS (m/z): $[M+H]^+ = 502.7$
^1H NMR (300 MHz, $CDCl_3$): 0.04 (s, 6H), 0.89 (s, 9H), 1.23-1.28 (m, 3H), 1.44-1.51 (m, 2H), 3.41 (s, 4H), 3.65-3.70 (t, $J = 6.9$ Hz, 2H), 5.18 (s, 2H), 6.53 (s, 1H), 6.86-6.90 (d, $J = 10.8$ Hz, 2H), 7.33-7.39 (m, 5H).

Example 54.

N-((5S)-3-{3,5-Difluoro-4-[exo-(1R,5S)-6-(2-oxo-ethyl)-3-aza-bicyclo[3.1.0]hex-3-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide



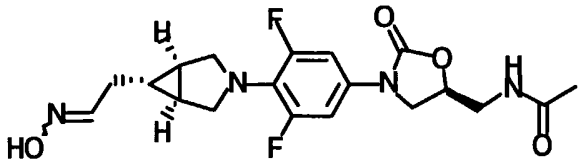
1-Hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide (0.06 g, 0.23 mmol) was added to a solution of *N*-((5S)-3-{3,5-Difluoro-4-[exo-(1R,5S)-6-(2-hydroxy-ethyl)-3-aza-bicyclo[3.1.0]hex-3-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide (0.05 g, 0.13 mmol) in DMSO (1 ml). The resulting mixture was stirred at room temperature for 2 hours. The reaction was quenched with H_2O and extracted thrice with Ethyl acetate, washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (5% MeOH/EtOAc) to afford the title compound.

MS (m/z): $[M+H]^+ = 393.8$.

^1H NMR (300 MHz, d^6- DMSO): 1.10-1.12 (m, 1H), 1.42 (s, 2H), 1.81 (s, 3H), 2.38-2.41 (m, 2H), 3.63-3.69 (m, 1H), 4.01-4.07 (t, $J = 9$ Hz, 1H), 4.50-4.75 (m, 7H), 7.19-7.23 (d, $J = 12.3$ Hz, 2H), 8.24 (t, 1H), 9.67 (d, $J = 1.5$ Hz, 1H).

Example 55.

N-((5S)-3-{3,5-Difluoro-4-[exo-(1R,5S)-6-(2-hydroxyimino-ethyl)-3-aza-bicyclo[3.1.0]hex-3-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide



Sodium acetate (0.04 g, 0.47 mmol) and NH_2OH•HCl (0.016 g, 0.23 mmol) were added to a solution of *N*-((5S)-3-{3,5-Difluoro-4-[exo-(1R,5S)-6-(2-oxo-ethyl)-3-aza-bicyclo[3.1.0]hex-3-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide (0.023 g, 0.06 mmol) dissolved in MeOH (2 ml). The resulting mixture was stirred

at room temperature for two hours. The solvent was removed in vacuo and the residue was purified by column chromatography (5% MeOH/EtOAc) to afford the title compound as mixture of two oxime isomers.

MS (m/z): $[M+H]^+ = 409.2$

^1H NMR (300 MHz, d^6- DMSO): 0.96-1.01 (m, 1H), 1.41 (s, 2H), 1.81 (s, 3H), 2.05-2.10 (m, 2H, major isomer), 2.18-2.23 (m, 2H, minor isomer), 3.36- 3.50 (m, 6H), 3.63-3.68 (m, 1H), 4.01-4.04 (t, $J = 8.7$ Hz, 1H), 4.65-4.72 (m, 1H), 6.71-6.75 (t, $J = 5.4$ Hz, 1H, minor isomer), 7.17-7.21 (d, $J = 12$ Hz, 2H), 7.31-7.35 (t, $J = 6$ Hz, 1H, major isomer), 8.18-8.22 (t, 1H), 10.41 (s, 1H, minor isomer), 10.76 (s, 1H, major isomer).

MIC Test Method

The *in vitro* MICs of test compounds were determined by a standard agar dilution method. A stock drug solution of each analog was prepared in the preferred solvent, usually DMSO:H_2O (1:3). Serial 2-fold dilutions of each sample are made using 1.0 ml aliquots of sterile distilled water. To each 1.0 ml aliquot of drug was added 9 ml of molten Mueller Hinton agar medium. The drug-supplemented agar was mixed, poured into 15 x 100 mm petri dishes, and allowed to solidify and dry prior to inoculation.

Vials of each of the test organisms are maintained frozen in the vapor phase of a liquid nitrogen freezer. Test cultures are grown overnight at 35°C on the medium appropriate for the organism. Colonies are harvested with a sterile swab, and cell suspensions are prepared in Trypticase Soy broth (TSB) to equal the turbidity of a 0.5 McFarland standard. A 1:20 dilution of each suspension was made in TSB. The plates containing the drug supplemented agar are inoculated with a 0.001 ml drop of the cell suspension using a Steers replicator, yielding approximately 10^4 to 10^5 cells per spot. The plates are incubated overnight at 35°C. Following incubation the Minimum Inhibitory Concentration (MIC μg/ml), the lowest concentration of drug that inhibits visible growth of the organism, was read and recorded. The data is shown in Table I.

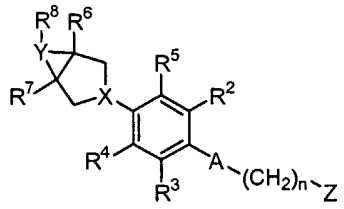
Table 1. Antimicrobial activity of selected compounds.

Example #	*S. aureus* UC9213	*S. pneumoniae* UC9912	*H. influenzae* 30063
	MIC, μg/mL	MIC, μg/mL	MIC, μg/mL
40	1	0.5	8
41	2	0.5	16
49	4	0.5	8
50	8	2	64
51	8	2	32
52	1	1	32

While the invention has been described and illustrated herein by references to various specific material, procedures and examples, it is understood that the invention is not restricted to the particular material combinations of material, and procedures selected for that purpose. Numerous variations of such details can be implied as will be appreciated by those skilled in the art.

WHAT IS CLAIMED IS:

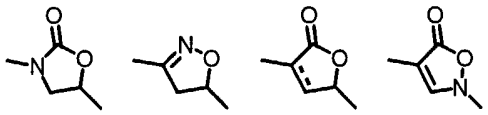
1. A compound of Formula I



I

wherein:

A is a structure i, ii, iii, or iv



i ii iii iv

where the dashed line in formula iii represents an optional double bond;

n is 0 or 1;

X is N or CH;

Y is N, O, or S;

Z is $NHC(=O)R^1$, $NHC(=S)R^1$, $CONHR^1$, $NHC(=NCN)R^1$, NH–het^1, O-het^1, S-het^1 or het^2;

R^1 is H, NH_2, NHC_{1-4}alkyl, C_{1-4}alkyl, C_{2-4}alkenyl, $(CH_2)_mC(=O)C_{1-4}$alkyl, OC_{1-4}alkyl, SC_{1-4}alkyl, $(CH_2)_mC_{3-6}$cycloalkyl, CH=CH-aryl, CH=CH-het^1, $CH_2C(=O)$-aryl, or $CH_2C(=O)$-het^1;

R^2 and R^3 are independently H or F;

R^4 and R^5 are independently H, Cl, F, CH_3, NH_2, or OH;

R^6 and R^7 are independently H, F, OH, C_{1-4}alkyl, or C_{1-4}heteroalkyl;

R^8 is H, F, OH, CN, $NR^{10}R^{11}$, C_{1-4}alkyl, C_{3-6}cycloalkyl, C_{1-4}heteroalkyl, aryl, het^1, OC_{1-4}alkyl, C_{1-4}alkylOR^{10}, C_{1-4}alkyl$NR^{10}R^{11}$, $O(C=O)C_{1-4}$alkyl, $C(=O)C_{1-4}$alkyl, C(=O)OH, $C(=O)NR^{10}OR^{11}$, $C(=NOC_{1-4}alkyl)H$, $C(=NOC_{1-4}alkyl)C_{1-4}$alkyl, C(=O)het^1, $C(=NOC_{1-4}alkyl)$het^1, $(CH_2)_mC(=O)NR^{10}R^{11}$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}C(=O)C_{1-4}$alkyl, $NR^{10}C(=O)C_{3-6}$cycloalkyl, $NR^{10}C(=O)OH$, $NR^{10}C(=O)H$, or OC_{1-4}alkyl$CONR^{10}R^{11}$, provided that when Y is is O or S, then R^8 is absent,

further wherein

each R^{10} and R^{11} are independently H, C_{1-4}alkyl, C_{3-6}cycloalkyl, aryl, het^1, C(=O)aryl, C(=O)het^1, SO_2C_{1-4}alkyl, or SO_2NH_2;

het^1 is a C-linked five- (5) or six- (6) membered heterocyclic ring having 1-4 heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen;

het^2 is a N-linked or C-linked five- (5) or six- (6) membered heterocyclic ring having 1-4 heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen;

each m is independently 0, 1, or 2;

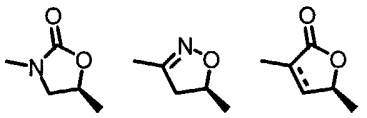
and a pharmaceutically acceptable salts thereof;

with the further provisos that

when Z is NHC(=O)R^1 or NHC(=S)R^1; n is 1; A is structure (i); R^2, R^3, R^6 and R^7 are H; X is N; Y is N; then R^8 is not C(=O)het^1; and

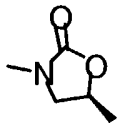
when Z is NHC(=O)R^1 or NHC(=S)R^1; n is 1; A is structure (i); R^2, R^3, R^6 and $R^7$are H; X is N; Y is N; and R^8 is $NR^{10}R^{11}$ or C_{1-4}alkyl$NR^{10}R^{11}$; then R^{10} and R^{11} are not het^1, aryl, C(=O)aryl, or C(=O)het^1.

2. The compound according to claim 1, wherein A is an optical configuration of structure i, ii, or iii:



i ii iii .

3. The compound according to claim 1, wherein A is an optical configuration of structure i:



i .

4. The compound of claim 3, wherein R^1 is C_{1-4} alkyl.

5. The compound of claim 3, wherein R^1 is methyl, difluoromethyl, ethyl, 2-fluoroethyl, or 2,2-difluoroethyl.

6. The compound of claim 3, wherein R^4 and R^5 are independently H or F.

7. The compound of claim 3, wherein R^6 and R^7 are H.

8. The compound of claim 3, wherein R^8 is H.

9. The compound of claim 3, wherein n is 0.

10. The compound of claim 3 selected from the group consisting of
N-({(5S)-3-[3,5-difluoro-4-(6-oxa-3-azabicyclo[3.1.0]hex-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;
N-({(5S)-3-[3,5-difluoro-4-(6-oxa-3-azabicyclo[3.1.0]hex-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanamide;
N-({(5S)-3-[4-(3,6-diazabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;
N-({(5S)-3-[4-(6-acetyl-3,6-diazabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;
N-({(5S)-3-[4-(6-methoxyacetyl-3,6-diazabicyclo[3.1.0]hex-3-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;
2-[3-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}2-fluorophenyl)-3,6-diazabicyclo[3.1.0]hex-6-yl]-2-oxoethyl acetate; and
N-((5S)-3-{3,5-Difluoro-4-[exo-(1R,5S)-6-(2-hydroxy-ethyl)-3-aza-bicyclo[3.1.0]hex-3-yl]-phenyl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide.

11. A method for the treatment of microbial infection in a mammal comprising administration of an effective amount of the compound of claim 1 to said mammal.

12. The method of claim 11 wherein said compound of claim 1 is administered to the mammal orally, parenterally, transdermally, or topically in a pharmaceutical composition.

13. The method of claim 11 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.

14. The method of claim 11 wherein said compound is administered in an amount of from about 1 to about 50 mg/kg of body weight/day.

15. A method for treating microbial infection of claim 11 wherein the infection is a skin infection.

16. The method of claim 11 wherein the infection is eye infection.

17. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US 03/28560

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/10 C07D413/14 C07D491/04 C07D417/14 C07D487/04
A61K31/422 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 06278 A (ARORA SUDERSHAN K ;MEHTA ANITA (IN); RAY ABHIJIT (IN); DAS BISWAJI) 24 January 2002 (2002-01-24) the whole document	1-17
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-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 February 2004	23/02/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Seitner, I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/28560

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	BARBACHYN M R ET AL: "IDENTIFICATION OF A NOVEL OXAZOLIDINONE (U-100480) WITH POTENT ANTIMYCOBACTERIAL ACTIVITY" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 39, no. 3, 2 February 1996 (1996-02-02), pages 680-685, XP000574382 ISSN: 0022-2623 the whole document ---	1,11
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Y	EP 0 807 630 A (DAIICHI SEIYAKU CO) 19 November 1997 (1997-11-19) page 3; example 1 ---	1,11
Y	WO 96 01262 A (HANMI PHARMACEUTICAL CO LTD ;MOON SOON KU (KR); LEE GWAN SUN (KR);) 18 January 1996 (1996-01-18) claims 1,10 ---	1,11
Y	LI Q ET AL: "SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF 2-PYRIDONES: A NOVEL SERIES OF POTENT DNA GYRASE INHIBITORS AS ANTIBACTERIAL AGENTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 39, 1996, pages 3070-3088, XP002064518 ISSN: 0022-2623 abstract; example 45U -----	1,11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/28560

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/28560

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International application No
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US 20100069449A1

D4

(19) **United States**

(12) **Patent Application Publication**

Oh et al.

