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Biphenyl Oxazolidinone Antibiotic

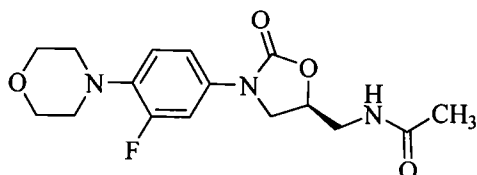
1. Field of The Invention

The present invention belongs to the pharmaceutical field and specifically relates to biphenyl oxazolidinone antibiotic, the pharmaceutically acceptable salts, and stereoisomers thereof. In addition to pharmaceutical compositions, the present invention also relates to methods and processes for preparing the same, and to the use of these compounds in the manufacture of a medicament for the treatment and/or prophylaxis of infectious diseases.

2. Background of The Invention

Oxazolidinone antibiotic is a new class of synthetic antimicrobial agent after sulfonamides and fluoroquinolones. It is effective against multiple resistant Gram-positive bacteria.

Linezolid is the first oxazolidinone antibiotic successfully launched.



It is potent to inhibit Gram-positive bacteria, there is no cross resistance with other antibiotics, its pharmacology mechanism is unique, by inhibiting early stage of protein synthesis in bacteria. Linezolid is mainly used to treat resistant Gram-positive bacterial infections, it is also used to treat infectious diseases associated with surgery.

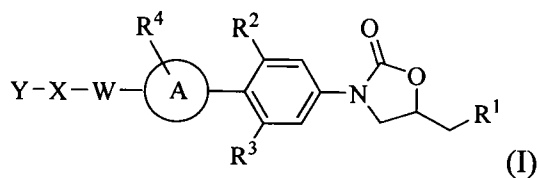
Infections caused by resistant Gram-positive bacteria is becoming a serious issue, there is only one oxazolidinone antibiotic available, Linezolid. There are increased incidences of resistance to this drug. The need to develop more effective oxazolidinone antibiotics is urgent.

3. Disclosure of The Invention

The present invention provides a new class of anti-infectious compounds with improved anti-bacterial activity.



According to a first aspect, the present invention provides a compound of general formula (I) or a pharmaceutically acceptable salt or stereoisomers thereof:



Wherein

R¹ is acetyl amino, hydroxyl, amino, C₁₋₆ alkyl amino, 1,2,3-triazolyl or isoxazolyl group;

R² and R³ are independently a hydrogen or halogen;

A ring can be un-substituted benzene or six-membered unsaturated heterocycle where R⁴ is hydrogen, or optionally substituted benzene or six-membered unsaturated heterocycle by one to four R⁴ groups where R⁴ is independently selected from halogen, C₁₋₆ alkyl or halogenated C₁₋₆ alkyl ;

W is a bond, -C(R⁵)(R⁶)-, -C(R⁵)(R⁶)-C(R⁷)(R⁸)- or -C(R⁵)(R⁶)-C(R⁷)(R⁸)-C(R⁹)(R¹⁰)-, wherein, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are independently a hydrogen, C₁₋₆ alkyl or halogen;

X is 3-8 membered heterocycle containing 1-4 heteroatoms, where heteroatom is selected from nitrogen, oxygen and sulfur;

Y is 5-6 membered heterocycle;

X, Y can further be substituted by halogen or C₁₋₆ alkyl group.

In another preferred embodiment, wherein

R¹ is acetyl amino, hydroxyl, amino, C₁₋₆ alkyl amino, 1,2,3-triazolyl or isoxazolyl group;

R² and R³ are independently a hydrogen or halogen;

A ring can be un-substituted benzene or pyridine where R⁴ is hydrogen, or optionally substituted benzene or pyridine by one to four R⁴ groups where R⁴ is independently selected from halogen, C₁₋₆ alkyl or halogenated C₁₋₆ alkyl;

W is a bond, -C(R⁵)(R⁶)-, -C(R⁵)(R⁶)-C(R⁷)(R⁸)- or -C(R⁵)(R⁶)-C(R⁷)(R⁸)-C(R⁹)(R¹⁰)-, wherein, R⁵ and R⁶ are independently a hydrogen or C₁₋₆ alkyl, and R⁷, R⁸, R⁹ and R¹⁰

are independently a hydrogen, C₁₋₆ alkyl or halogen;

X is 3-8 membered heterocycle containing 1-4 heteroatoms, where heteroatom is selected from nitrogen, oxygen and sulfur;

Y is 5-6 membered heterocycle;

X, Y can further be substituted by halogen or C₁₋₆ alkyl group.

In another preferred embodiment, wherein

R¹ is acetyl amino, hydroxyl, 1,2,3-triazolyl or isoxazolyl group;

R² and R³ are independently a hydrogen or halogen;

A ring can be un-substituted benzene or pyridine where R⁴ is hydrogen, or optionally substituted benzene or pyridine by one to four R⁴ groups where R⁴ is independently selected from halogen, C₁₋₄ alkyl or halogenated C₁₋₄ alkyl;

W is a bond, -C(R⁵)(R⁶)-, -C(R⁵)(R⁶)-C(R⁷)(R⁸)- or -C(R⁵)(R⁶)-C(R⁷)(R⁸)-C(R⁹)(R¹⁰)-, wherein, R⁵ and R⁶ are independently a hydrogen or methyl, and R⁷, R⁸, R⁹ and R¹⁰ are independently a hydrogen, methyl or fluorine;

X is 5-6 membered heterocycle containing 1-3 heteroatoms, where heteroatom is selected from nitrogen, oxygen and sulfur;

Y is 5-6 membered heterocycle;

X, Y can further be substituted by halogen or C₁₋₄ alkyl group.

In another preferred embodiment, wherein

R¹ is acetyl amino;

R² and R³ are independently a hydrogen, fluorine or chlorine;

A ring can be un-substituted benzene where R⁴ is hydrogen, or optionally substituted benzene by one to two R⁴ groups where R⁴ is independently selected from fluorine, chlorine, methyl or trifluoromethyl;

W is a bond, -C(R⁵)(R⁶)-, -C(R⁵)(R⁶)-C(R⁷)(R⁸)- or -C(R⁵)(R⁶)-C(R⁷)(R⁸)-C(R⁹)(R¹⁰)-, wherein, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are independently a hydrogen;

X is selected from azetidine, tetrahydropyrrole, tetrahydrofuran, tetrahydrothiophene, tetrahydrooxazole, tetrahydroisoxazole, tetrahydrothiazole, tetrahydropyrazole, pyrrole, oxazole, pyrazole, piperazine or piperidine;

Y is selected from triazole, tetrazole, imidazole, pyrrole, tetrahydropyrrole or pyridine;
X, Y can further be substituted by fluorine or methyl group.

In another preferred embodiment, wherein

R¹ is acetyl amino;

R² and R³ are independently a hydrogen, fluorine or chlorine;

A ring can be un-substituted benzene where R⁴ is hydrogen, or optionally substituted benzene which is substituted by one to two R⁴ groups where R⁴ is independently selected from fluorine, chlorine, methyl or trifluoromethyl;

W is a bond, -C(R⁵)(R⁶)- or -C(R⁵)(R⁶)-C(R⁷)(R⁸)-,

wherein, R⁵, R⁶, R⁷ and R⁸ are independently a hydrogen;

X is selected from azetidine, tetrahydropyrrole, pyrrole, pyrazole, piperidine or piperazine;

Y is selected from 1,2,3-triazole, 1,2,4-triazole, 1,2,3,4-tetrazole, 1,2,3,5-tetrazole, imidazole, pyrrole or pyridine.

In a further preferred embodiment, wherein

R¹ is acetyl amino;

R² and R³ are independently a hydrogen or fluorine;

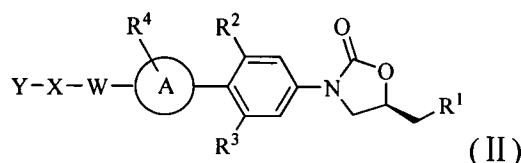
A ring is un-substituted benzene where R⁴ is hydrogen;

W is a bond or -C(R⁵)(R⁶)-, wherein, R⁵ and R⁶ are independently a hydrogen;

X is selected from azetidine, tetrahydropyrrole, pyrrole or piperazine;

Y is selected from 1,2,3-triazole or 1,2,3,4-tetrazole.

In another aspect, the present invention provides a compound of general formula (II) or a pharmaceutically acceptable salt or stereoisomers thereof:



Wherein

R¹ is acetyl amino, hydroxyl, amino, C₁₋₆ alkyl amino, 1,2,3-triazolyl or isoxazolyl group;

R² and R³ are independently a hydrogen or halogen;

A ring can be un-substituted benzene or six-membered unsaturated heterocycle where R⁴ is hydrogen, or optionally substituted benzene or six-membered unsaturated heterocycle by one to four R⁴ groups where R⁴ is independently selected from halogen, C₁₋₆ alkyl or halogenated C₁₋₆ alkyl ;

W is a bond, -C(R⁵)(R⁶)-, -C(R⁵)(R⁶)-C(R⁷)(R⁸)- or -C(R⁵)(R⁶)-C(R⁷)(R⁸)-C(R⁹)(R¹⁰)-, wherein, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are independently a hydrogen, C₁₋₆ alkyl or halogen;

X is 3-8 membered heterocycle containing 1-4 heteroatoms, where heteroatom is selected from nitrogen, oxygen and sulfur;

Y is 5-6 membered heterocycle;

X, Y can further be substituted by halogen or C₁₋₆ alkyl group.

In another preferred embodiment, wherein

R¹ is acetyl amino, hydroxyl, amino, C₁₋₆ alkyl amino, 1,2,3-triazolyl or isoxazolyl group;

R² and R³ are independently a hydrogen or halogen;

A ring can be un-substituted benzene or pyridine where R⁴ is hydrogen, or optionally substituted benzene or pyridine by one to four R⁴ groups where R⁴ is independently selected from halogen, C₁₋₆ alkyl or halogenated C₁₋₆ alkyl;

W is a bond, -C(R⁵)(R⁶)-, -C(R⁵)(R⁶)-C(R⁷)(R⁸)- or -C(R⁵)(R⁶)-C(R⁷)(R⁸)-C(R⁹)(R¹⁰)-, wherein, R⁵ and R⁶ are independently a hydrogen or C₁₋₆ alkyl, and R⁷, R⁸, R⁹ and R¹⁰ are independently a hydrogen, C₁₋₆ alkyl or halogen;

X is 3-8 membered heterocycle containing 1-4 heteroatoms, where heteroatom is selected from nitrogen, oxygen and sulfur;

Y is 5-6 membered heterocycle;

X, Y can further be substituted by halogen or C₁₋₆ alkyl group.