(10) **Pub. No.: US 2010/0069449 A1**

(43) **Pub. Date: Mar. 18, 2010**

(54) **NOVEL OXAZOLIDINONE DERIVATIVE WITH DIFLUOROPHENYL MOIETY, PHARMACEUTICALLY ACCEPTABLE SALT THEREOF, PREPARATION METHOD THEREOF AND ANTIBIOTIC COMPOSITION CONTAINING THE SAME AS AN ACTIVE INGREDIENT**

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MINNEAPOLIS, MN 55402-0903 (US)

(73) Assignee: **Korea Institute of Science & Technology**, Seoul (KR)

(21) Appl. No.: **12/277,364**

(22) Filed: **Nov. 25, 2008**

Related U.S. Application Data

(63) Continuation of application No. 12/313,625, filed on Nov. 20, 2008.

(30) **Foreign Application Priority Data**

Sep. 16, 2008 (KR) KR10-2008-0090659

Publication Classification

(51) **Int. Cl.**

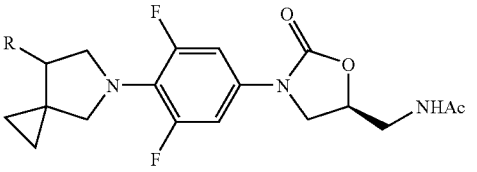
A61K 31/422	(2006.01)
C07D 413/10	(2006.01)
A61P 31/04	(2006.01)

(52) **U.S. Cl.** **514/376**; 548/216

(57) **ABSTRACT**

Novel oxazolidinone derivatives with a difluorophenyl moiety, represented by Chemical Formula 1, pharmaceutically acceptable salts thereof, a preparation method thereof, and a pharmaceutical composition containing the same as an active ingredient are provided. Exhibiting potent inhibitory activity against Gram-positive bacteria including *Haemophilus influenza* and Coagulase negative staphylococci and resistant bacteria including vancomycin-resistant enterococci (VRE), the pharmaceutical composition is useful as an antibiotic.

[Chemical Formula 1]



(wherein, R is as defined in the specification)

NOVEL OXAZOLIDINONE DERIVATIVE WITH DIFLUOROPHENYL MOIETY, PHARMACEUTICALLY ACCEPTABLE SALT THEREOF, PREPARATION METHOD THEREOF AND ANTIBIOTIC COMPOSITION CONTAINING THE SAME AS AN ACTIVE INGREDIENT

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This patent application claims the benefit of priority from Korean Patent Application No. 10-2008-0090659 filed Sep. 16, 2008, the contents of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] The present invention relates to novel oxazolidinone derivatives with a difluorophenyl moiety, pharmaceutically acceptable salts thereof, a method for preparing the same, and an antibiotic composition containing the same as an active ingredient.

[0004] 2. Description of the Related Art

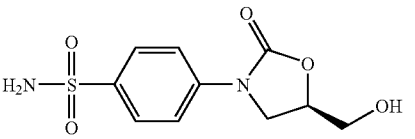
[0005] According to statistics in 1992, as many as 68% of methicillin-resistant *Staphylococcus aureus* (hereinafter referred to as "MRSA") strains show multidrug-resistance. Vancomycin, the most potent among currently available antibiotics, is the only antibiotic that is inhibitory of multidrug-resistant MRSA. However, a *Staphylococcus aureus* strain resistant to vancomycin was found in Japan in May, 1997. In fact, much earlier, in the 1980s, the emergence of vancomycin-resistant enterococci (hereinafter referred to as "VRE") had been reported from hospitals of the U.S.A. and Britain. In the U.S.A., VRE has increased to 13.6% in 1993 from 0.4% in 1989, and emerged as a hot topic in the medical world. Thus, the effectiveness of the glycopeptide type antibiotic vancomycin, which had been regarded as the last fortress against gram-positive bacteria, was called into doubt.

[0006] This great anxiety has disappeared with the emergence of linezolid. Food and Drug Administration (FDA) approval was granted for the antibiotic linezolid (U-100766) in April 2000. It is sold in the U.S. under the trade name Zyvox. Since the quinolone class, 35 years have passed before the development of this novel class antibiotic.

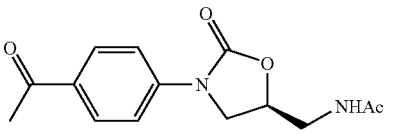
[0007] To date, a wide spectrum of various classes of antibiotics is available and various strains are also observed to have resistance thereto. With the expansion of the use of antibiotics, bacteria themselves undergo extensive mutations resulting in an explosive increase in resistance thereto. Furthermore, more frequent use of various antibiotics leads to a higher complexity of antibiotic resistance than in the past.

[0008] The antibiotic activity of the oxazolidinone class compounds was first discovered by researchers at E.I. DuPont. This company synthesized the oxazolidinone compounds in 1987 and reported that Dup-721 showed inhibitory activity against Gram-negative anaerobes and *Mycobacterium tuberculosis* as well as gram-positive strains including MRSA and MRSE.

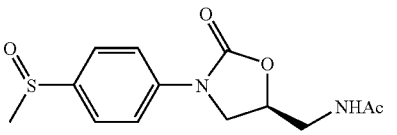
S-6123



DuP-721



DuP-105



[0009] However, studies on Dup-105 and Dup-721 were not further undertaken because fatal toxicity was observed in conjunction therewith in Stage 1 of clinical testing conducted by Upjohn. Based on the finding that oxazolidinone compounds have antibacterial activity, Upjohn succeeded in developing antibiotic compounds U-100766 (Linezolid) and U-100562 (Eperezolid) in 1996. These compounds are similar to vancomycin in antibacterial activity against Gram-positive strains, but show very poor inhibitory activity against Gram-negative strains.

[0010] At this time, it is necessary to develop novel antibiotics as various bacterial strains are resistant to most antibiotics currently being used clinically. Particularly, novel oxazolidinone antibiotics are imperatively needed to circumvent the problem of resistant strains.

[0011] Culminating in the present invention, with the goal of overcoming the problems encountered in the prior art, intensive and thorough research was conducted by the present inventors into novel oxazolidinone class antibiotics with more potent anti-bacterial activity, which resulted in the finding that oxazolidinone derivatives with difluorophenyl moieties are highly inhibitory of resistant strains including Gram-positive bacteria and VRE.

SUMMARY OF THE INVENTION

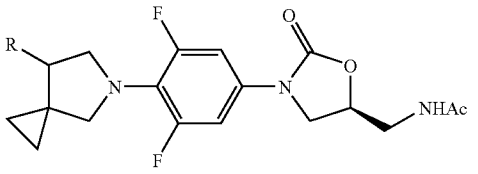
[0012] It is therefore an object of the present invention to provide a novel oxazolidinone derivative and a pharmaceutically acceptable salt thereof.

[0013] It is another object of the present invention to provide a method for preparing the novel oxazolidinone derivative.

[0014] It is a further object of the present invention to provide an antibiotic composition containing the oxazolidinone derivative or the pharmaceutically acceptable salt thereof as an active ingredient.

[0015] In order to achieve the above object, the present invention provides a novel oxazolidinone derivative with a difluorophenyl moiety, represented by the following Chemical Formula 1, and a pharmaceutically acceptable salt thereof:

[Chemical Formula 1]



[0016] (wherein, R is hydroxy, amino, halogen, hydrazine, hydroxylamine, an alkyloxyimine of C_1~C_4 or allyloxyimine)

[0017] Also, the present invention provides a method for preparing the oxazolidinone derivative.

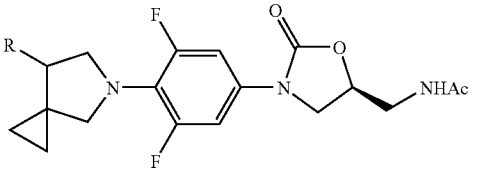
[0018] Further, the present invention provides an antibiotic composition containing the oxazolidinone derivative or a pharmaceutically acceptable salt thereof as an active ingredient

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0019] A detailed description will be given of the present invention, below.

[0020] In accordance with an aspect thereof, the present invention provides a novel oxazolidinone derivative having a difluorophenyl moiety, represented by the following Chemical Formula 1.

[Chemical Formula 1]



[0021] wherein, R is hydroxy, amino, halogen, hydrazine, hydroxyimine, an alkyloxyimine of C_1~C_4, or allyloxyimine.

[0022] Preferably, R is hydroxy, amino, fluoro, chloro, bromo, hydrazine, hydroxyimine, methoxyimine, ethoxyimine, propoxyimine, isopropoxyimine, butoxyimine, isobutoxyimine or allyloxyimine.

[0023] Concrete examples of the novel oxazolidinone derivatives with difluorophenyl moieties in accordance with the present invention include:

[0024] (1) (S)—N-{{3-[3,5-difluoro-4-(7-hydroxy-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide;

[0025] (2) (S)—N-{{3-[3,5-difluoro-4-(7-fluoro-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide;

[0026] (3) (S)—N-{{3-[3,5-difluoro-4-(7-hydroxyimino-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide;

[0027] (4) (S)—N-{{3-[3,5-difluoro-4-(7-methoxyimino-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide;

[0028] (5) (S)—N-{{3-[3,5-difluoro-4-(7-hydrazino-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide;

[0029] (6) (S)—N-{{3-[3,5-difluoro-4-(7-ethoxyimino-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide;

[0030] (7) (S)—N-{{3-[3,5-difluoro-4-(7-allyoxyimino-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide; and

[0031] (8) (S)—N-{{3-[3,5-difluoro-4-(7-amino-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide.

[0032] Structures of the oxazolidinone derivatives of Chemical Formula 1 in accordance with the present invention are summarized in Table 1, below.

TABLE 1

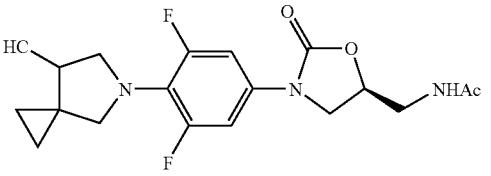
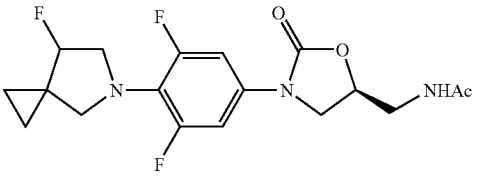
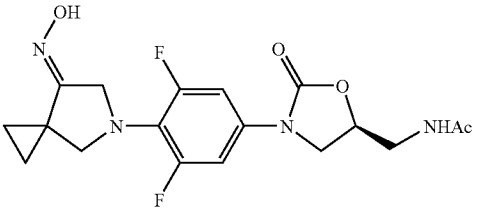
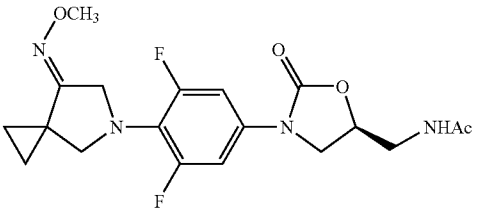
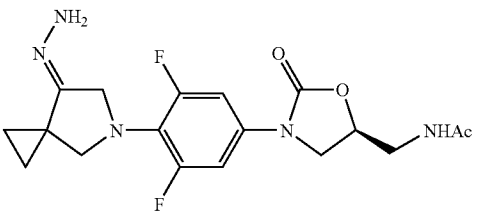
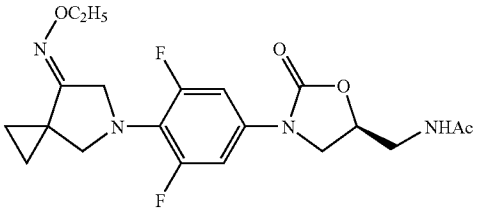
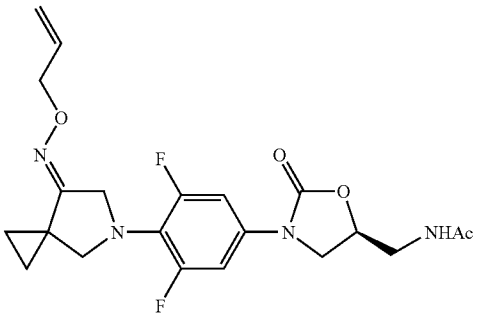
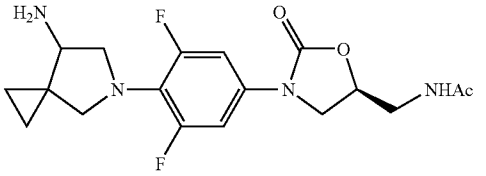
Cpd.	Structures
1	
2	
3	
4	
5	

TABLE 1-continued

Cpd.	Structures
6	
7	
8	

[0033] The oxazolidinone derivatives according to the present invention, represented by Chemical Formula 1, may be used in the form of pharmaceutically acceptable salts. Within the range of these salts are included, for example, acid addition salts formed with pharmaceutically acceptable free acids. As the free acids, non-toxic inorganic acids such as hydrochloric acid, bromic acid, sulfonic acid, phosphoric acid, etc., and non-toxic organic acids such as citric acid, acetic acid, lactic acid, maleic acid, fumaric acid, gluconic acid, methanesulfonic acid, glycolic acid, succinic acid, tartaric acid, 4-toluenesulfonic acid, galucturonic acid, embonic acid, glutamic acid, aspartic acid, etc. are useful, with preference for hydrochloric acid or methanesulfonic acid.