In another preferred embodiment, wherein

R¹ is acetyl amino, hydroxyl, 1,2,3-triazolyl or isoxazolyl group;

R² and R³ are independently a hydrogen or halogen;

A ring can be un-substituted benzene or pyridine where R^4 is hydrogen, or optionally substituted benzene or pyridine by one to four R^4 groups where R^4 is independently selected from halogen, C_{1-4} alkyl or halogenated C_{1-4} alkyl;

W is a bond, $-C(R^5)(R^6)-$, $-C(R^5)(R^6)-C(R^7)(R^8)-$ or $-C(R^5)(R^6)-C(R^7)(R^8)-C(R^9)(R^{10})-$, wherein, R^5 and R^6 are independently a hydrogen or methyl, and R^7 , R^8 , R^9 and R^{10} are independently a hydrogen, methyl or fluorine;

X is 5-6 membered heterocycle containing 1-3 heteroatoms, where heteroatom is selected from nitrogen, oxygen and sulfur;

Y is 5-6 membered heterocycle;

X, Y can further be substituted by halogen or C_{1-4} alkyl group.

In another preferred embodiment, wherein

R^1 is acetyl amino;

R^2 and R^3 are independently a hydrogen, fluorine or chlorine;

A ring can be un-substituted benzene where R^4 is hydrogen, or optionally substituted benzene by one to two R^4 groups where R^4 is independently selected from fluorine, chlorine, methyl or trifluoromethyl;

W is a bond, $-C(R^5)(R^6)-$, $-C(R^5)(R^6)-C(R^7)(R^8)-$ or $-C(R^5)(R^6)-C(R^7)(R^8)-C(R^9)(R^{10})-$, wherein, R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are independently a hydrogen;

X is selected from azetidine, tetrahydropyrrole, tetrahydrofuran, tetrahydrothiophene, tetrahydrooxazole, tetrahydroisoxazole, tetrahydrothiazole, tetrahydropyrazole, pyrrole, oxazole, pyrazole, piperazine or piperidine;

Y is selected from triazole, tetrazole, imidazole, pyrrole, tetrahydropyrrole or pyridine;

X, Y can further be substituted by fluorine or methyl group.

In another preferred embodiment, wherein

R^1 is acetyl amino;

R^2 and R^3 are independently a hydrogen, fluorine or chlorine;

A ring can be un-substituted benzene where R^4 is hydrogen, or optionally substituted benzene which is substituted by one to two R^4 groups where R^4 is independently selected from fluorine, chlorine, methyl or trifluoromethyl;

W is a bond, $-C(R^5)(R^6)-$ or $-C(R^5)(R^6)-C(R^7)(R^8)-$,

wherein, R^5 , R^6 , R^7 and R^8 are independently a hydrogen;

X is selected from azetidine, tetrahydropyrrole, pyrrole, pyrazole, piperidine or piperazine;

Y is selected from 1,2,3-triazole, 1,2,4-triazole, 1,2,3,4-tetrazole, 1,2,3,5-tetrazole, imidazole, pyrrole or pyridine.

In a further preferred embodiment, wherein

R^1 is acetyl amino;

R^2 and R^3 are independently a hydrogen or fluorine;

A ring is un-substituted benzene where R^4 is hydrogen;

W is a bond or $-C(R^5)(R^6)-$, wherein, R^5 and R^6 are independently a hydrogen;

X is selected from azetidine, tetrahydropyrrole, pyrrole or piperazine;

Y is selected from 1,2,3-triazole or 1,2,3,4-tetrazole.

The following are definitions of terms used in this specification of the present invention.

Unless indicated otherwise, the term “halogen” refers to fluorine, chlorine, bromine and iodine.

The term “ C_{1-6} alkyl” refers to straight, branched, or cyclic alkyl containing 1 to 6 carbon(s). Examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, 2-methylbutyl, neopentyl, 1-ethyl propyl, n-hexyl, isohexyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 2-ethylbutyl, 1,2-dimethylpropyl, cyclopropyl, cyclobutyl, 1-methylcyclobutyl, cyclopentyl, cyclohexyl and so on. The term “ C_{1-4} alkyl” refers to the above examples that contain 1 to 4 carbon(s).

The term “3 to 8 membered cyclic group containing 1 to 4 heteroatom(s)” refers to “3 to 8 membered saturated cyclic group containing 1 to 4 heteroatom(s)” and “3 to 8 membered unsaturated cyclic group containing 1 to 4 heteroatom(s)”, where

heteroatom means nitrogen, oxygen, sulfur atom and so on.

The examples of “3 to 8 membered saturated cyclic group containing 1 to 4 heteroatom(s)” include, but are not limited to, aziridine, azetidine, 1,2-diazetidine, pyrrolidine, imidazolidine, pyrazolidine, piperidine, piperazine, oxirane, thiirane, oxetane, 1,2-dioxetane, thietane, tetrahydrofuran, tetrahydrothiophene, 1,3-dioxolane, 1,3-dithiolane, tetrahydro-2*H*-pyran, 1,4-dioxane, 1,3-dioxane, 1,3-oxathiane, oxazolidine, morpholine and so on. Preferred examples include aziridine, azetidine, pyrrolidine, imidazolidine, pyrazolidine, piperidine, piperazine, oxirane, tetrahydrofuran, tetrahydrothiophene, 1,3-dioxolane, 1,3-dithiolane, tetrahydro-2*H*-pyran, 1,4-dioxane, 1,3-dioxane, 1,3-oxathiane, oxazolidine, morpholine and so on.

The examples of “3 to 8 membered unsaturated cyclic group containing 1 to 4 heteroatom(s)” include, but are not limited to, azete, 1,2-dihydro-1,2-diazete, pyrrole, 2,3-dihydro-1*H*-pyrrole, 2,5-dihydro-1*H*-pyrrole, imidazole, 4,5-dihydro-1*H*-imidazole, pyrazole, 4,5-dihydro-1*H*-pyrazole, 1,2,3-triazole, 1,2,4-triazole, pyridine, pyridin-2(1*H*)-one, pyridin-4(1*H*)-one, pyridazine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, azepine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, azocine, 1,4-dihydro-1,4-diazocine, 1,2-dithiete, furan, 2,3-dihydrofuran, 2,5-dihydrofuran, thiophene, 2,3-dihydrothiophene, 2,5-dihydrothiophene, 3*H*-1,2-dithiole, 1,3-dithiole, 2*H*-pyran, 2*H*-pyran-2-one, 3,4-dihydro-2*H*-pyran, 4*H*-pyran, 4*H*-pyran-4-one, 1,4-dioxine, 1,4-dithiine, 1,4-oxathiine, oxepine, thiepine, 1,4-dioxocine, oxazole, 4,5-dihydrooxazole, 2,3-dihydrooxazole, isoxazole, 4,5-dihydroisoxazole, 2,3-dihydroisoxazole, 1,2,3-oxadiazole, 1,2,5-oxadiazole, thiazole, 4,5-dihydrothiazole, 2,3-dihydrothiazole, isothiazole, 1,2,3-thiadiazole, 2*H*-1,2-oxazine, 4*H*-1,2-oxazine, 6*H*-1,2-oxazine, 2*H*-1,3-oxazine, 4*H*-1,3-oxazine, 6*H*-1,3-oxazine, 5,6-dihydro-4*H*-1,3-oxazine, 2*H*-1,4-oxazine, 4*H*-1,4-oxazine, 2*H*-1,3-thiazine, 4*H*-1,3-thiazine, 6*H*-1,3-thiazine, 5,6-dihydro-4*H*-1,3-thiazine, 2*H*-1,4-thiazine, 4*H*-1,4-thiazine and so on. Preferred examples include pyrrole, 2,3-dihydro-1*H*-pyrrole, 2,5-dihydro-1*H*-pyrrole, imidazole, 4,5-dihydro-1*H*-imidazole, pyrazole, 4,5-dihydro-1*H*-pyrazole, 1,2,3-triazole,

1,2,4-triazole, pyridine, pyridin-2(1*H*)-one, pyridin-4(1*H*)-one, pyridazine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, furan, 2,3-dihydrofuran, 2,5-dihydrofuran, thiophene, 2,3-dihydrothiophene, 2,5-dihydrothiophene, 3*H*-1,2-dithiole, 1,3-dithiole, 2*H*-pyran, 2*H*-pyran-2-one, 3,4-dihydro-2*H*-pyran, 4*H*-pyran, 4*H*-pyran-4-one, 1,4-dioxine, 1,4-dithiine, 1,4-oxathiine, oxazole, 4,5-dihydrooxazole, 2,3-dihydrooxazole, isoxazole, 4,5-dihydroisoxazole, 2,3-dihydroisoxazole, 1,2,3-oxadiazole, 1,2,5-oxadiazole, thiazole, 4,5-dihydrothiazole, 2,3-dihydrothiazole, isothiazole, 1,2,3-thiadiazole, 2*H*-1,2-oxazine, 4*H*-1,2-oxazine, 6*H*-1,2-oxazine, 2*H*-1,3-oxazine, 4*H*-1,3-oxazine, 6*H*-1,3-oxazine, 5,6-dihydro-4*H*-1,3-oxazine, 2*H*-1,4-oxazine, 4*H*-1,4-oxazine, 2*H*-1,3-thiazine, 4*H*-1,3-thiazine, 6*H*-1,3-thiazine, 5,6-dihydro-4*H*-1,3-thiazine, 2*H*-1,4-thiazine, 4*H*-1,4-thiazine and so on. Preferred examples include pyrrole, 2,3-dihydro-1*H*-pyrrole, 2,5-dihydro-1*H*-pyrrole, imidazole, 4,5-dihydro-1*H*-imidazole, pyrazole, 4,5-dihydro-1*H*-pyrazole, 1,2,3-triazole, 1,2,4-triazole, pyridine, pyrimidine, pyrazine, furan, 2,3-dihydrofuran, 2,5-dihydrofuran, thiophene, 2,3-dihydrothiophene, 2,5-dihydrothiophene, 2*H*-pyran, 2*H*-pyran-2-one, 3,4-dihydro-2*H*-pyran, 4*H*-pyran, 4*H*-pyran-4-one, oxazole, 4,5-dihydrooxazole, 2,3-dihydrooxazole, isoxazole, 4,5-dihydroisoxazole, 2,3-dihydroisoxazole, 1,2,3-oxadiazole, 1,2,5-oxadiazole, thiazole, 4,5-dihydrothiazole, 2,3-dihydrothiazole, isothiazole, 1,2,3-thiadiazole and so on.

The term “5 to 6 membered nitrogen-containing heterocyclic group” refers to “5 membered saturated nitrogen-containing heterocyclic group”, “5 membered unsaturated nitrogen-containing heterocyclic group”, “6 membered saturated nitrogen-containing heterocyclic group”, and “6 membered unsaturated nitrogen-containing heterocyclic group”.

Exemplary “5 membered saturated nitrogen-containing heterocyclic group” include, but are not limited to, pyrrolidine, imidazolidine, pyrazolidine and so on.