[0034] It should be understood that in addition to the oxazolidinone derivatives of Chemical Formula 1 and pharmaceutically acceptable salts thereof, solvates, hydrates and racemates that can be prepared therefrom are included within the scope of the present invention.

[0035] The acid addition salts of the compounds according to the present invention may be prepared using a typical method, for example, by dissolving the compound of Chemical Formula 1 in a water-miscible organic solvent, e.g., acetone, methanol, ethanol, or acetonitrile, adding excess organic acid or excess inorganic acid in water thereto to form precipitates or crystals. Subsequently, the solvent or excess acid is evaporated, followed by drying or suction filtering the precipitates to prepare acid addition salts thereof.

[0036] In accordance with another aspect thereof, the present invention provides a method for preparing the novel oxazolidinone derivative.

[0037] The method for preparing the novel oxazolidinone derivative of the present invention, as illustrated in Reaction Scheme 1, comprises:

[0038] Reacting a compound of Chemical Formula 2 with trifluoronitrobenzene of Chemical Formula 3 to give a compound of Chemical Formula 4 (Step 1);

[0039] Reducing the compound of Chemical Formula 4 through hydrogenation to a compound of Chemical Formula 5 (Step 2);

[0040] Introducing a carbobenzyloxy (CBZ) group into the amine group of the compound of Chemical Formula 5 to give a compound of Chemical Formula 6 (Step 3);

[0041] Adding n-butyl lithium and (R)-glycidyl butyrate to the compound of Chemical Formula 6 to give a compound of Chemical Formula 7 (Step 4);

[0042] Mesylating the hydroxy group of the compound of Chemical Formula 7 to give a compound of Chemical Formula 8 (Step 5);

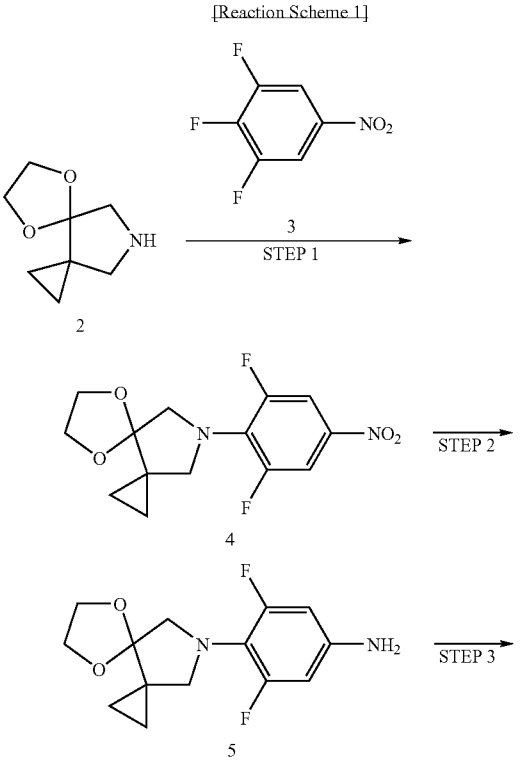
[0043] Azidating the compound of Chemical Formula 8 with sodium azide to a compound of Chemical Formula 9 (Step 6);

[0044] Reducing and acetylating the compound of Chemical Formula 9 to a compound of Chemical Formula 10 (Step 7);

[0045] Deprotecting the compound of Chemical Formula 10 to give a compound of Chemical Formula 11 (Step 8); and

[0046] Reducing the compound of Chemical Formula 11 to a compound of Chemical Formula 1a (Step 9).

[Reaction Scheme 1]



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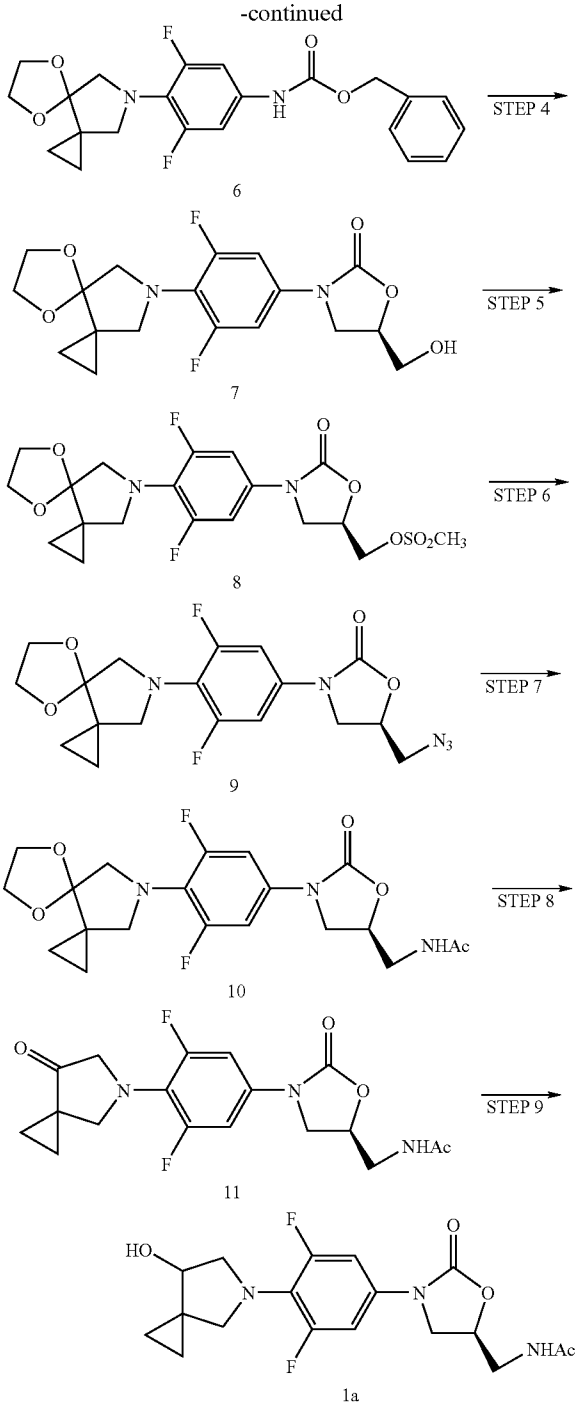
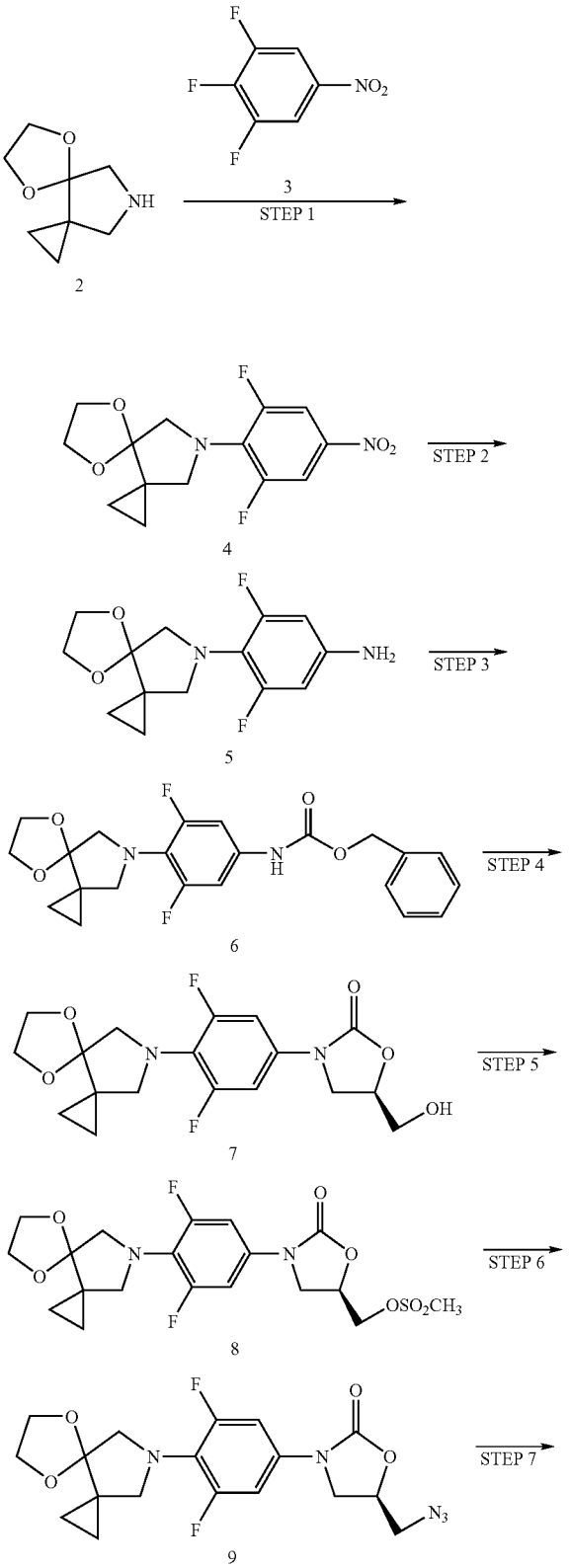


[Reaction Scheme 2]



[0047] (wherein the compound of Chemical Formula 1a is included within the range of Chemical Formula 1)

[0048] The method according to the present invention, as illustrated in the following Reaction Scheme 2, may further comprise:

[0049] halogenating or aminating the compound of Chemical Formula 1a to a compound of Chemical Formula 1b (Step 10) after Step 9.

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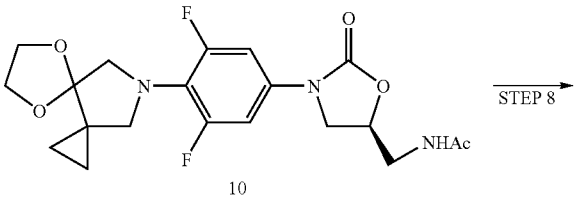

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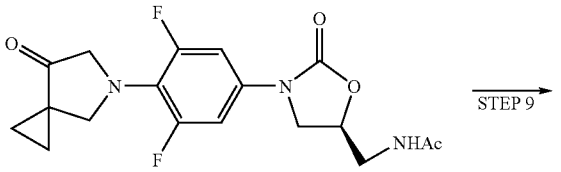

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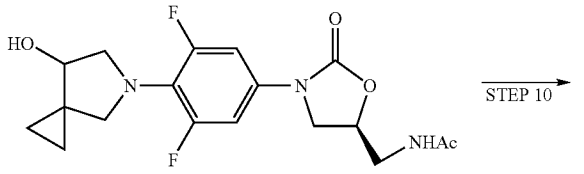
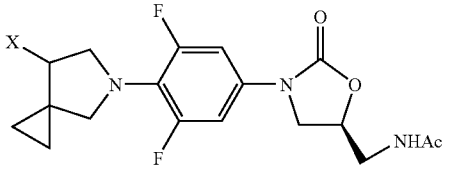


1a



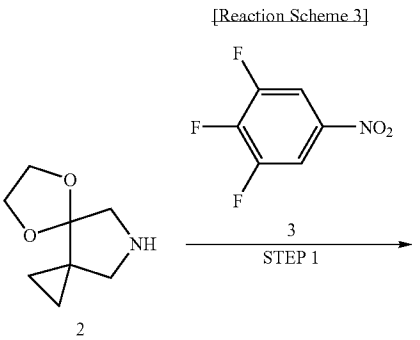
1b

[0050] (wherein X is a halogen or an amine, and the compounds of Chemical Formulas 1a and 1b are included within the range of Chemical Formula 1.)

[0051] Also, the method according to the present invention, as illustrated in the following Reaction Scheme 3, may further comprise:

[0052] Reacting the compound of Chemical Formula 11 with an amine chloride salt to give a compound of Chemical Formula 1c (Step 9') after Step 8.

[Reaction Scheme 3]



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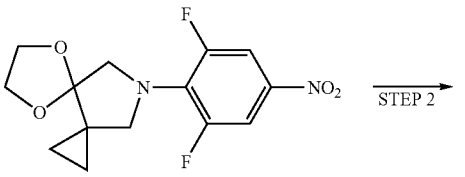

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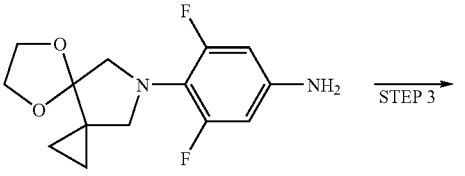

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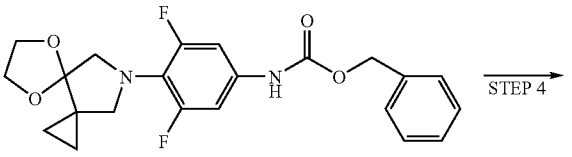

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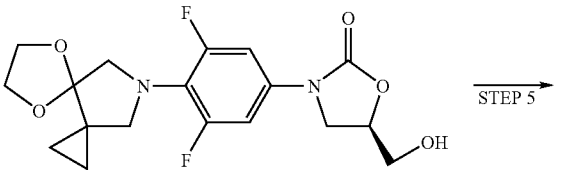

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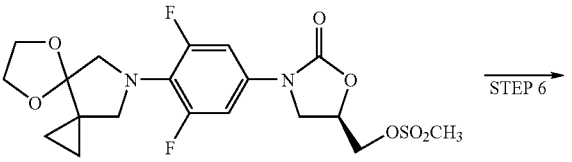

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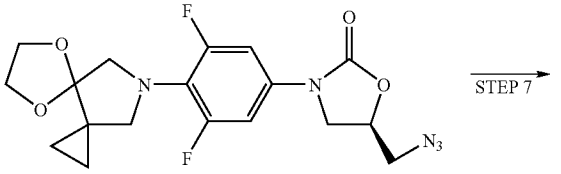

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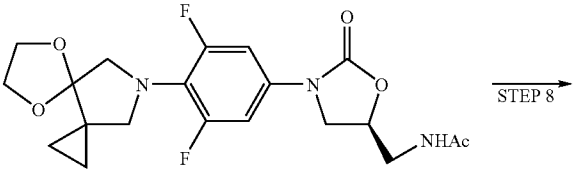

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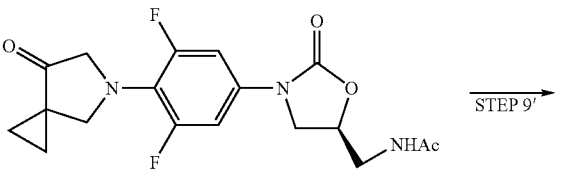

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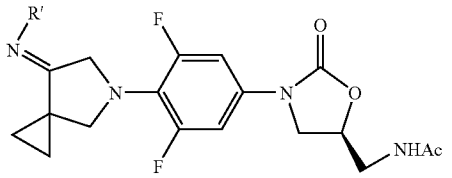


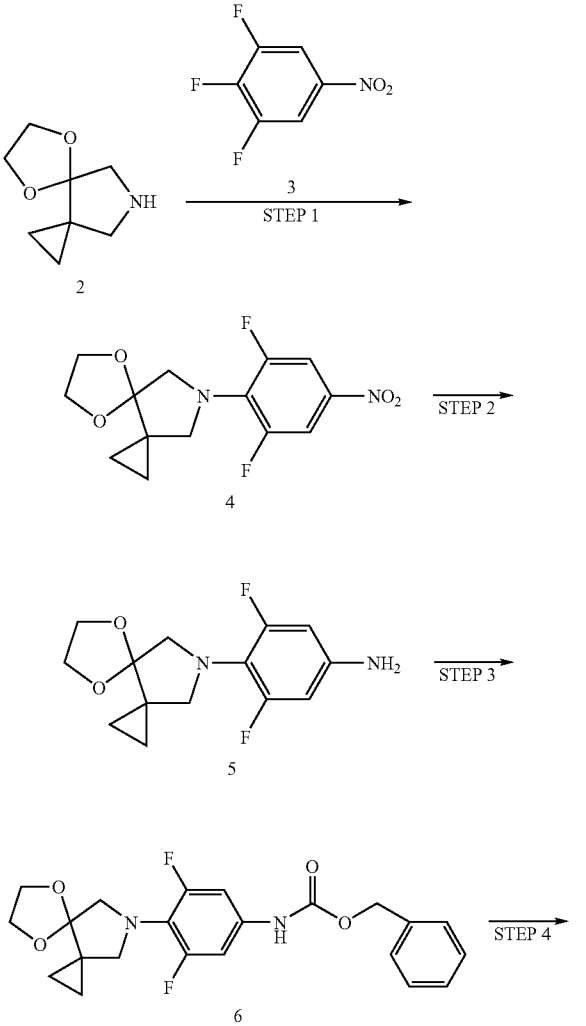
1c

[0053] (wherein R' is a hydroxy, methoxy or amine group, and the compound of Chemical Formula 1c is included within the range of Chemical Formula 1.)

[0054] When R' is a hydroxy, as illustrated in the following Reaction Scheme 4, the method may further comprises:

[0055] Reacting a nucleophile with the compound of Chemical Formula 1c in the presence of a base to give a compound of Chemical Formula 1d (Step 10') after Step 9'.

[Reaction Scheme 4]



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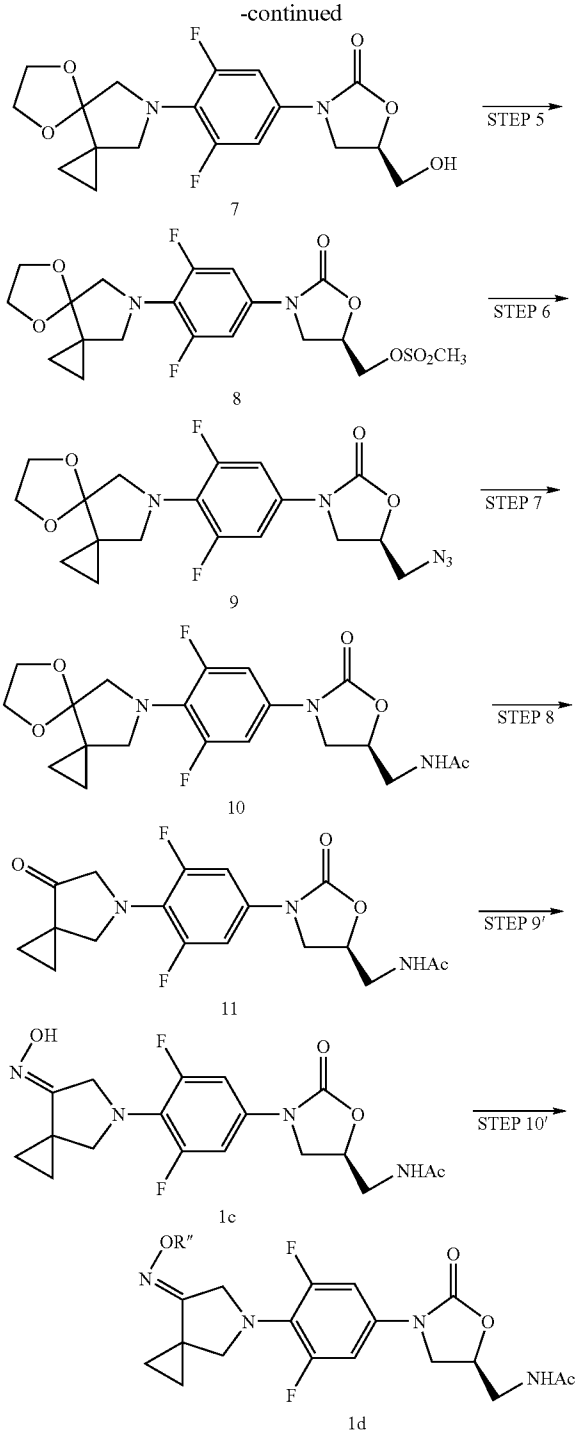


[0056] (wherein R" is a C_1~C_4 alkyl or allyl, and the compounds of Chemical Formulas 1c and 1d are included within the range of Chemical Formula 1.)

[0057] In Step 1, the compound of Chemical Formula 2 is reacted with the trifluoronitrobenzene compound of Chemical Formula 3 to produce the compound of Chemical Formula 4. In greater detail, the compound of Chemical Formula 2 and

3,4,5-trifluoronitrobenzene are refluxed for 3 hours in acetonitrile to obtain the compound of Chemical Formula 4.

[0058] Next, hydrogenation is conducted to reduce the compound of Chemical Formula 4, obtained in Step 1, to the compound of Chemical Formula 5 in Step 2. The compound of Chemical Formula 4 is hydrogenated with H_2 in the presence of Pd/C to the arylamine compound of Chemical Formula 5.

[0059] Then, Step 3 is designed to introduce a carbobenzyloxy (CBZ) group onto the amine group of the compound of Chemical Formula 5, obtained in Step 2, so as to produce the compound of Chemical Formula 6. In this regard, the compound of Chemical Formula 5 is dissolved in acetone and mixed with a sodium hydrogen carbonate solution, after which benzylchloroformate is dropwise added to the reaction mixture in an ice bath to afford the compound of Chemical Formula 6.

[0060] Thereafter, Step 4 uses n-butyl lithium and (R)-glycidyl butyrate in producing an oxazolidinone moiety of Chemical Formula 7 from the compound of Chemical Formula 6, obtained in Step 3. Concretely, n-butyl lithium is dropwise added to a solution of the compound of Chemical Formula 6 in tetrahydrofuran at −78° C., followed by the addition of (R)-glycidyl butyrate thereto. While the temperature is elevated to room temperature, the reaction proceeds to form the oxazolidinone moiety of Chemical Formula 7.

[0061] Next, the hydroxy group of the compound of Chemical Formula 7, obtained in Step 4, is mesylated to the compound of Chemical Formula 8 in Step 5. In detail, the compound of Chemical Formula 7 is reacted with mesyl chloride in the presence of triethyl amine in methylene chloride to give the compound of Chemical Formula 8.

[0062] Subsequently, azidation is conducted to change the compound of Chemical Formula 8, obtained in Step 5, to the compound of Chemical Formula 9 in Step 6. In detailed steps, sodium azide is added to a solution of the compound of Chemical Formula 8 in DMF and stirred at 60° C. for 16 hours to give the compound of Chemical Formula 9.

[0063] In Step 7, the compound of Chemical Formula 9, obtained in Step 6, is reduced and then acetylated to the compound of Chemical Formula 10. Concretely, the compound of Chemical Formula 9 is reduced in the presence of Pd/C in an H_2 atmosphere, followed by acetylation with pyridine and anhydrous acetic acid to produce the compound of Chemical Formula 10.

[0064] Step 8 is deprotection of the compound of Chemical Formula 10, obtained in Step 7, forming the compound of Chemical Formula 11. For this, the compound of Chemical Formula 10 is dissolved in p-toluene sulfonic acid monohydrate and refluxed for 3 hours to give the compound of Chemical Formula 11.

[0065] Afterwards, reduction is performed on the compound of Chemical Formula 11 obtained in Step 8 to give the compound of Chemical Formula 1a. In more detail, with the aid of $NaBH_4$, the oxo group of the compound of Chemical Formula 11 is reduced to the hydroxy group of the compound of Chemical Formula 1a.

[0066] In Step 10, the compound of Chemical Formula 1a obtained in Step 9 is halogenated or aminated to the compound of Chemical Formula 1b. For instance, DAST may be used to substitute the hydroxy group of the compound of Chemical Formula 1a with a fluoro group. Alternatively, the hydroxy group of the compound of Chemical Formula 1a may be mesylated by reaction with amine and mesyl chloride, then azidated with sodium azide, and then reduced to an amine in the presence of palladium.

[0067] On the other hand, in Step 9', the compound of Chemical Formula 11 obtained in Step 8 is reacted with an amine chloride salt to produce the compound of Chemical Formula 1c. For instance, the compound of Chemical Formula 11 may be dissolved in ethanol, mixed with a 50% aqueous hydroxylamine solution, sodium ethoxide and water, and refluxed for 5 hours to give the hydroxyimine compound. Alternatively, the compound of Chemical Formula 11 may be dissolved in methanol and reacted with a 30~35% methoxylamine chloride salt and triethyl amine at room temperature for 10 hours with stirring to give a methoxyimine compound. In an additional alternative, the compound of Chemical Formula 11 is reacted with hydrazine chloride in the presence of triethyl amine in ethanol to afford a hydrazine compound.

[0068] In Step 10', the compound of Chemical Formula 1c obtained in Step 9' is used as a nucleophile to conduct a nucleophilic substitution in the presence of a base, leading to the compound of Chemical Formula 1d. In greater detail, when the compound of Chemical Formula 1c is a hydroxyimine compound, it is reacted with ethyl bromide or allyl bromide in the presence of potassium hydroxide to give an ethoxyimine compound or allyloxyimine compound.

[0069] For the identification of the oxazolidinone derivatives or intermediates therefor prepared as explained above in accordance with the present invention, various analytical technologies including IR spectrometry, NMR spectrometry, mass spectrometry, liquid chromatography, X-ray crystallography, optical rotation, and comparison between calculated and measured values from elemental analysis of typical compounds may be performed.

[0070] In accordance with a further aspect thereof, the present invention provides an antibiotic composition containing the oxazolidinone derivative or a pharmaceutically acceptable salt thereof as an active ingredient.

[0071] In accordance with still a further aspect thereof, the present invention provides a method for the treatment of bacterial diseases by administering an oxazolidinone derivative represented by Chemical Formula 1 or a pharmaceutically acceptable salt thereof at a therapeutically effective dose to a subject in need thereof.