Exemplary “5 membered unsaturated nitrogen-containing heterocyclic group” include, but are not limited to, pyrrole, imidazole, pyrazole, 4,5-dihydropyrazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,3,4-tetrazole, 1,2,3,5-tetrazole and so on.

Exemplary “6 membered saturated nitrogen-containing heterocyclic group”

include, but are not limited to, piperidine, piperazine and so on.

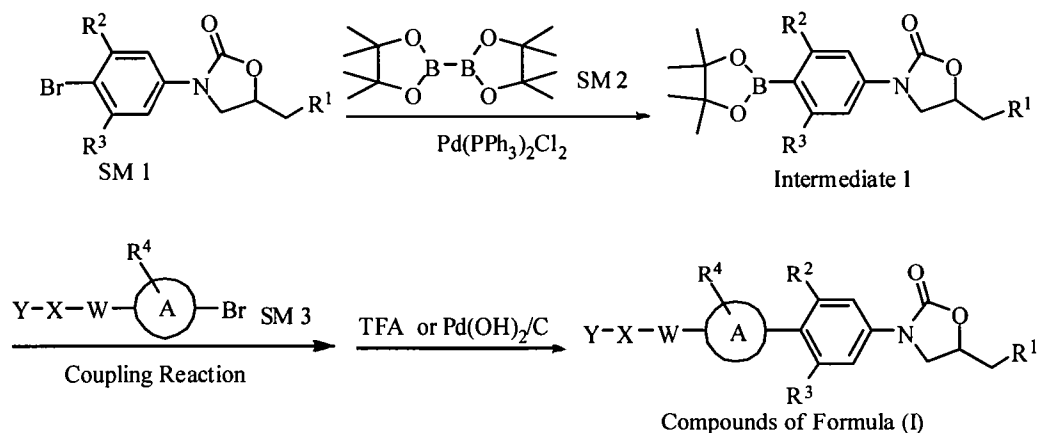
Exemplary “6 membered unsaturated nitrogen-containing heterocyclic group” include, but are not limited to, pyridine, pyridazine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine and so on.

In some specific embodiments, the present invention provides compounds selected from the group consisting of:

Compound	Chemical Name	Structure
1	<i>N</i> -[[(5 <i>S</i>)-3-[4'-[[2-(1 <i>H</i> -1,2,3-triazol-5-yl)pyrrolidin-1-yl]methyl]-2-fluorobiphenyl-4-yl]-2-oxo-oxazolidin-5-yl]methyl]acetamide	
2	<i>N</i> -[[(5 <i>S</i>)-3-[4'-[[3-(1 <i>H</i> -1,2,3-triazol-5-yl)pyrrolidin-1-yl]methyl]-2-fluorobiphenyl-4-yl]-2-oxo-oxazolidin-5-yl]methyl]acetamide	
3	<i>N</i> -[[(5 <i>S</i>)-3-[4'-[[2-(1 <i>H</i> -1,2,3-triazol-5-yl)pyrrolidin-5-yl]methyl]-2-fluorobiphenyl-4-yl]-2-oxo-oxazolidin-5-yl]methyl]acetamide	
4	<i>N</i> -[[(5 <i>S</i>)-3-[4'-[[2-(1 <i>H</i> -1,2,3-triazol-5-yl)pyrrolidin-5-yl]-2-fluorobiphenyl-4-yl]-2-oxo-oxazolidin-5-yl]methyl]acetamide	
5	(<i>S</i>)- <i>N</i> -[[3-[4'-[[3-(1 <i>H</i> -1,2,3-triazol-4-yl)-1 <i>H</i> -pyrrol-1-yl]methyl]-2-fluorobiphenyl-4-yl]-2-oxo-oxazolidin-5-yl]methyl]acetamide	

The present invention also provides such preparation methods:

Reaction Scheme:



Step 1 Preparation of Intermediate 1

Dissolve SM 1 and SM 2 in a polar solvent (such as 1,4-dioxane or THF and so on). To the solution is added an inorganic base (such as potassium acetate, sodium acetate, potassium carbonate or sodium carbonate and so on) and Pd catalyst, and the reaction affords intermediate 1.

Step 2 Preparation of Compounds of Formula (I)

Dissolve intermediate 1 and SM 3 in a polar solvent mixture containing water and / or alcohol (such as 1,4-dioxane / EtOH / H₂O or 1,4-dioxane / H₂O). To the solution is added an inorganic base (such as Cs₂CO₃, Na₂CO₃ and so on) and Pd catalyst, and the coupling reaction affords compounds of formula (I).

The groups R¹, R², R³, R⁴, X, Y and W in the above scheme are as defined aforementioned, wherein different X and Y groups in SM 3 may be prepared from different raw materials. Details can be found in the section of reaction examples.

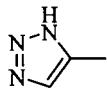
The term “pharmaceutically acceptable salt” means acid addition salts useful for administering the compounds of this invention, and includes but are not limited to, organic acid salts, such as formate, acetate, propionate, benzene sulfonate, benzoate, toluene sulfonate, 2,3-dihydroxy-succinate, camsilate, citrate, mesylate, esilate, propyl sulfonate, fumarate, gluconate, glutamine, isethionate, lactate, maleate, malate, mandelate, mucate, embonate, pantothenate, succinate, tartrate and so on; inorganic acid salts, such as hydrochloride, hydrobromate, hydriodate, sulfate, phosphate,

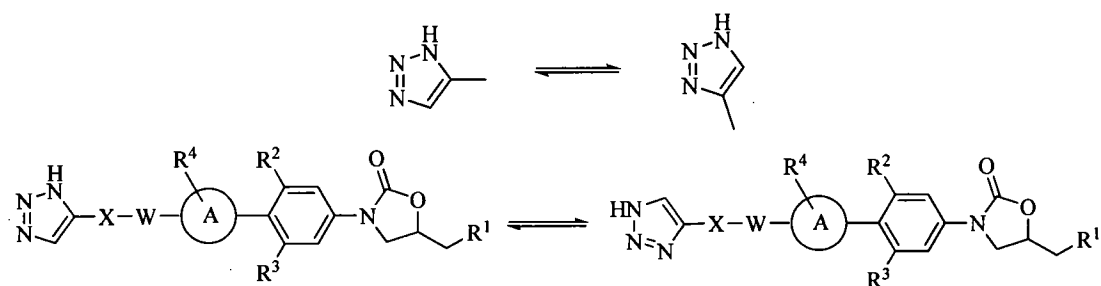
nitrate and so on.

Compounds of the current invention contain one or more asymmetric centers, and therefore they can be used as a pure enantiomer, a pure diastereoisomer or a mixture of any combination of existing stereoisomers. The invention includes all stereoisomers of these compounds.

If compounds contain olefin double bond, the current invention claims both cis isomer and trans isomers, unless specified otherwise.

The compounds of the present invention can form tautomers, via the migration of one or more double bonds and hydrogen(s). The invention claims all the tautomers and their mixtures thereof.

For example, as shown in compounds of formula (I) as well as their intermediates in the preparation, Y represents , and can tautomerize during the preparation. In the scope of the present invention, when we prepare one tautomer of compounds or intermediates, we claim all their possible tautomers as equivalent. Examples are shown below:



Another embodiment of this invention pertains to a pharmaceutical composition comprising any compound of formula (I), or a pharmaceutically acceptable salts or stereoisomers thereof and one or more pharmaceutical carrier(s) and/or diluent(s). Such composition can be manufactured into any clinically or pharmaceutically acceptable dosage forms, preferably oral or injectable formations.

The compounds of the present invention, or a pharmaceutically acceptable salt, and/or stereoisomers thereof, can be administered to a patient through oral or parenteral route in any suitable formulation.

When the compound is administered through parenteral routes, it can be

formulated into an injectable dosage form. The term “an injectable dosage form” as used herein, refers to the formulation made of the compound and being injectable, which comprises solutions, emulsions or suspensions, or the sterile powders or concentrated solutions for reconstitution or dilution into sterile injectable solutions or suspensions immediately before use. The injectable dosage form can be classified into an injectable liquid, a sterile powder for injection, and a concentrated solution for injection. The term “injectable liquid” as used herein, refers to a sterile liquid containing the present compound for solution-type injection, emulsion injection or suspension injection made of the compound, which can be administrated via intramuscular injection, intravenous injection, intravenous infusion. The specifications of the volume of the injection may be 1 ml, 2 ml, 5 ml, 10 ml, 20 ml, 50 ml, 100 ml, 200 ml, 250 ml, 500 ml and etc, of which the large volume (usually not less than 100ml) injection for intravenous infusion is also known as an intravenous feeding. The term “sterile powder for injection” as used herein, refers to the sterile powder or clumpy substance made of the compound for reconstituting into an injectable solution or homogeneous suspension with a suitable sterile solution immediately before use. It can be used as injection after being reconstituted with suitable solvent for injection, as intravenous infusion after being reconstituted with intravenous transfusion. The sterile powder can be prepared by means of crystallization with solvent, spray drying, or lyophilization (i.e. freeze-dried) methods. The term “concentrated solution for injection” as used herein, means the sterile concentrated solution made of the compound, which can be diluted for intravenous infusion just prior to use.

The injectable dosage form can be produced by the conventional methods in the art of formulations, and aqueous solvents or non-aqueous solvents may be selected. The most commonly used aqueous solvent is water for injection, as well as 0.9% sodium chloride solution or other suitable aqueous solutions. The commonly used non-aqueous solvent is vegetable oil, mainly soy bean oil for injection, and others aqueous solutions of alcohol, propylene glycol, polyethylene glycol, and *etc.* During the preparation of an injectable dosage form, additives may not be used or may be

used, and suitable additives may also be added in accordance with the nature of the compounds, such as osmotic pressure regulators, pH regulators, solubilizers, fillers, antioxidants, antibacterial agents or preservatives, emulsifiers, suspending agents, and so on. Commonly used osmotic pressure regulators include sodium chloride, glucose, potassium chloride, magnesium chloride, calcium chloride, sorbitol, *etc.*, preferably sodium chloride or glucose. Commonly used pH regulators include acetic acid-sodium acetate, lactic acid, citric acid-sodium citrate, sodium bicarbonate-sodium carbonate, *etc.* Commonly used solubilizers include polysorbate 80, propylene glycol, lecithin, polyoxyethylenated castor oil, *etc.* Commonly used fillers include lactose, mannitol, sorbitol, dextran, *etc.* Commonly used antioxidants include sodium sulfite, sodium bisulfite, sodium pyrosulfite, *etc.* Commonly used antibacterial agents or preservatives include phenol, cresol, trichlorobutanol, *etc.* Commonly used containers for injection include glass ampoules, glass bottles, plastic ampoules, plastic bottles, *etc.*

When the compound is administered orally, it can be formulated into solid dosage forms for oral administration, for example, tablets, capsules, pills, granules, and so on. It also can be formulated into liquid dosage forms for oral administration, such as oral solutions, oral suspensions, syrups and the like. The term “tablets” as used herein, refers to those solid preparations which are prepared by homogeneously mixing and pressing the compounds and suitable auxiliary materials into circular or irregular troches, mainly in common tablets for oral administration, including also buccal tablets, sublingual tablets, buccal wafer, chewable tablets, dispersible tablets, soluble tablets, effervescent tablets, sustained-release tablets, controlled-release tablets, enteric-coated tablets and the like. The term “capsules” as used herein, refers to those solid preparations which are prepared by filling the compounds, or the compounds together with suitable auxiliary materials into hollow capsules or sealing into soft capsule materials. According to the solubility and release property, capsules can be divided into hard capsules (regular capsules), soft capsules (soft shell capsules), sustained-release capsules, controlled-release capsules, enteric-coated capsules and the like. The term “pills” as used herein, refers to spherical or near-spherical solid

preparations which are prepared by mixing the compounds and suitable auxiliary materials via suitable methods, including dropping pills, dragee, pilule and the like. The term “granules” as used herein, refers to dry granular preparations which are prepared by mixing the compounds and suitable auxiliary materials and have a certain particle size. Granules can be divided into soluble granules (generally referred to as granules), suspension granules, effervescent granules, enteric-coated granules, sustained-release granules, controlled-release granules and the like. The term “oral solutions” as used herein, refers to a settled liquid preparation which is prepared by dissolving the compounds in suitable solvents for oral administration. The term “oral suspensions” as used herein, refers to suspensions for oral administration, which are prepared by dispersing the insoluble compounds in liquid vehicles, also including dry suspension or concentrated suspension. The term “syrups” as used herein, refers to a concentrated sucrose aqueous solution containing the compounds.

Suitable carriers for the present invention include, but are not limited to, bulking agents, adhesives, disintegrants, lubricants and the like which can be used for the preparation of the solid dosage forms for oral administration. Commonly used bulking agents include starch, sugar powder, calcium phosphate, calcium sulfate dihydrate, dextrin, microcrystalline cellulose, lactose, pregelatinized starch, mannitol and the like. Commonly used adhesives include sodium carboxymethylcellulose, PVP-K30, hydroxypropyl cellulose, starch slurry, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, gelling starch and the like. Commonly used disintegrants include dry starch, crospovidone, croscarmellose, sodium carboxymethyl starch, low-substituted hydroxypropyl cellulose and the like. Commonly used lubricants include magnesium stearate, talc, sodium dodecyl sulfate, micronized silica gel and the like.

The present invention also provides uses of the present compounds for the treatment of infectious diseases. The compounds of the present invention have excellent antibacterial activities against gram-positive bacteria, and with antibacterial activities against resistant gram-positive bacteria. The compounds of the present invention can be used to safely treat the diseases caused by a gram-positive bacteria.

Antibacterial Activity:

The following *in vitro* anti-bacterial experiments further illustrate the benefits of compounds said hereinbefore. However it should not be interpreted that the compounds said hereinbefore only have these benefits.

Bacterial strains for test: All the bacterial strains are clinically isolated strains obtained from public sources such as clinics and hospitals.

Methicillin-resistant *Staphylococcus aureus* (MRSA), Methicillin-resistant *Staphylococcus epidermidis* (MRSE), Vancomycin-resistant *enterococci* (VRE)

Compounds to be tested: The compounds in the present invention are prepared in-house, and their chemical names and structures can be found in the preparation section of each compound.

Experimental Method: Agar Dilution Method, see reference National Committee for Clinical Laboratory Standards. 2006. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Seventh Edition M7-A7.

Experimental Results and Conclusions:

In vitro antibacterial activities of the test compounds against G⁺ bacteria

Table 1.

Compound	MIC ₉₀ (µg/mL)		
	MRSA	MRSE	VRE
Compound 1	1	0.5	/

Table 2.

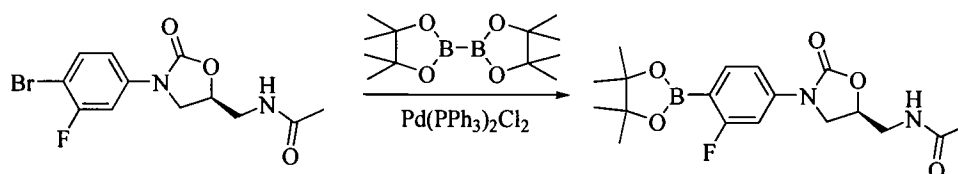
Compound	MIC (µg/ mL)		
	MRSA	MRSE	VRE
Compound 1	0.25	0.125	0.5
Compound 5	0.5	0.5	0.5

Experimental results indicate that the compounds of the present invention are active against the bacteria tested, could be used as clinical therapy.

4. Examples

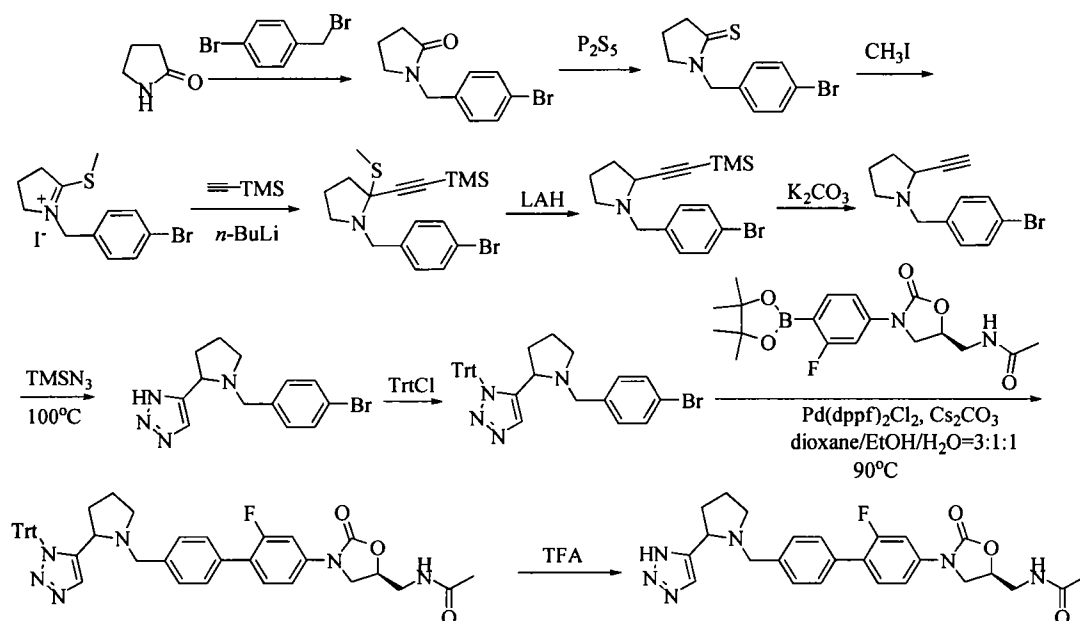
The present invention will be further illustrated with the following examples. However the scope of this invention is not limited in any way to these examples. Any variations and modifications obvious to one skilled in the art are intended to be included within the scope of the present invention.

Example 1 Preparation of (*S*)-*N*-[[3-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-oxo-oxazolidin-5-yl]methyl]acetamide

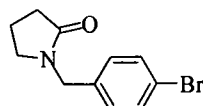


To a oven-dried reaction flask was added 1,4-dioxane (30 mL), (*S*)-*N*-[[3-(4-bromo-3-fluorophenyl)-2-oxo-oxazolidin-5-yl]methyl]acetamide (3.31 g, 10 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.54 g, 10 mmol), K₂CO₃ (0.98 g, 10 mmol), and under Ar was added Pd(PPh₃)₂Cl₂ (0.3 g). The reaction was heated to 90 °C overnight under argon and then cooled to room temperature and filtered through a pad of Celite. The filtrate was extracted with EtOAc and brine, and the organic phase was dried over Na₂SO₄ and concentrated to afford the crude product as an off-white solid (3.22 g). (All (*S*)-*N*-[[3-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-oxo-oxazolidin-5-yl]methyl]acetamide used in the examples below was prepared with this procedure)

Example 2 Preparation of *N*-[[[(5*S*)-3-[4'-[[2-(1*H*-1,2,3-triazol-5-yl)pyrrolidin-1-yl]methyl]-2-fluorobiphenyl-4-yl]-2-oxo-oxazolidin-5-yl]methyl]acetamide (Compound 1)

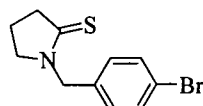


(1) Preparation of 1-(4-bromobenzyl)pyrrolidin-2-one



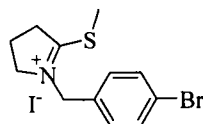
To an oven-dried flask was added a DMSO (50 mL) solution of pyrrolidin-2-one (2.10 g, 24.5 mmol) followed by NaH (1.04 g, 24.5 mmol) and stirred at 40 °C for 5h. It was cooled to 25 °C and slowly added 1-bromo-4-(bromomethyl)benzene (6.44 g, 24.5 mmol) and stirred 10 h at room temperature. The reaction mixture was dissolved in EtOAc (50 mL) and washed with water, dried over Na₂SO₄, and concentrated to afford product (5.20 g).

(2) Preparation of 1-(4-bromobenzyl)pyrrolidine-2-thione



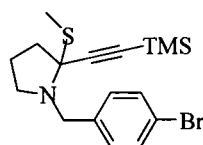
To an oven-dried reaction flask was added 1-(4-bromobenzyl)pyrrolidin-2-one (2.5 g, 9.84 mmol). After it was completely dissolved in toluene (30 mL), P₂S₅ (1.31 g, 5.9 mmol) was added and stirred 2 h. The reaction mixture was evaporated, washed with aqueous ammonia solution, and dried under vacuum to afford product (2.4 g).

(3) Preparation of 1-(4-bromobenzyl)-5-(methylthio)-3,4-dihydro-2H-pyrrolium iodide



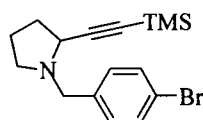
To an oven-dried reaction flask was added 1-(4-bromobenzyl)pyrrolidine-2-thione (3.1 g, 11.3 mmol). After it was completely dissolved in THF (20 mL), MeI (1.6 g, 11.3 mmol) was added and stirred 18 h. The product was collected by filtration as white solid (4.03 g).