[0072] In accordance with a further aspect thereof, the present invention provides a method for killing a bacterial strain infecting a subject, comprising administering the oxazolidinone derivative represented by Chemical Formula 1 or a pharmaceutically acceptable salt thereof at a therapeutically effective dose to a subject in need thereof.

[0073] The oxazolidinone derivatives or pharmaceutically acceptable salts thereof, useful as active ingredients in the antibiotic composition according to the present invention, were found to have anti-bacterial activity as potent as or more potent than that of the commercially available antibiotic Linezolid as they were measured to range in MIC from 0.781 to 3.125 mg/ml in an in vitro assay. Particularly, they showed an MIC of 0.781 mg/ml against Gram-positive bacteria including *Haemophilus influenza* and non-pathogenic Coagulase negative staphylococci as well as resistant bacteria including vancomycin resistant enterococci (VRE), which has a higher inhibitory activity to Linezolid (MIC: 1.563~3.125 mg/ml) (see Table 2). Accordingly, the oxazolidinone derivatives according to the present invention are useful as novel antibiotics.

[0074] For clinical practice, the pharmaceutical composition containing the oxazolidinone derivative or a pharmaceutically acceptable salt thereof in accordance with the present invention may be formulated into the following oral or non-oral dosage forms, but are not limited thereto.

[0075] Oral dosage preparations of the compounds of the present invention may take the form of tablets, pills, hard/soft capsules, solutions, suspensions, emulsions, syrups, granules, elixirs and the like. These dosage forms may comprise diluents (e.g., lactose, dextrose, sucrose, manitol, sorbitol, cellulose and/or glycine), lubricants (e.g., silica, talc, stearic acid and magnesium or calcium salts thereof, and/or polyeth-

ylene glycol) in addition to the active ingredient. For example, tablets may further comprise a binder, such as magnesium aluminum silicate, starch paste, gelatin, methyl cellulose, sodium carboxyethyl cellulose, and/or polyvinylpyrrolidone, and optionally a disintegrant such as starch, agar, alginic acid or sodium salts thereof or an effervescent mixture and/or an adsorbent, a colorant, a flavor, and a sweetener.

[0076] The pharmaceutical composition containing the derivative of Chemical Formula 1 as an active ingredient may be administered in a non-oral manner. Non-oral dosage forms may be injections via subcutaneous, intravenous, intramuscular, or intrathoracic routes.

[0077] As for non-oral dosage forms, they may be prepared by mixing the oxazolidinone derivative of Chemical Formula 1 or pharmaceutically acceptable salt thereof with a stabilizer or buffer in water and loading the solution or suspension onto ampule or vial unit forms. The composition intended for oral or non-oral administration is sterilized or sterile and may comprise auxiliary agents such as preservatives, stabilizers, wetable powders or emulsifying agents, osmosis-adjusting salts, and/or buffers, and other therapeutically useful agents. It may be formulated using admixture, granulation or coating methods.

[0078] The effective dosage of the active ingredient in accordance with the present invention depends on various factors, including the patient's age, weight, gender, route of administration, state of health, severity of diseases, etc. Typically, the compound according to the present invention may be administered at a daily dose ranging from 0.01 to 1,000 mg and preferably from 1 to 500 mg for 70 kg adult patients. The compound may be administered in a single dose or may be divided into multiple doses per day according to the instructions of a physician or pharmacist.

EXAMPLE 1

Preparation of (S)—N-{{3-[3,5-Difluoro-4-(7-hydroxy-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide

Step 1: Preparation of 3,5-difluoro-4(7,7-ethylenedioxy-5-azaspiro[2,4]heptan-5-yl)nitrobenzen

[0079] To a solution of 7,7-ethylenedioxy-5-azaspiro[2,4]heptane in acetonitrile (50 mL) was dropwise added 3,4,5-trifluoronitrobenzene (5.3 g, 31.6 mmol) and the reaction mixture was refluxed for 3 hours. After the reaction was terminated, the reaction mixture was cooled to room temperature and the solvent was removed therefrom by vacuum distillation. It was diluted with ethyl acetate and water, and the organic phase thus formed was dried over magnesium sulfate. The residue was filtered, concentrated in a vacuum, and purified through column chromatography (n-hexane/ethyl acetate=4:1) to afford the target compound (3.5 g, yield 66%).

[0080] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.66 (t, 2H, J=5.3 Hz), 0.95 (t, 2H, J=5.3 Hz), 3.67 (d, 2H, J=2.3 Hz), 3.75 (d, 2H, J=3.5 Hz), 3.97 (s, 4H), 7.49 (s, 1H), 7.90 (s, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 8.1, 25.3, 56.4, 58.3, 65.4, 112.1, 112.5, 112.9, 121.8, 141.9, 147.5, 150.7.

Steps 2~3: Preparation of N-carbobenzyloxy-[3,5-difluoro-4-(7,7-ethylenedioxy-5-azaspiro[2,4]heptan-5-yl)phenyl]aniline

[0081] (S)—N-{{3-[3,5-difluoro-4-(7-hydroxy-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide (2.5 g, 8.5 mmol), obtained in Step 1, was placed together with 10% Pd/C (1.3 g, 50%) in a Paar shaker flask and dissolved in THF (60 mL), followed by shaking for 2 hours at H_2 40 psi. After the reaction terminated, the reaction mixture was filtered through cellite and the filtrate was distilled in a vacuum to remove the solvent therefrom before performing the following sequential processes. To a solution of the product in acetone (40 mL) was added a 10% $NaHCO_3$ solution (2 mL), and then droplets of benzylchloroformate (1.6 mL, 11.4 mmol) in an ice bath. When the reaction terminated after stirring at room temperature for 3 hours, the solvent was removed by vacuum distillation. The residue was dissolved in ethyl acetate and mixed with water and the organic phase thus obtained was dried over anhydrous magnesium sulfate. After filtration, the filtrate was distilled in a vacuum to remove the solvent, followed by purification through column chromatography (n-hexane/ethyl acetate=5:1) to afford the target compound (1.9 g, yield 55%).

[0082] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.64 (t, 2H, J=5.3 Hz), 0.93 (t, 2H, J=5.3 Hz), 3.45 (s, 2H), 3.56 (d, 2H, J=1.7 Hz), 3.93 (s, 4H), 5.18 (s, 2H), 7.49 (s, 1H), 7.90 (s, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 8.6, 25.7, 57.0, 59.3, 65.0, 66.9, 108.6, 112.8, 112.9, 115.1, 115.2, 128.3, 128.5, 128.9, 133.6, 136.2, 150.5, 153.7.

Step 4: Preparation of (R)—{N-3-[3,5difluoro-4-(7,7-ethylenedioxy-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}

[0083] To a solution of N-carbobenzyloxy-[3,5-difluoro-4-(7,7-ethylenedioxy-5-azaspiro[2,4]heptan-5-yl)phenyl] aniline (2.1 g, 5.1 mmol), obtained in Step 3, in purified tetrahydrofuran (50 mL) was dropwise added 1.6 M n-butyl lithium-hexane solution (3.5 mL, 5.6 mmol) at −78° C. 10 min later, droplets of (R)-glycidyl butyrate (0.8 mL, 4.7 mmol) were slowly added. The temperature was elevated to room temperature with stirring for 16 hours. After the reaction terminated, the reaction mixture was mixed with a saturated aqueous ammonium chloride solution (10 mL) and then extracted with ethyl acetate and water. The organic phase thus formed was dried over anhydrous magnesium sulfate and filtered. After the removal of the solvent through vacuum distillation, the filtrate was purified using column chromatography (n-hexane/ethyl acetate=1:1) to afford the target compound (1.3 g, yield 66%).

[0084] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.64 (t, 2H, J=5.4 Hz), 0.94 (t, 2H, J=5.4 Hz), 3.47 (d, 2H, J=1.5 Hz), 3.57 (d, 2H, J=2.4 Hz), 3.88 (d, 2H, J=8.5 Hz), 3.94 (s, 4H), 3.97 (d, 2H, J=8.5 Hz), 4.71 (m, 1H), 7.15 (s, 1H), 7.30 (s, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 8.6, 25.6, 46.6, 59.1, 62.7, 65.1, 72.9, 107.7, 108.1, 112.8, 114.5, 114.6, 129.0, 133.8, 150.2, 154.9.

Step 5: Preparation of (R)—{N-3-[3,5-difluoro-4-(7,7-ethylenedioxy-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl methanesulfonate

[0085] To a methylenechloride solution (50 mL) of (R)—{N-3-[3,5difluoro-4-(7,7-ethylenedioxy-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methanol (1.3 g, 3.4 mmol), obtained in Step 4, was added triethylamine (1.1 mL, 7.8 mmol) and then droplets of mesylchloride (0.4 mL, 4.4 mmol) in an ice bath, followed by stirring at room temperature for 3 hours. After the reaction terminated, the reaction mixture was extracted with methylene chloride and water and the organic phase thus formed was dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated in a vacuum to remove the solvent therefrom and purified through column chromatography (n-hexane/ethyl acetate=1:1) to afford the target compound (0.9 g, yield 62%).

[0086] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.62 (t, 2H, J=5.4 Hz), 0.91 (t, 2H, J=5.4 Hz), 3.08 (s, 3H), 3.46 (d, 2H, J=1.6 Hz), 3.55 (d, 2H, J=2.1 Hz), 3.85 (t, 2H, J=4.6 Hz), 3.92 (s, 4H), 4.07 (t, 2H, J=8.9 Hz), 4.87 (m, 1H), 7.15 (s, 1H), 7.30 (s, 1H); ^{13}C-NMR (300 MHz, $CdCl_3$) δ 8.6, 25.6, 37.7, 46.8, 56.8, 59.0, 65.1, 68.4, 69.5, 108.3, 112.7, 114.8, 128.3, 128.4, 134.2, 150.1, 153.8.

Step 6: Preparation of (R)—{N-3-[3,5-difluoro-4-(7,7-ethylenedioxy-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl azide

[0087] To a solution of (R)—{N-3-[3,5-difluoro-4-(7,7-ethylenedioxy-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl methanesulfate (0.9 g, 2.1 mmol), obtained in Step 5, in DMF (20 mL) was added sodium azide (0.5 g, 8.0 mmol), followed by heating at 60° C. for 16 hours. After the reaction terminated, the reaction mix was cooled to room temperature and let to stand for 30 min and extracted with ethyl acetate and water. The organic phase thus formed was dried over anhydrous magnesium sulfate and filtered. The filtrate was distilled in a vacuum to remove the solvent therefrom and purified through column chromatography (n-hexane/ethyl acetate=1:1) to afford the target compound (0.6 g, yield 65%).

[0088] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.63 (t, 2H, J=5.3 Hz), 0.92 (t, 2H, J=5.3 Hz), 3.48 (s, 2H), 3.56 (d, 2H, J=6.3 Hz), 3.78 (t, 2H, J=7.5 Hz), 3.93 (s, 4H), 4.02 (t, 2H, J=8.9 Hz), 4.75 (m, 1H), 7.15 (s, 1H), 7.30 (s, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 8.6, 25.6, 47.8, 53.1, 56.9, 65.1, 70.5, 108.2, 112.7, 114.8, 114.9, 128.7, 134.1, 150.2, 154.0.

Step 7: Preparation of (S)—N-{{3-[3,5-difluoro-4-(7,7-ethylenedioxy-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide

[0089] To a solution of (R)—{N-3-[3,5-difluoro-4-(7,7-ethylenedioxy-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methylazide (0.6 g, 1.6 mmol), obtained in Step 6, in ethyl acetate (15 mL) was added 10% palladium-charcoal (30 mg) and the reaction mixture was stirred at room temperature under 1 atm of H_2, for 14 hours. When the reaction terminated, the solvent was removed by vacuum distillation. After the reducing atmosphere was changed to a nitrogen atmosphere, the reaction mixture was added with pyridine (0.2 mL, 1.9 mmol) and anhydrous acetic acid (0.5 mL, 5.3 mmol) and stirred at 0° C. for 30 min and then at room temperature for 2 hours. When the reaction terminated, the reaction mixture was filtered through cellite, and the filtrate was distilled in a vacuum to remove the solvent therefrom, followed by purification through column chromatography (n-hexane/ethyl acetate=1:2) to afford the target compound (0.5 g, yield 84%).

[0090] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.64 (t, 2H, J=5.3 Hz), 0.92 (t, 2H, J=5.3 Hz), 2.03 (s, 3H), 3.46 (s, 2H), 3.56 (d, 2H, J=2.4 Hz), 3.71 (t, 2H, J=7.3 Hz), 3.94 (s, 4H), 4.00 (t, 2H, J=9.0 Hz), 4.75 (m, 1H), 7.15 (s, 1H), 7.30 (s, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 8.6, 22.9, 25.6, 41.9, 47.8, 56.8, 59.0, 65.1, 71.9, 108.1, 112.7, 114.8, 114.9, 128.8, 134.0, 150.1, 154.7, 171.4.