(4) Preparation of 1-(4-bromobenzyl)-2-(methylthio)-2-[(trimethylsilyl)ethynyl]pyrrolidine



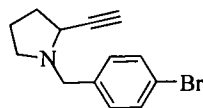
To a THF (20 mL) solution of ethynyltrimethylsilane (1.3 g, 13 mmol) was added BuLi (7.5 mL 2.0 mol/L, 15 mmol) slowly at -78 °C and stirred at the same temperature for 15 min. The solution was added dropwise to a THF (50 mL) solution of 1-(4-bromobenzyl)-5-(methylthio)-3,4-dihydro-2*H*-pyrrolium iodide (5.36 g, 13 mmol) at -78 °C and stirred at -20 °C to -30 °C for 2 h and quenched with saturated NH₄Cl aqueous solution (5 mL). The reaction was concentrated, extracted with EtOAc and dried over Na₂SO₄. Concentrated and purified by column chromatography to afford product (4.0 g).

(5) Preparation of 1-(4-bromobenzyl)-2-[(trimethylsilyl)ethynyl]pyrrolidine



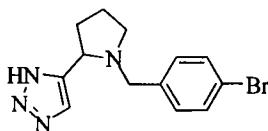
To an oven-dried reaction flask at -20 °C was added a THF (100 mL) solution of 1-(4-bromobenzyl)-2-(methylthio)-2-[(trimethylsilyl)ethynyl]pyrrolidine (10.7 g, 28 mmol) followed by LAH (1.1 g, 28 mmol) portionwise and stirred 2 h. Afterwards H₂O (2.0 g, 0.111 mol) was added and filtered. The filtrate was concentrated and purified by column chromatography to afford product (5.9 g).

(6) Preparation of 1-(4-bromobenzyl)-2-ethynylpyrrolidine



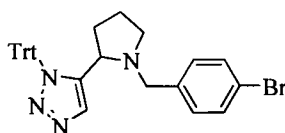
To an oven-dried reaction flask was added 1-(4-bromobenzyl)-2-[(trimethylsilyl)ethynyl]pyrrolidine (1.9 g, 5.65 mmol). After it was completely dissolved in MeOH (12 mL), K_2CO_3 (1.64 g, 12 mmol) was added and stirred at room temperature for 40 min. After filtration, the filtrate was concentrated to dryness and redissolved in CH_2Cl_2 (16 mL), washed with brine, dried over Na_2SO_4 , and concentrated to afford product (1.43 g).

(7) Preparation of 5-[1-(4-bromobenzyl)pyrrolidin-2-yl]-1*H*-1,2,3-triazole



To an oven-dried reaction flask was added 1-(4-bromobenzyl)-2-ethynylpyrrolidine (4.9 g, 18.5 mmol), $TMSN_3$ (3.2 g, 27.8 mmol), a mixture of solvents (DMF / MeOH = 27 / 3 mL) and under N_2 , CuI (0.7 g, 3.7 mmol) and stirred at 100 °C for 14 h. The reaction was cooled to room temperature and added ice-cold water, extracted with Et_2O , dried over Na_2SO_4 , and purified by column chromatography (EtOAc / PE) to afford product (4.6 g).

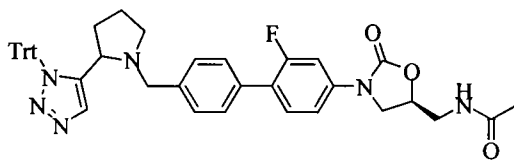
(8) Preparation of 5-[1-(4-bromobenzyl)pyrrolidin-2-yl]-1-trityl-1*H*-1,2,3-triazole



To an oven-dried reaction flask was added 5-[1-(4-bromobenzyl)pyrrolidin-2-yl]-1*H*-1,2,3-triazole (1.5 g, 4.9 mmol) and Et_3N (1.2 g, 11.7 mmol). After they were completely dissolved in CH_2Cl_2 (10 mL), $TrtCl$ (3.0 g, 10.8 mmol) was added dropwise at 0 °C and stirred at room temperature for 2 h. H_2O (10 mL) was added, and the aqueous phase was washed with CH_2Cl_2 . The combined organic phases were dried over Na_2SO_4 and purified by column chromatography (PE / EtOAc) to afford product (2.6 g).

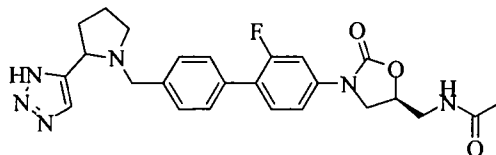
(9) Preparation of *N*-[[[(5*S*)-3-[2-fluoro-4'-[[2-(1-trityl-1*H*-1,2,3-triazol-5-yl]

pyrrolidin-1-yl)methyl]biphenyl-4-yl]-2-oxooxazolidin-5-yl)methyl]acetamide



To an oven-dried reaction flask was added 5-[1-(4-bromobenzyl)pyrrolidin-2-yl]-1-trityl-1*H*-1,2,3-triazole (2.7 g, 4.9 mmol), (*S*)-*N*-[[3-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-oxooxazolidin-5-yl)methyl]acetamide (1.9 g, 4.9 mmol), Cs₂CO₃ (1.6 g, 4.9 mmol) and a solvent mixture (1,4-dioxane / EtOH / H₂O = 15 / 5 / 5 mL) and under N₂ protection, Pd(dppf)₂Cl₂ (0.19 g, 0.255 mmol). The reaction mixture was stirred at 90 °C for 2.5 h and, after the removing of solvent, the resulting off-white solid was washed with H₂O and purified by column chromatography (EtOAc / PE = 5 / 1) to afford product (2.4 g).

(10) Preparation of *N*-[[3-[(5*S*)-3-[4'-[[2-(1*H*-1,2,3-triazol-5-yl)pyrrolidin-1-yl)methyl]-2-fluorobiphenyl-4-yl]-2-oxooxazolidin-5-yl)methyl]acetamide

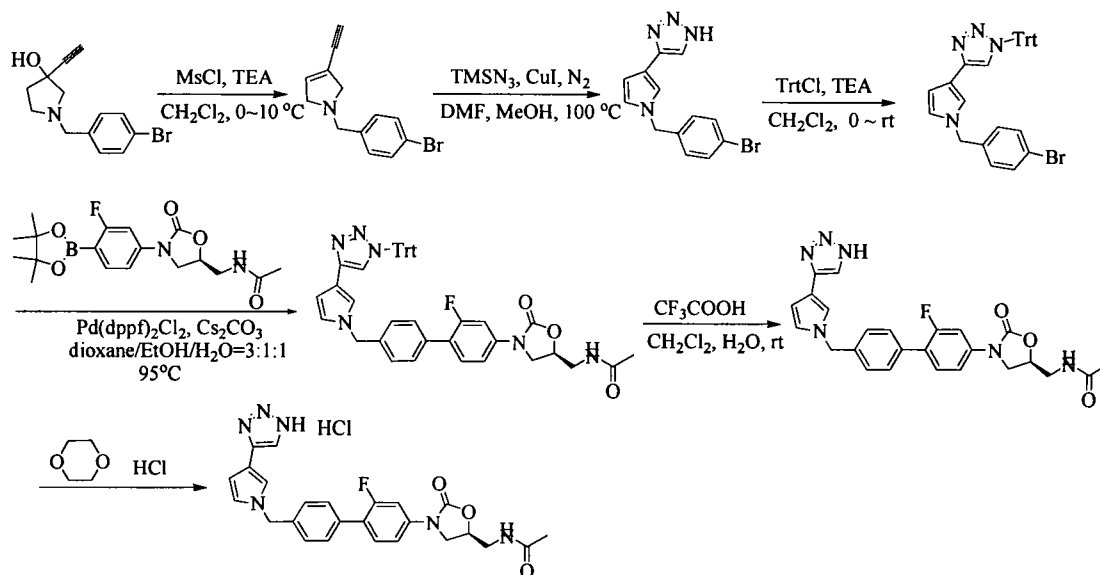


To an oven-dried reaction flask was added *N*-[[3-[(5*S*)-3-[2-fluoro-4'-[[2-(1-trityl-1*H*-1,2,3-triazol-5-yl)pyrrolidin-1-yl)methyl]biphenyl-4-yl]-2-oxooxazolidin-5-yl)methyl]acetamide (2.4 g, 3.3 mmol). After it was dissolved in CH₂Cl₂ (40 mL), TFA (4 mL) and H₂O (3 mL) were added and stirred at room temperature for 8 h. The pH of reaction mixture was adjusted to 9 with aqueous Na₂CO₃ solution, and the aqueous phase was extracted with CH₂Cl₂. The combined organic phases were washed with H₂O, dried, and concentrated to afford the crude product as a white solid that was recrystallized in MeOH / Et₂O to afford product (785 mg).

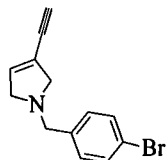
Formula: C₂₅H₂₇FN₆O₃ Molecular Weight: 478.52 Mass (M+H): 479

¹H-NMR (DMSO-*d*₆, 300 MHz): δ 8.29 (1H, t), 7.80 (1H, s), 7.61-7.33 (7H, m), 4.79-4.74 (1H, m), 4.17 (1H, t), 3.82-3.71 (3H, m), 3.46-3.42 (2H, m), 3.17 (1H, d), 2.92 (1H, m), 2.27-2.17 (2H, m), 1.95-1.85 (6H, m).

Example3 Preparation of (S)-N-[[3-[4'-[[3-(1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrol-1-yl]methyl]-2-fluorobiphenyl-4-yl]-2-oxooxazolidin-5-yl]methyl]acetamide hydrochloride (Compound 5 Hydrochloride Salt)

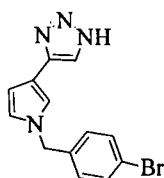


(1) Preparation of 1-(4-bromobenzyl)-3-ethynyl-2,5-dihydro-1*H*-pyrrole



To an oven-dried reaction flask was added 1-(4-bromobenzyl)-3-ethynylpyrrolidin-3-ol (5 g, 17.9 mmol) and triethyl amine (11 g, 110 mmol) and dissolved in CH₂Cl₂ (40 mL) under stirring. At 0-10 °C CH₂Cl₂ (10 mL) solution of MsCl (6.2 g, 54.1 mmol) was added dropwise. After 12 h, H₂O (40 mL) was added, and the aqueous phase was extracted 3 times with CH₂Cl₂. The combined organic phases were dried over Na₂SO₄ and evaporated to afford the crude product as a black oil (4.5 g).

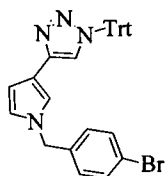
(2) Preparation of 4-[1-(4-bromobenzyl)-1*H*-pyrrol-3-yl]-1*H*-1,2,3-triazole



To an oven-dried reaction flask was added 1-(4-bromobenzyl)-3-ethynyl-2,5-dihydro-1*H*-pyrrole (4.69 g, 17.9 mmol), TMSN₃

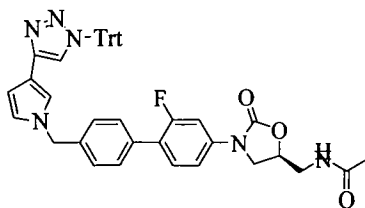
(3.09 g, 26.8 mmol), and CuI (0.69 g, 3.6 mmol) and dissolved in DMF (45 mL) / MeOH (5 mL). Under N₂ the reaction was heated to 100 °C and stirred overnight. H₂O (20 mL) was then added, and the precipitate and aqueous phase were separately washed with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated to afford the crude product as a black oil (5.0 g).