Step 8: Preparation of (S)—N-{{3-[3,5-difluoro-4-(7-oxo-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide

[0091] To a solution of (S)—N-{{3-[3,5-difluoro-4-(7,7-ethylenedioxy-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide (0.5 g, 1.4 mmol), obtained in Step 7, in a mixture of acetone (40 mL) and water (10 mL) was added p-toluenesulfonic acid monohydrate (0.5 g, 2.7 mmol), followed by refluxing for 3 hours. When the reaction terminated, the reaction mixture was distilled in a vacuum to remove the solvent therefrom. After the addition of triethyl amine (1 mL), extraction was conducted with methylene chloride. The organic phase was dried over anhydrous magnesium sulfate and filtered The filtrate was concentrated in a vacuum and purified through column chromatography (n-hexane/ethyl acetate=1:2) to afford the target compound (0.3 g, yield 45%).

[0092] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.17 (q, 2H, J=3.6 Hz), 1.44 (q, 2H, J=3.5 Hz), 2.02 (s, 3H), 3.67 (t, 2H, J=3.0 Hz), 3.75 (t, 2H, J=7.8 Hz), 3.96 (d, 2H, J=1.6 Hz), 4.02 (t, 2H, J=8.9 Hz), 4.77 (m, 1H), 7.19 (s, 1H), 7.35 (s, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 18.1, 23.2, 41.9, 47.7, 55.3, 58.3, 71.8, 108.1, 114.4, 115.9, 130.5, 133.1, 151.0, 154.4, 171.2, 212.3.

Step 9: Preparation of (S)—N-{{3-[3,5-difluoro-4-(7-hydroxy-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide

[0093] To a solution of (S)—N-{{3-[3,5-difluoro-4-(7-oxo-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide (120 mg, 3.3 mol), obtained in Step 8, in tetrahydrofuran (15 mL) was slowly added sodium borohydride (12.6 mg, 3.3 mol) in an ice bath, followed by stirring for 2 hours. When the reaction terminated, the reaction mixture was neutralized with acetic acid and extracted with ethyl acetate and water. The organic phase thus formed was dried over anhydrous magnesium sulfate and filtered. After the removal of the solvent by vacuum distillation, the filtrate was purified through flat-TLC (n-hexane/ethyl acetate=1:1) to afford the target compound (94 mg, yield 77%).

[0094] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.17 (q, 2H, J=3.6 Hz), 1.44 (q, 2H, J=3.5 Hz), 2.02 (s, 3H), 3.5 (s, 1H), 3.67 (t, 2H, J=3.0 Hz), 3.75 (t, 2H, J=7.8 Hz), 3.96 (d, 2H, J=1.6 Hz), 4.02 (t, 2H, J=8.9 Hz), 4.77 (m, 1H), 7.19 (s, 1H), 7.35 (s, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 18.1, 23.2, 41.9, 47.7, 55.3, 58.3, 71.8, 108.1, 114.4, 115.9, 130.5, 133.1, 151.0, 154.4, 171.2.

EXAMPLE 2

Preparation of (S)—N-{{3-[3,5-Difluoro-4-(7-fluoro-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide

[0095] To a solution of (S)—N-{{3-[3,5-difluoro-4-(7-hydroxy-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide (94.0 mg, 2.6 mol), obtained in Example 1, in methylene chloride (10 mL) was dropwise added DAST (0.2 mL, 3.0 mol) in an ice bath, followed by stirring at room temperature for 3 hours. When the reaction terminated, the reaction mixture was extracted with water. The organic phase thus formed was distilled in a vacuum to remove the solvent therefrom and purified through flat-TLC (n-hexane/ethyl acetate=1:1) to afford the target compound (47 mg, yield 11%).

[0096] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.17 (q, 2H, J=3.6 Hz), 1.44 (q, 2H, J=3.5 Hz), 2.02 (s, 3H), 3.4 (s, 1H), 3.67 (t, 2H, J=3.0 Hz), 3.75 (t, 2H, J=7.8 Hz), 3.96 (d, 2H, J=1.6 Hz), 4.02 (t, 2H, J=8.9 Hz), 4.77 (m, 1H), 7.19 (s, 1H), 7.35 (s, 1H);

^{13}C-NMR (300 MHz, $CDCl_3$) δ 18.1, 23.2, 41.9, 47.7, 55.3, 58.3, 71.8, 108.1, 114.4, 115.9, 130.5, 133.1, 151.0, 154.4, 171.2.

EXAMPLE 3

Preparation of (S)—N-{{3-[3,5-Difluoro-4-(7-hydroxyimino-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide

[0097] To a solution of (S)—N-{{3-[3,5-difluoro-4-(7-oxo-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide (60.0 mg, 0.2 mmol), obtained in Step 8 of Example 1, in ethanol were added NH_2OH HCl (37.0 mg, 5.1 mmol), CH_3CO_2Na (40.0 mg, 5.1 mmol) and water, followed by refluxing for 5 hours. When the reaction terminated, the reaction mixture was cooled to room temperature and extracted with ethyl acetate and water. The organic phase thus formed was dried over anhydrous magnesium sulfate. After the removal of the solvent by vacuum distillation, the residue was purified through flat-TLC (n-hexane/ethyl acetate=1:1) to afford the target compound (27 mg, yield 41%).

[0098] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.17 (q, 2H, J=3.6 Hz), 1.44 (q, 2H, J=3.5 Hz), 2.02 (s, 3H), 3.67 (t, 2H, J=3.0 Hz), 3.75 (t, 2H, J=7.8 Hz), 3.96 (d, 2H, J=1.6 Hz), 4.02 (t, 2H, J=8.9 Hz), 4.77 (m, 1H), 7.19 (s, 1H), 7.35 (s, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 18.1, 23.2, 41.9, 47.7, 55.3, 58.3, 71.8, 108.1, 114.4, 115.9, 130.5, 133.1, 151.0, 154.4, 171.2.

EXAMPLE 4

[0099] Preparation of (S)—N-{{3-[3,5-Difluoro-4-(7-methoxyimino-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide

[0100] To a solution of (S)—N-{{3-[3,5-difluoro-4-(7-oxo-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide (60.0 mg, 0.2 mmol), obtained in Step 8 of Example 1, in methanol was added triethyl amine (0.1 mL, 0.6 mmol), followed by stirring for 10 min. Then, the mixture was slowly added with droplets of methoxylamine chloride (0.04 mL, 0.5 mmol) in an ice bath and then stirred at room temperature for 12 hours. After the reaction terminated, the solvent was removed by vacuum distillation and the reaction mix was extracted with methylene chloride and water. The organic phase thus formed was dried over anhydrous magnesium sulfate and filtered. After concentration by vacuum distillation, the filtrate was purified through flat-TLC (n-hexane/ethyl acetate=1:1) to afford the target compound (30 mg, yield 47%).

[0101] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.17 (q, 2H, J=3.6 Hz), 1.44 (q, 2H, J=3.5 Hz), 2.02 (s, 3H), 3.67 (t, 2H, J=3.0 Hz), 3.75 (t, 2H, J=7.8 Hz), 3.96 (d, 2H, J=1.6 Hz), 4.02 (t, 2H, J=8.9 Hz), 4.77 (m, 1H), 7.19 (s, 1H), 7.35 (s, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 18.1, 23.2, 41.9, 47.7, 55.3, 58.3, 71.8, 108.1, 114.4, 115.9, 130.5, 133.1, 151.0, 154.4, 171.2, 212.3.

EXAMPLE 5

Preparation of (S)—N-{{3-[3,5-Difluoro-4-(7-hydrazino-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide

[0102] A solution of (S)—N-{{3-[3,5-difluoro-4-(7-oxo-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide (60.0 mg, 0.2 mmol), obtained in Step 8 of Example 1, in ethanol was added with triethyl amine (0.1 mL, 0.7 mmol) and stirred for 10 min, and then slowly added with droplets of hydrazine acid chloride (45.0 mg, 0.5 mmol) in an ice bath and stirred for 3 hours. After the reaction terminated, the reaction mixture was distilled in a vacuum to remove the solvent therefrom and extracted with ethyl acetate and water. The organic phase thus obtained was dried over anhydrous magnesium sulfate, filtered and concentrated in a vacuum. Purification of the concentrate through flat-TLC (n-hexane/ethylacetate=1:1) afforded the target compound (22 mg, yield 35%).

[0103] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.17 (q, 2H, J=3.6 Hz), 1.44 (q, 2H, J=3.5 Hz), 2.02 (s, 3H), 3.67 (t, 2H, J=3.0 Hz), 3.75 (t, 2H, J=7.8 Hz), 3.96 (d, 2H, J=1.6 Hz), 4.02 (t, 2H, J=8.9 Hz), 4.77 (m, 1H), 7.19 (s, 1H), 7.35 (s, 1H); ^{13}C-NMR (300 MHz, $CDCl_3$) δ 18.1, 23.2, 41.9, 47.7, 55.3, 58.3, 71.8, 108.1, 114.4, 115.9, 130.5, 133.1, 151.0, 154.4, 171.2, 212.3.

EXAMPLE 6

Preparation of (S)—N-{{3-[3,5-Difluoro-4-(7-ethoxyimino-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide

[0104] While being maintained at 0° C., KOH (0.13 g, 2.4 mmol) was added to a solution of the (S)—N-{{3-[3,5 -difluoro-4-(7-hydroxydimono?-5-azaspiro[2,4]heptan-5-yl) phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide (0.8 g, 1.4 mmol) obtained in Example 3 in 10 mL of DMF, and then slowly droplets of ethyl bromide (0.4 mL, 5.6 mmol) were added with stirring for 3 hours. After the reaction terminated, the reaction mixture was poured into cold water and extracted with ethyl acetate. The organic phase was washed with water and brine and dehydrated over anhydrous magnesium sulfate. Purification through flash column chromatography (n-hexane/ethyl acetate=1:4) afforded the target compound in a white pure form (0.52 g).

[0105] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.06-1.25 (m, 5H), 1.44 (q, 2H, J=3.5 Hz), 2.02 (s, 3H), 3.67 (t, 2H, J=3.0 Hz), 3.75 (t, 2H, J=7.8 Hz), 4.02-4.07 (m, 4H), 4.77 (m, 1H), 7.19 (s, 1H), 7.35 (s, 1H).

EXAMPLE 7

Preparation of (S)—N-{{3-[3,5-Difluoro-4-(7-allyloxyimino-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide

[0106] The same procedure as Example 6, with the exception that allyl bromide was used instead of ethyl bromide, to afford the target compound (yield 67%).

[0107] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.14 (q, 2H, J=3.8 Hz), 1.45 (q, 2H, J=3.3 Hz), 2.05 (s, 3H), 3.67 (t, 2H, J=3.0 Hz), 3.75 (t, 2H, J=7.8 Hz), 4.38-4.45 (m, 5H), 5.11-5.19 (m, 4H), 5.78-5.84 (m, 2), 4.77 (m, 1H), 7.19 (s, 1H), 7.35 (s, 1H).

EXAMPLE 8

Preparation of (S)—N-{{3-[3,5-difluoro-4-(7-amino-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide

[0108] A solution of (S)—N-{{3-[3,5-difluoro-4-(7-hydroxy-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide (1.3 g, 3.4 mmol), obtained in Example 1, in methylene chloride (50 mL) was admixed with triethyl amine (1.1 mL, 7.8 mmol) and then droplets of mesyl chloride (0.4 mL, 4.4 mmol) were added thereto in an ice bath with stirring at room temperature for 3 hours. After the reaction terminated, the reaction mixture was extracted

with methylene chloride and water, ant the organic phase thus formed was dried over anhydrous magnesium sulfate and filtered. After the removal of the solvent therefrom through vacuum distillation, the filtrate was purified through column chromatography (n-hexane/ethyl acetate=1:1).

[0109] This purified compound (0.9 g, 2.1 mmol) was dissolved in DMF (20 mL) and reacted with sodium azide (0.5 g, 8.0 mmol) with heating at 60° C. for 16 hours. After the reaction terminated, the reaction mixture was cooled at room temperature for 30 min and extracted with ethyl acetate and water. The organic phase thus formed was dried over anhydrous magnesium sulfate and filtered. After the removal of the solvent by vacuum distillation, the filtrate was purified through column chromatography (n-hexane/ethyl acetate=1:1).

[0110] In turn, this purified compound (0.6 g, 1.6 mmol) was dissolved in ethyl acetate (15 mL) and mixed with 10% palladium-charcoal (30 mg) before stirring at room temperature for 14 hours under 1 atm of H_2. After the reaction terminated, the solvent was removed by vacuum distillation. The reducing atmosphere was changed to a nitrogen atmosphere, after which to the reaction mixture were added pyridine (0.2 mL, 1.9 mmol) and anhydrous acetic acid (0.5 mL, 5.3 mmol) with stirring at 0° C. for 30 min and then stirring at room temperature for 2 hours. After the reaction terminated, the reaction mixture was filtered through cellite. After the removal of the solvent by vacuum distillation, the filtrate was purified through column chromatography (n-hexane/ethyl acetate=1:2) to afford the target compound (yield 34%).

[0111] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.19 (q, 2H, J=3.4 Hz), 1.46 (q, 2H, J=3.5 Hz), 2.02 (s, 3H), 3.67 (t, 2H, J=3.0 Hz), 3.70 (t, 2H, J=7.8 Hz), 3.96 (d, 2H, J=1.5 Hz), 4.02 (t, 2H, J=8.6 Hz), 4.74 (m, 1H), 7.19 (s, 1H), 7.35 (s, 1H); ^{13}C-NMR (300 Mz, $CDCl_3$) δ 18.1, 23.2, 41.6, 47.5, 55.3, 58.0, 71.8, 108.1, 114.0, 115.2, 130.5, 133.1, 151.0, 154.4, 171.2, 212.3.

EXPERIMENTAL EXAMPLE

Assay for Anti-Bacterial Activity

[0112] The oxazolidinone derivatives according to the present invention were assayed for inhibitory activity against various bacteria as described in the following.

[0113] To this end, the compound of Example 2 and the currently used oxazolidinone class Linezolid were examined for minimal inhibitory concentration (hereinafter, referred to as "MIC") against Gram-positive strains and resistant bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant enterococci by an agar dilution method using Muller-Hinton agar.

[0114] As used herein, the term MIC is intended to refer to the lowest concentration of an antibiotic that will inhibit the growth of a microorganism. MIC values are expressed as μg/ml. Bacterial strains used for this assay included *Haemophilus influenza,* Coagulase negative staphylococci, *Staphylcoccus aureus*(MRSA), *Enterococcus faecalis*(VER), *Enterococcus faecium*(VR 1, VR 2), and Vancomycin resistant enterococci 1~6.

[0115] After being incubated for 18 hours in a Muller-Hinton broth, the strains were transferred to fresh broth at a concentration of approximately 10^7 CFU/ml. Isolates were distributed with a multipoint inoculator (MIC-2000 Dynatech) at 10^4 CFU per spot onto agar plates containing the compound of the Examples or Comparative Examples. MICs were determined, and the results are summarized in Table 2, below.

TABLE 2

Strains	Inhibitory Activity (MIC, mg/ml) C. Example (Linezolid)	Example 2
a	3.125	0.781
b	3.125	0.781
c	1.563	1.563
d	1.563	1.563
e	1.563	1.563
f	1.563	1.563
g	1.563	3.125
h	1.563	1.563
i	1.563	3.125
j	1.563	0.781
k	1.563	0.781
l	1.563	0.781

a: *Haemophilus influenz*)
b: *Coagulase negative staphylococi*)
c: *Staphylcoccus aureus* (MRSA))
d: *Enterococcus faecalis* (VRE)
e: *Enterococcus faecium* (VR 1)
f: *Enterococcus faecium* (VR 2)
g: Vancomycin resistant *enterococci* 1
h: Vancomycin resistant *enterococci* 2
i: Vancomycin resistant *enterococci* 3
j: Vancomycin resistant *enterococci* 4
k: Vancomycin resistant *enterococci* 5
l: Vancomycin resistant *enterococci* 6

[0116] As shown in Table 2, the oxazolidinone derivative according to the present invention was found to have to have anti-bacterial activity as potent as or more potent than that of the commercially available antibiotic Linezolid because its MIC was within the range of 0.781~3.125 mg/ml. Particularly, the oxazolidinone derivative according to the invention showed an MIC of 0.781 mg/ml against Gram-positive bacteria including *Haemophilus influenza* and non-pathogenic Coagulase negative staphylococci as well as resistant bacteria including vancomycin resistant enterococci (VRE), which is superior in inhibitory activity to Linezolid (SC: 1.563~3.125 mg/ml). Accordingly, the oxazolidinone derivatives according to the present invention are useful as novel antibiotics.

[0117] Depending on the purposes for which they are used, dosages of the oxazolidinone derivatives of Chemical Formula 1 according to the present invention may be formulated in various forms. Formulation examples are given to illustrate dosage preparations containing the compounds of Chemical Formula 1 as active ingredients and not to limit the scope of the present invention.

FORMULATION EXAMPLE 1

Tablet (Direct Compression)

[0118] After being sieved, 5.0 mg of the active ingredient was mixed with 14.1 mg of lactose, 0.8 mg of crospovidone, 0.8 mg of USNF and 0.1 mg of magnesium stearate, and directly compressed into tablets.

FORMULATION EXAMPLE 2

Tablet (Wet Granulation)

[0119] 5.0 mg of the active ingredient was sieved and mixed with 16.0 mg of lactose and 4.0 mg of starch. To this mixture was added a suitable amount of a solution of 0.3 mg of polysorbate 80 in pure water, followed by micro granulation. The micro granules thus obtained were dried, sieved, and

mixed with 2.7 mg of colloidal silicon dioxide and 2.0 mg of magnesium stearate. The mixture was compressed into tablets.

FORMULATION EXAMPLE 3

Powder and Capsule

[0120] After being sieved, 5 mg of the active ingredient was admixed with 14.8 mg of lactose, 10.0 mg of polyvinyl pyrrolidone and 0.2 mg of magnesium stearate. The admixture was loaded into hard No. 5 gelatin capsules using a suitable device.

FORMULATION EXAMPLE 4

Injection

[0121] An injection comprising 180 mg of mannitol, 26 mg of Na_2HPO_4. $12H_2O$ and 2974 mg of distilled water in addition to 100 mg of the active ingredient was prepared.

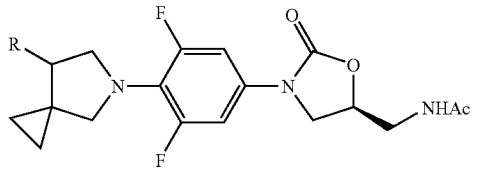
[0122] Exhibiting potent inhibitory activity against Gram positive bacteria including *Haemophilus influenza* and non-pathogenic Coagulase negative staphylococci, as well as resistant bacteria including VRE, as described above, the oxazolidinone derivatives or pharmaceutically acceptable salts thereof in accordance with the present invention are usable as an active ingredient for antibiotics.

[0123] Although the preferred embodiments of the present invention have been disclosed for illustrative purposes, those skilled in the art will appreciate that various modifications, additions and substitutions are possible, without departing from the scope and spirit of the invention as disclosed in the accompanying claims.

What is claimed is:

1. An oxazolidinone compound, represented by Chemical Formula 1 below, or a pharmaceutically acceptable salt thereof:

[Chemical Formula 1]



wherein R is a hydroxy, an amino, a halogen, hydrazine, a hydroxyimine, an alkyloxyimine of C_1-C_4 or an allyloxyimine.

2. The oxazolidinone compound or the pharmaceutically acceptable salt thereof according to claim **1**, wherein R is hydroxy, amino, fluoro, chloro, bromo, hydrazine, hydroxyimine, methoxyimine, ethoxyimine, propoxyimine, isopropoxyimine, butoxyimine, isobutoxyimine or allyloxyimine.

3. The oxazolidinone compound or the pharmaceutically acceptable salt thereof according to claim **1**, wherein the oxazolidinone compound is selected from a group consisting of:

(1) (S)—N-{{3-[3,5-difluoro-4-(7-hydroxy-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide;

(2) (S)—N-{{3-[3,5-fluoro-4-(7-fluoro-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide;

(3) (S)—N-{{3-[3,5-difluoro-4-(7-hydroxyimino-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide;

(4) (S)—N-{{3-[3,5-difluoro-4-(7-methoxyimino-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide;

(5) (S)—N-{{3-[3,5-difluoro-4-(7-hydrazino-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide;

(6) (S)—N-{{3-[3,5-difluoro-4-(7-ethoxyimino-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide;

(7) (S)—N-{{3-[3,5-difluoro-4-(7-allyloxyimino-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide; and

(8) (S)—N-{{3-[3,5-difluoro-4-(7-amino-5-azaspiro[2,4]heptan-5-yl)phenyl]-2-oxo-5-oxazolidinyl}methyl}acetamide.

4. A method for preparing the oxazolidinone compound of claim **1**, as illustrated in the following Reaction Scheme 1, comprising:

reacting a compound of Chemical Formula 2 with trifluoronitrobenzene of Chemical Formula 3 to give a compound of Chemical Formula 4 (Step 1);

reducing the compound of Chemical Formula 4 through hydrogenation to a compound of Chemical Formula 5 (Step 2);

introducing a carbobenzyloxy (CBZ) group into the amine group of the compound of Chemical Formula 5 to give a compound of Chemical Formula 6 (Step 3);

adding n-butyl lithium and (R)-glycidyl butyrate to the compound of Chemical Formula 6 to give a compound of Chemical Formula 7 (Step 4);

mesylating the hydroxy group of the compound of Chemical Formula 7 to give a compound of Chemical Formula 8 (Step 5);

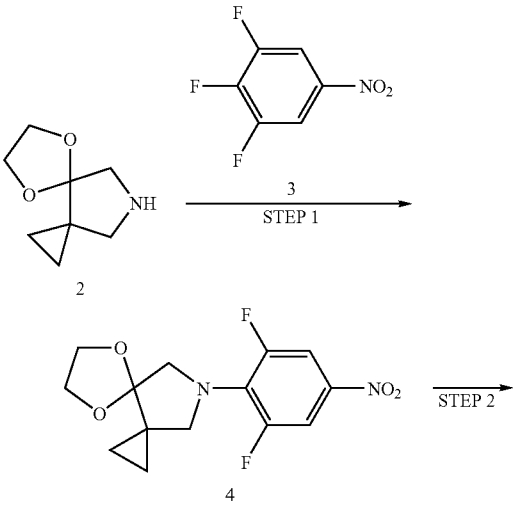
azidating the compound of Chemical Formula 8 with sodium azide to a compound of Chemical Formula 9 (Step 6);

reducing and acetylating the compound of Chemical Formula 9 to a compound of Chemical Formula 10 (Step 7);

deprotecting the compound of Chemical Formula 10 to give a compound of Chemical Formula 11 (Step 8); and

reducing the compound of Chemical Formula 11 to a compound of Chemical Formula 1a (Step 9).

[Reaction Scheme 1]



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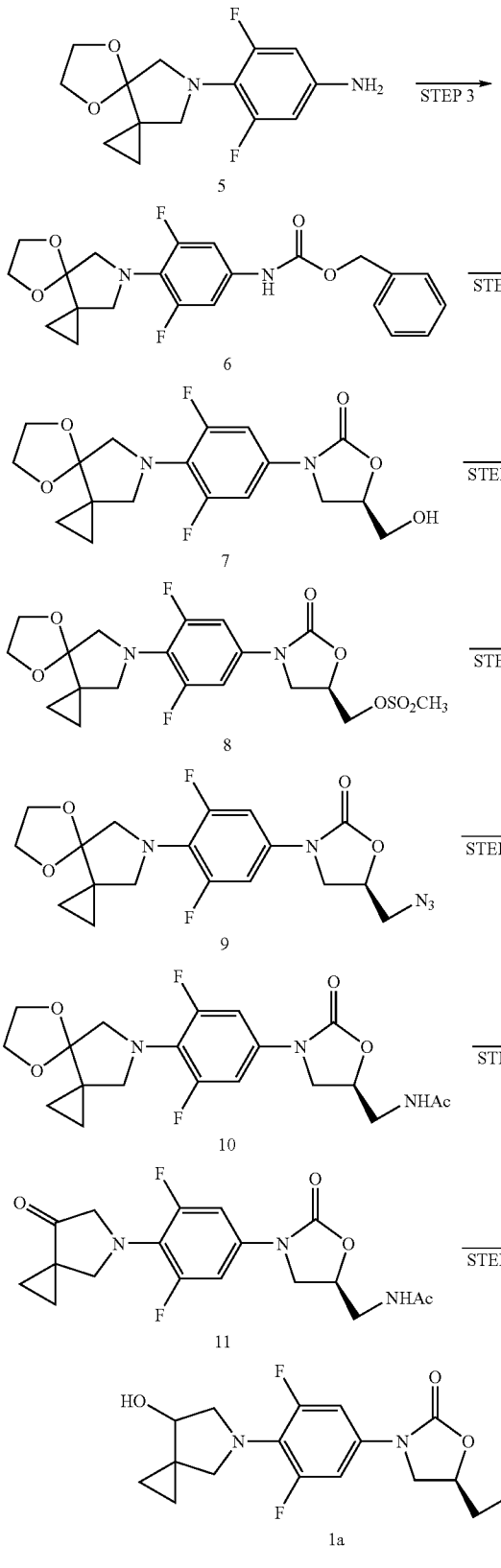
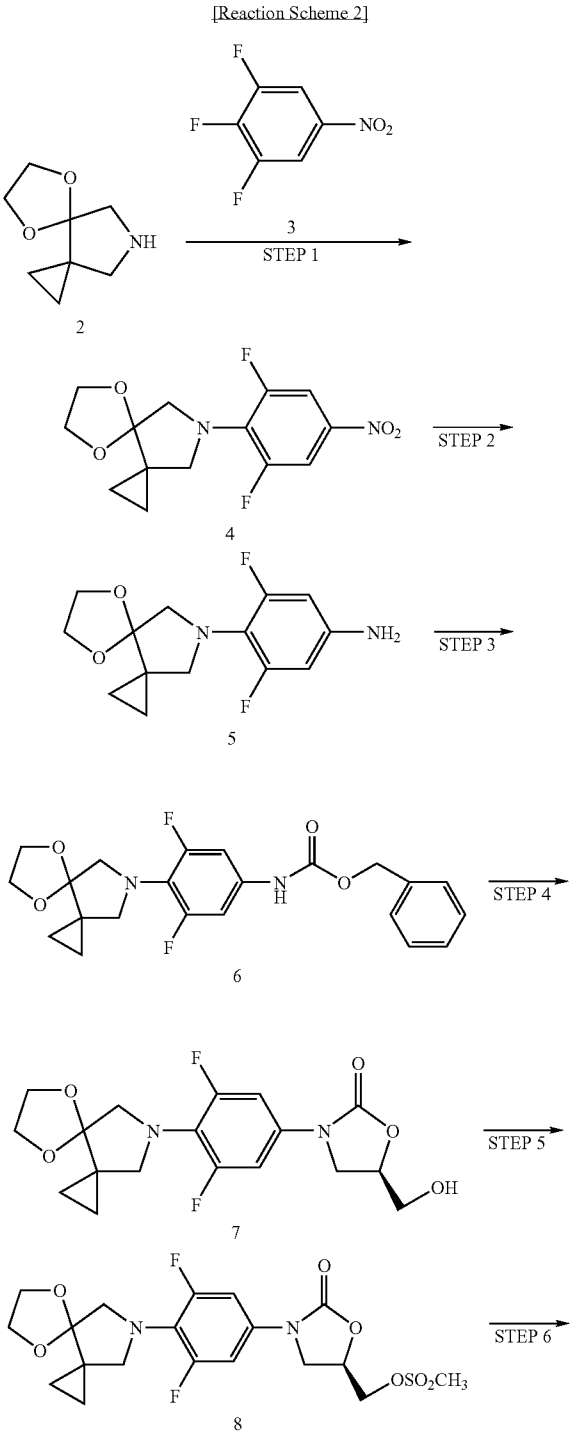