(3) Preparation of 4-[1-(4-bromobenzyl)-1*H*-pyrrol-3-yl]-1-*trityl*-1*H*-1,2,3-triazole



To an oven-dried reaction flask was added 4-[1-(4-bromobenzyl)-1*H*-pyrrol-3-yl]-1-*trityl*-1*H*-1,2,3-triazole (5.0 g, 16.56 mmol), Et₃N (4.0 g, 39.7 mmol) and dissolved in CH₂Cl₂ (25 mL) under stirring. At 5 °C CH₂Cl₂ (10 mL) solution of TrtCl (10.2 g, 36.42 mmol) was added dropwise, and the reaction was stirred for 20 min before adding ice-water (10 mL). The organic phase was extracted with H₂O three times, dried over Na₂SO₄, concentrated, and purified by column chromatography (EtOAc / PE = 1 / 5) to afford the product as a yellow solid (0.5 g).

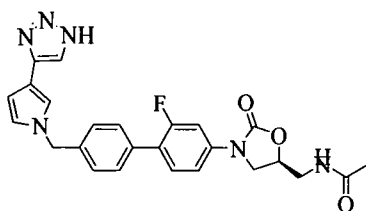
(4) Preparation of (*S*)-*N*-[[3-[2-fluoro-4'-[[3-(1-*trityl*-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrol-1-yl]methyl]biphenyl-4-yl]-2-oxo-oxazolidin-5-yl]methyl]acetamide



To an oven-dried reaction flask was added 4-[1-(4-bromobenzyl)-1*H*-pyrrol-3-yl]-1-*trityl*-1*H*-1,2,3-triazole (0.5 g, 0.919 mmol), (*S*)-*N*-[[3-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-oxo-oxazolidin-5-yl]methyl]acetamide (0.38 g, 1.01 mmol), Cs₂CO₃ (0.9 g, 2.757 mmol) and dissolved in a mixed solvent (1,4-dioxane / EtOH / H₂O = 6 / 2 / 2 mL). Under N₂,

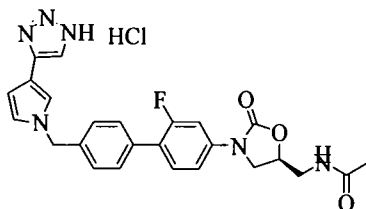
$\text{Pd(dppf)}_2\text{Cl}_2$ (54.7 mg, 0.067 mmol) was added, and the reaction was stirred at 95 °C for 24 h. The reaction mixture was concentrated and added H_2O (10 mL) and extracted three times with CH_2Cl_2 . The combined organic phases were washed with brine, dried over Na_2SO_4 , concentrated, and purified by column chromatography ($\text{EtOAc} / \text{PE} = 5 / 1$) to afford the product as a yellow solid (0.3 g).

(5) Preparation of (*S*)-*N*-[[3-[4'-[[3-(1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrol-1-yl]methyl]-2-fluorobiphenyl-4-yl]-2-oxooxazolidin-5-yl]methyl]acetamide



To an oven-dried reaction flask was added (*S*)-*N*-[[3-[2-fluoro-4'-[[3-(1-trityl-1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrol-1-yl]methyl]biphenyl-4-yl]-2-oxo-oxazolidin-5-yl]methyl]acetamide (0.3 g, 0.419 mmol) and dissolved in CH_2Cl_2 (4 mL). TFA (0.4 mL) and H_2O (0.4 mL) were added, and the mixture was stirred at room temperature for 1 h. H_2O (4 mL) was added, and the pH was adjusted to 8~9 with aqueous Na_2CO_3 solution. The precipitate was rinsed with ether to afford product as a light yellow solid (135 mg).

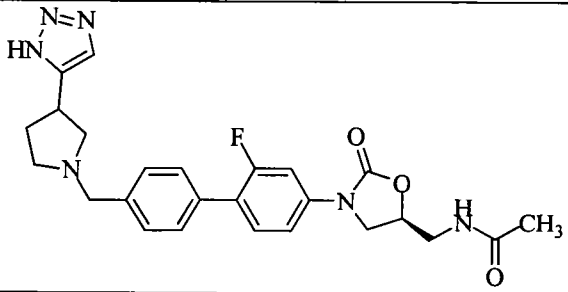
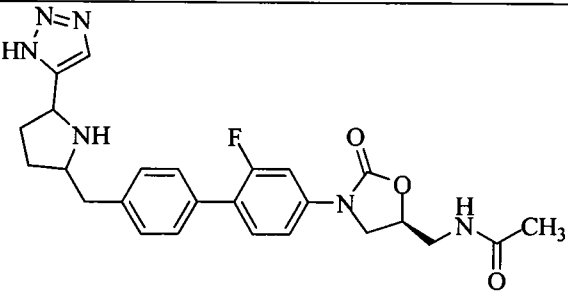
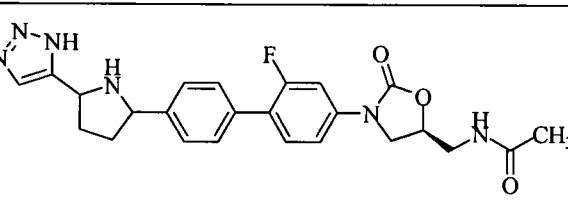
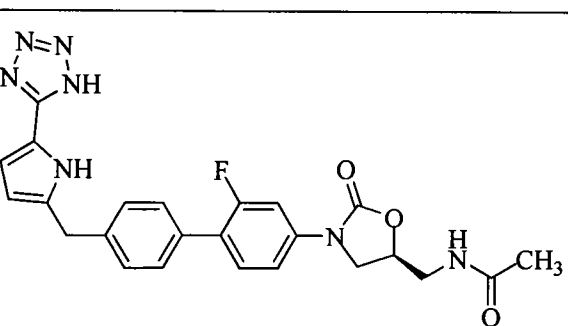
(6) Preparation of (*S*)-*N*-[[3-[4'-[[3-(1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrol-1-yl]methyl]-2-fluorobiphenyl-4-yl]-2-oxo-oxazolidin-5-yl]methyl]acetamide hydrochloride

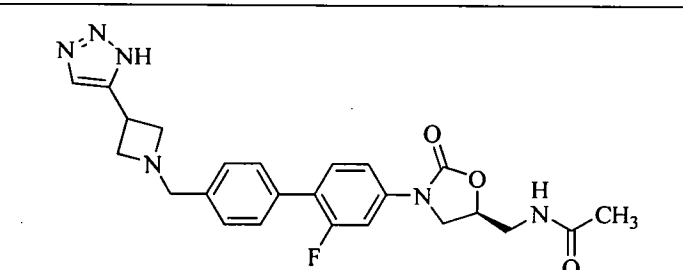
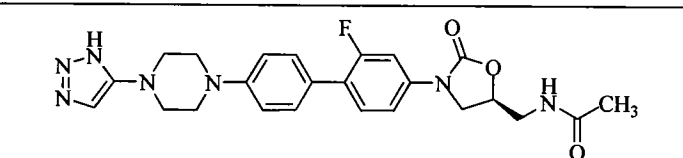
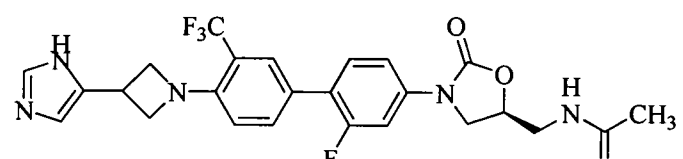
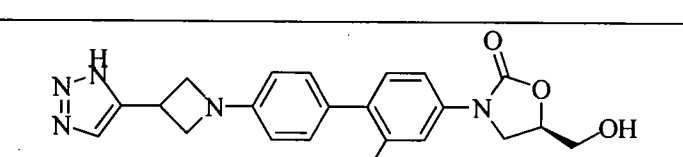
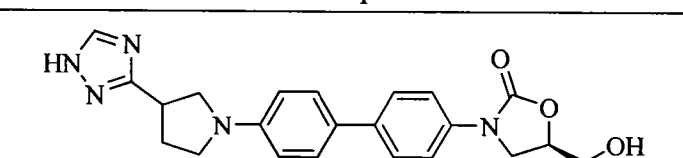
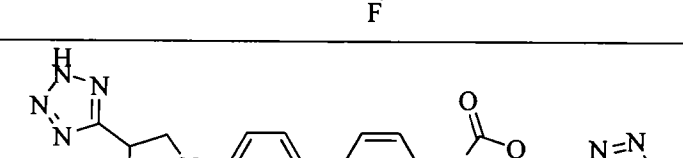
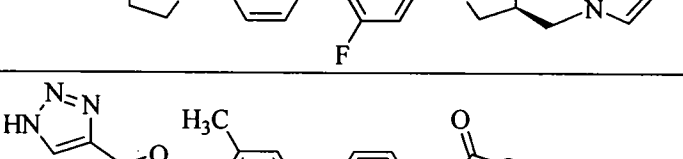
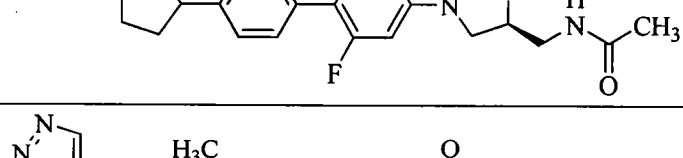