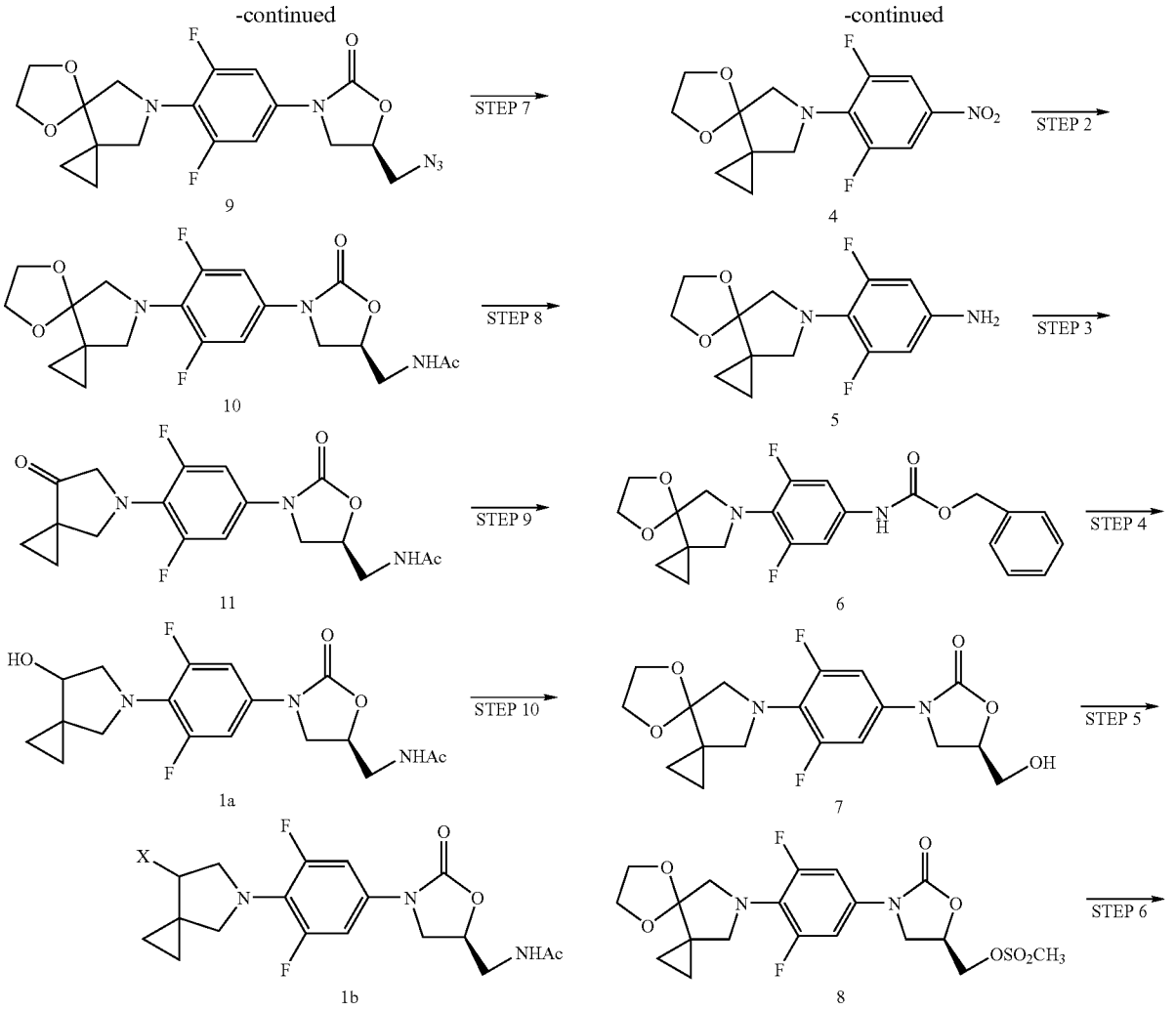
(wherein the compound of Chemical Formula 1a is included within the range of Chemical Formula 1).

5. The method according to claim **4**, as illustrated in the following Reaction Scheme 2, further comprising:

halogenating or aminating the compound of Chemical Formula 1a to a compound of Chemical Formula 1b (Step 10) after Step 9.

[Reaction Scheme 2]



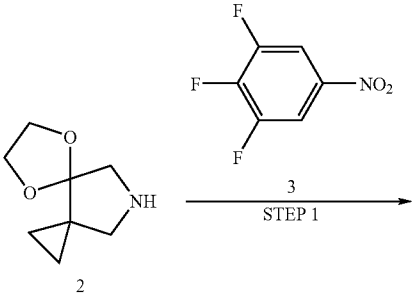


(wherein X is a halogen or an amine, and the compounds of Chemical Formulas 1a and 1b are included within the range of Chemical Formula 1.)

6. The method according to claim **4**, as illustrated in the following Reaction Scheme 3, further comprising:

reacting the compound of Chemical Formula 11 with an amine chloride salt to give a compound of Chemical Formula 1c (Step 9') after Step 8.

[Reaction Scheme 3]



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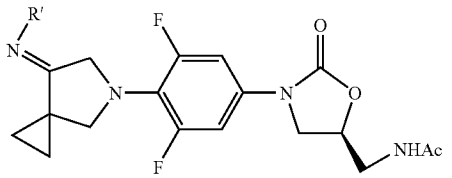


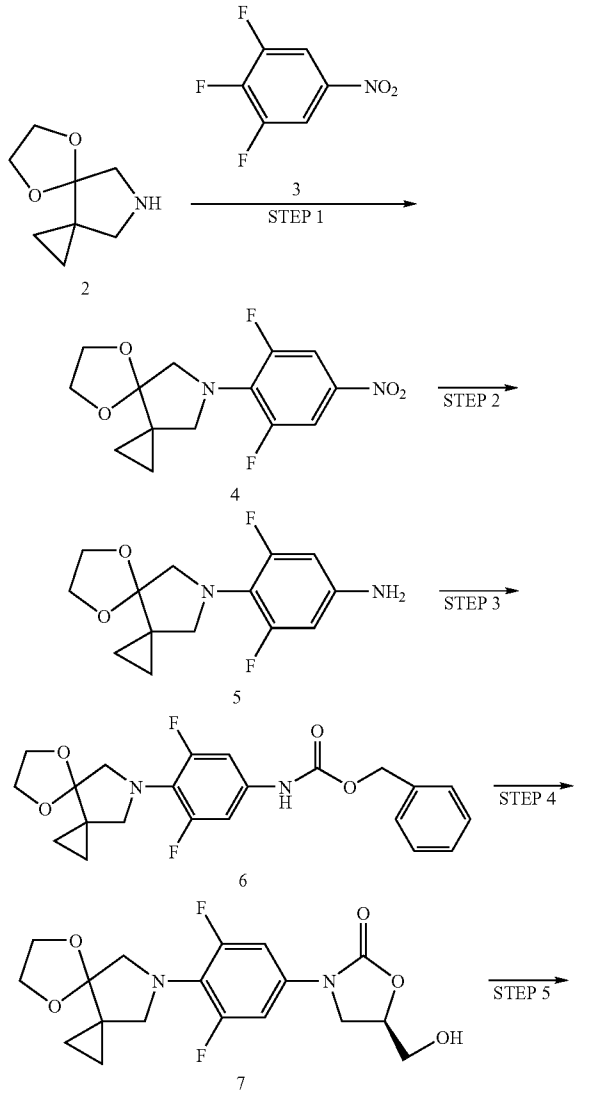
1c

(wherein R' is a hydroxy, methoxy or amine group, and the compound of Chemical Formula 1c is included within the range of Chemical Formula 1.)

7. The method according to claim **6**, as illustrated in the following Reaction Scheme 4, further comprising:

reacting a nucleophile with the compound of Chemical Formula 1c in the presence of a base to give a compound of Chemical Formula 1d (Step 10') after Step 9'.

[Reaction Scheme 4]



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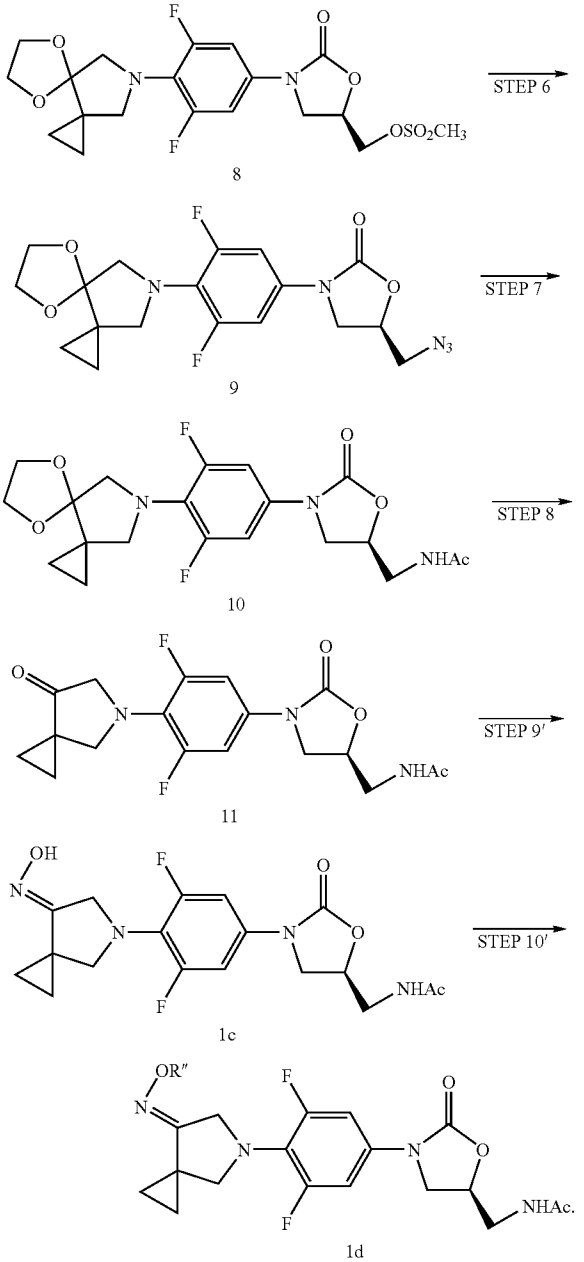

(wherein R" is C_1~C_4 alkyl or allyl, and the compounds of Chemical Formulas 1c and 1d are included within the range of Chemical Formula 1.)

8. A method for treating diseases caused by bacteria, comprising administering the oxazolidinone compound or pharmaceutically acceptable salt thereof of claim **1** at a therapeutically effective dose to a subject in need thereof.

9. The method according to claim **8**, wherein the bacteria is a Gram-positive strain or a resistant strain.

10. The method according to claim **9**, wherein the Gram-positive strain is *Haemophilus influenza* or Coagulase negative staphylococi.

11. The method according to claim **9**, wherein the resistant strain is vancomycin-resistant enterococci.

12. A method for killing a bacterial strain infecting a subject, comprising administering the oxazolidinone compound of claim **1** or the pharmaceutically acceptable salt thereof at a therapeutically effective dose to the subject.

13. The method according to claim **12**, wherein the bacterial strain is a Gram-positive strain or a resistant strain.

14. The method according to claim **13**, wherein the Gram-positive strain *Haemophilus influenza* or Coagulase negative staphylococi.

15. The method according to claim **13**, wherein the resistant strain is vancomycin-resistant enterococci.

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