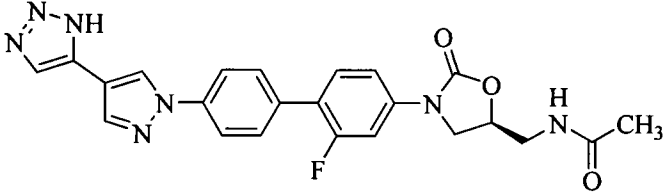
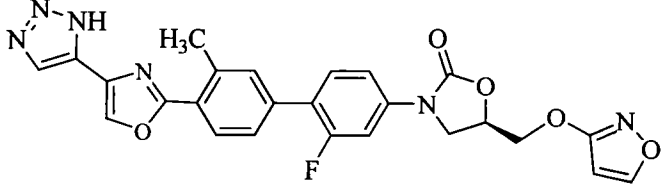
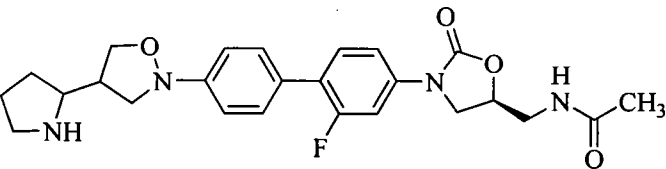
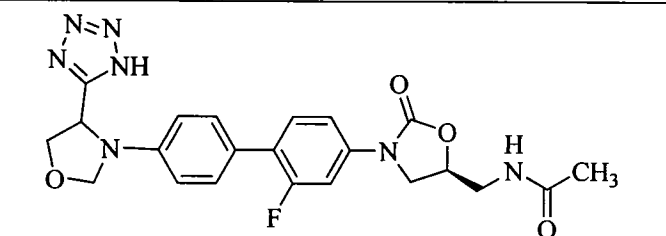
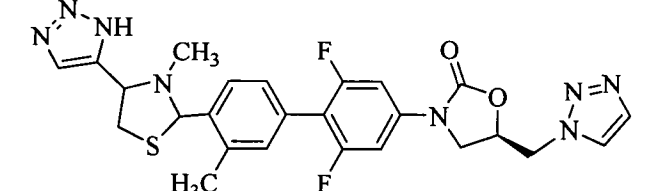
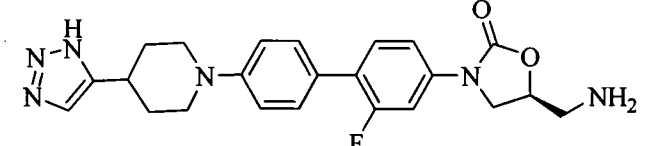
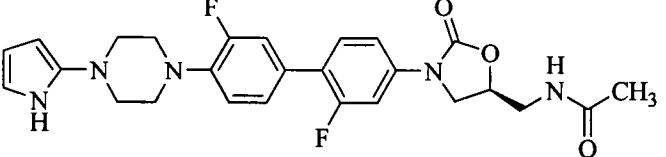
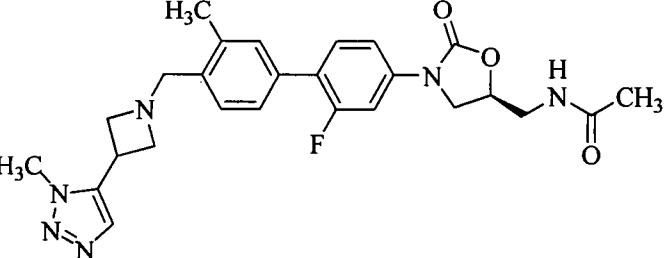
To 1,4-dioxane (5 mL) solution of (*S*)-*N*-[[3-[4'-[[3-(1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrol-1-yl]methyl]-2-fluorobiphenyl-4-yl]-2-oxo-oxazolidin-5-yl]methyl]acetamide (199 mg, 0.419 mmol) was added a saturated HCl solution in dioxane (10 mL) with stirring. The solid formed was filtered and rinsed with ether to afford a light yellow solid (140 mg).

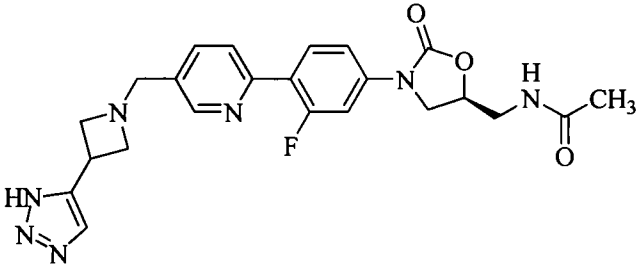
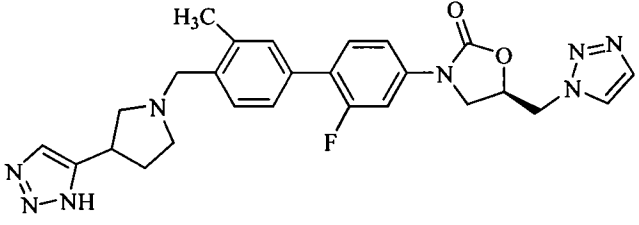
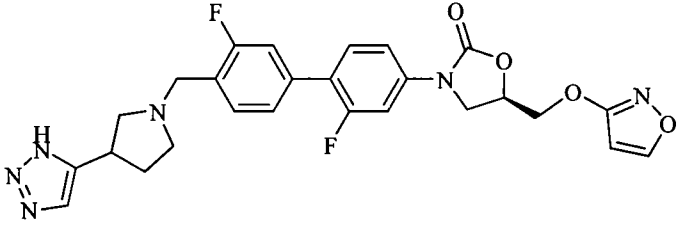
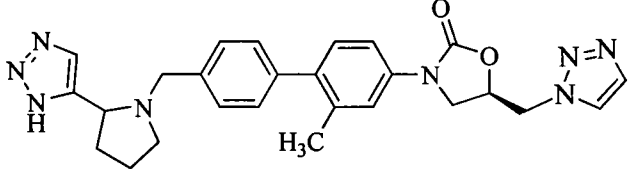
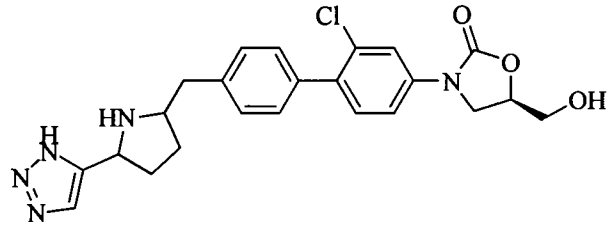
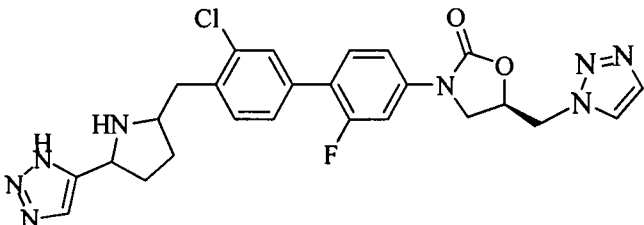
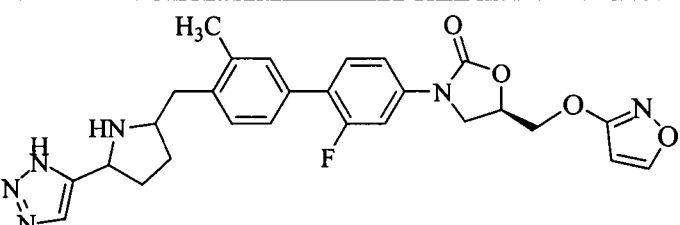
Formula: $C_{25}H_{23}FN_6O_3$ Molecular Weight: 474.49 Mass (M+H): 475
 1H -NMR(DMSO- d_6 , 300 MHz): δ 8.29 (1H, t), 7.84 (1H, s), 7.61-7.52 (4H, m), 7.42-7.29 (4H, m), 6.95 (1H, t), 6.42 (1H, d), 5.19 (2H, s), 4.78-4.73 (2H, m), 4.16 (1H, s), 3.78 (1H, dd), 3.44-3.41 (1H, m), 1.84 (3H, s).

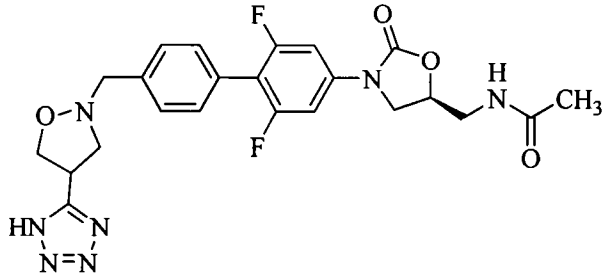
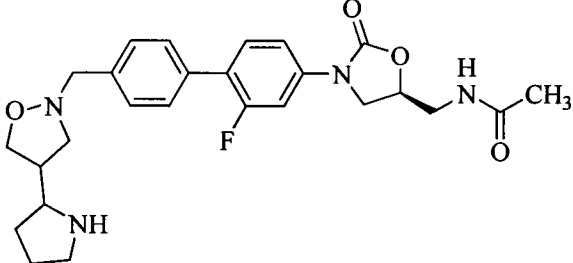
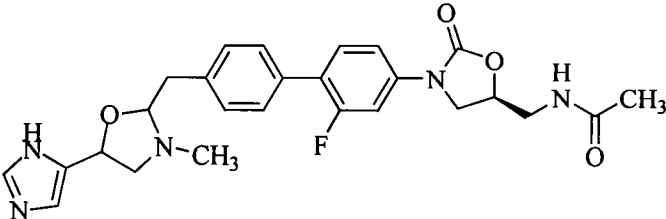
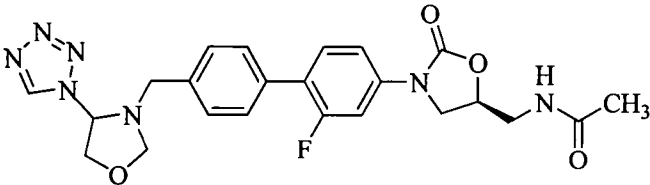
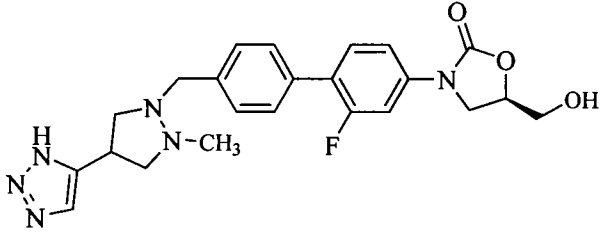
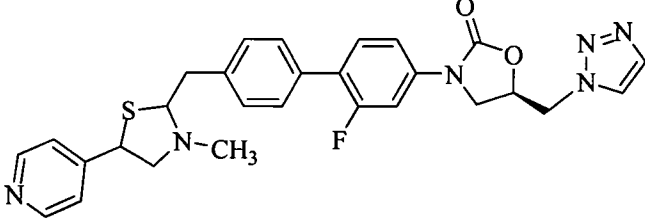
The following compounds can also be prepared according to the method described above:

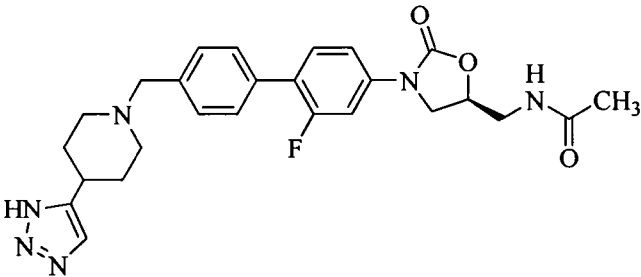
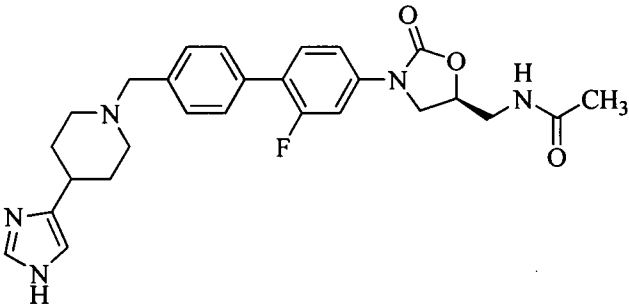
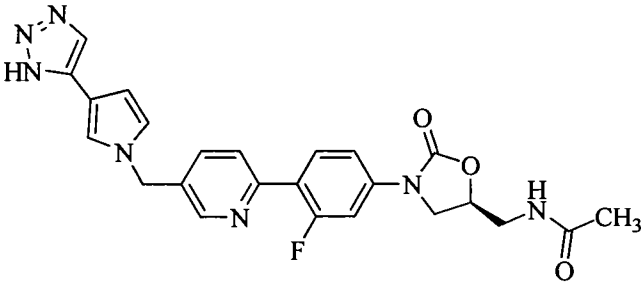
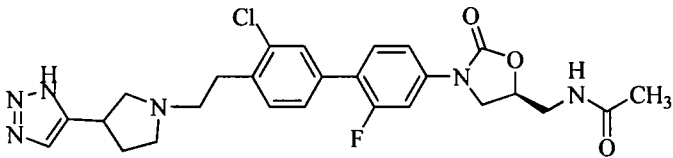
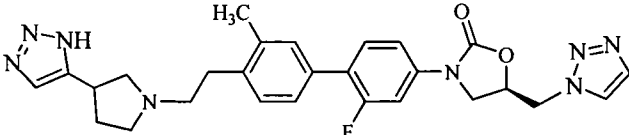
Compound	Structure	Mass(M+H)
2		479
3		479
4		465
6		476

Compound	Structure	Mass(M+H)
7		465
8		480
9		518
10		410
11		424
12		476
13		480
14		496

Compound	Structure	Mass(M+H)
15		462
16		503
17		469
18		468
19		539
20		437
21		496
22		493

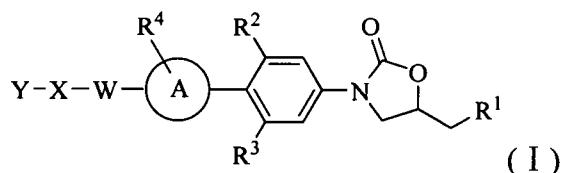
Compound	Structure	Mass(M+H)
23		466
24		503
25		523
26		485
27		454
28		523
29		519

Compound	Structure	Mass(M+H)
36		500
37		483
38		494
39		482
40		453
41		531

Compound	Structure	Mass(M+H)
42		493
43		492
44		476
45		527
46		517

CHAIMS

1. Compounds of general formula (I) or a pharmaceutically acceptable salt or its stereoisomers thereof:



Wherein

R^1 is acetyl amino, hydroxyl, amino, C_{1-6} alkyl amino, 1,2,3-triazolyl or isoxazolyl group;

R^2 and R^3 are independently a hydrogen or halogen;

A ring can be un-substituted benzene or six-membered unsaturated heterocycle where R^4 is hydrogen, or optionally substituted benzene or six-membered unsaturated heterocycle by one to four R^4 groups where R^4 is independently selected from halogen, C_{1-6} alkyl or halogenated C_{1-6} alkyl ;

W is a bond, $-C(R^5)(R^6)-$, $-C(R^5)(R^6)-C(R^7)(R^8)-$ or $-C(R^5)(R^6)-C(R^7)(R^8)-C(R^9)(R^{10})-$, wherein, R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are independently a hydrogen, C_{1-6} alkyl or halogen;

X is 3-8 membered heterocycle containing 1-4 heteroatoms, where heteroatom is selected from nitrogen, oxygen and sulfur;

Y is 5-6 membered heterocycle;

X, Y can further be substituted by halogen or C_{1-6} alkyl group.

2. A compound claimed in claim 1, or its pharmaceutically acceptable salt or its stereoisomers:

Wherein

R^1 is acetyl amino, hydroxyl, amino, C_{1-6} alkyl amino, 1,2,3-triazolyl or isoxazolyl group;

R^2 and R^3 are independently a hydrogen or halogen;

A ring can be un-substituted benzene or pyridine where R^4 is hydrogen, or optionally substituted benzene or pyridine by one to four R^4 groups where R^4 is independently

selected from halogen, C₁₋₆ alkyl or halogenated C₁₋₆ alkyl;

W is a bond, -C(R⁵)(R⁶)-, -C(R⁵)(R⁶)-C(R⁷)(R⁸)- or -C(R⁵)(R⁶)-C(R⁷)(R⁸)-C(R⁹)(R¹⁰)-, wherein, R⁵ and R⁶ are independently a hydrogen or C₁₋₆ alkyl, and R⁷, R⁸, R⁹ and R¹⁰ are independently a hydrogen, C₁₋₆ alkyl or halogen;

X is 3-8 membered heterocycle containing 1-4 heteroatoms, where heteroatom is selected from nitrogen, oxygen and sulfur;

Y is 5-6 membered heterocycle;

X, Y can further be substituted by halogen or C₁₋₆ alkyl group.

3. A compound claimed in claim 2, or its pharmaceutically acceptable salt or its stereoisomers:

Wherein

R¹ is acetyl amino, hydroxyl, 1,2,3-triazolyl or isoxazolyl group;

R² and R³ are independently a hydrogen or halogen;

A ring can be un-substituted benzene or pyridine where R⁴ is hydrogen, or optionally substituted benzene or pyridine by one to four R⁴ groups where R⁴ is independently selected from halogen, C₁₋₄ alkyl or halogenated C₁₋₄ alkyl;

W is a bond, -C(R⁵)(R⁶)-, -C(R⁵)(R⁶)-C(R⁷)(R⁸)- or -C(R⁵)(R⁶)-C(R⁷)(R⁸)-C(R⁹)(R¹⁰)-, wherein, R⁵ and R⁶ are independently a hydrogen or methyl, and R⁷, R⁸, R⁹ and R¹⁰ are independently a hydrogen, methyl or fluorine;

X is 5-6 membered heterocycle containing 1-3 heteroatoms, where heteroatom is selected from nitrogen, oxygen and sulfur;

Y is 5-6 membered heterocycle;

X, Y can further be substituted by halogen or C₁₋₄ alkyl group.

4. A compound claimed in claim 3, or its pharmaceutically acceptable salt or its stereoisomers:

Wherein

R¹ is acetyl amino;

R² and R³ are independently a hydrogen, fluorine or chlorine;

A ring can be un-substituted benzene where R⁴ is hydrogen, or optionally substituted benzene by one to two R⁴ groups where R⁴ is independently selected from fluorine,

chlorine, methyl or trifluoromethyl;

W is a bond, $-C(R^5)(R^6)-$, $-C(R^5)(R^6)-C(R^7)(R^8)-$ or $-C(R^5)(R^6)-C(R^7)(R^8)-C(R^9)(R^{10})-$, wherein, R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are independently a hydrogen;

X is selected from azetidine, tetrahydropyrrole, tetrahydrofuran, tetrahydrothiophene, tetrahydrooxazole, tetrahydroisoxazole, tetrahydrothiazole, tetrahydropyrazole, pyrrole, oxazole, pyrazole, piperazine or piperidine;

Y is selected from triazole, tetrazole, imidazole, pyrrole, tetrahydropyrrole or pyridine;

X, Y can further be substituted by fluorine or methyl group.

5. A compound claimed in claim 4, or its pharmaceutically acceptable salt or its stereoisomers:

Wherein

R^1 is acetyl amino;

R^2 and R^3 are independently a hydrogen, fluorine or chlorine;

A ring can be un-substituted benzene where R^4 is hydrogen, or optionally substituted benzene which is substituted by one to two R^4 groups where R^4 is independently selected from fluorine, chlorine, methyl or trifluoromethyl;

W is a bond, $-C(R^5)(R^6)-$ or $-C(R^5)(R^6)-C(R^7)(R^8)-$,

wherein, R^5 , R^6 , R^7 and R^8 are independently a hydrogen;

X is selected from azetidine, tetrahydropyrrole, pyrrole, pyrazole, piperidine or piperazine;

Y is selected from 1,2,3-triazole, 1,2,4-triazole, 1,2,3,4-tetrazole, 1,2,3,5-tetrazole, imidazole, pyrrole or pyridine.

6. A compound claimed in claim 5, or its pharmaceutically acceptable salt or its stereoisomers:

Wherein

R^1 is acetyl amino;

R^2 and R^3 are independently a hydrogen or fluorine;

A ring is un-substituted benzene where R^4 is hydrogen;

W is a bond or $-C(R^5)(R^6)-$, wherein, R^5 and R^6 are independently a hydrogen;

X is selected from azetidine, tetrahydropyrrole, pyrrole or piperazine;

Y is selected from 1,2,3-triazole or 1,2,3,4-tetrazole.

7. A compound claimed in claim 6, or its pharmaceutically acceptable salt or its stereoisomers and selected from the following compounds:

N-[[[(5*S*)-3-[4'-[[2-(1*H*-1,2,3-triazol-5-yl)pyrrolidin-1-yl]methyl]-2-fluorobiphenyl-4-yl]-2-oxo-oxazolidin-5-yl]methyl]acetamide,

N-[[[(5*S*)-3-[4'-[[3-(1*H*-1,2,3-triazol-5-yl)pyrrolidin-1-yl]methyl]-2-fluorobiphenyl-4-yl]-2-oxo-oxazolidin-5-yl]methyl]acetamide,

N-[[[(5*S*)-3-[4'-[[2-(1*H*-1,2,3-triazol-5-yl)pyrrolidin-5-yl]methyl]-2-fluorobiphenyl-4-yl]-2-oxo-oxazolidin-5-yl]methyl]acetamide,

N-[[[(5*S*)-3-[4'-[2-(1*H*-1,2,3-triazol-5-yl)pyrrolidin-5-yl]-2-fluorobiphenyl-4-yl]-2-oxo-oxazolidin-5-yl]methyl]acetamide, and

(*S*)-*N*-[[[3-[4'-[[3-(1*H*-1,2,3-triazol-4-yl)-1*H*-pyrrol-1-yl]methyl]-2-fluorobiphenyl-4-yl]-2-oxooxazolidin-5-yl]methyl]acetamide.

8. The compound of any of claims 1 to 7, or its pharmaceutically acceptable salt or its stereoisomers, wherein the pharmaceutically acceptable salt is selected from benzene sulfonate, benzoate, toluene sulfonate, mesylate, citrate, maleate, fumarate, tartrate, hydrochloride, hydrobromate, sulfate or phosphate.

9. A pharmaceutical composition comprising a compound of any of claims 1 to 7, or its pharmaceutically acceptable salt or its stereoisomers and one or more pharmaceutical carriers and / or diluent, characterized in that the said composition is any clinically or pharmaceutically acceptable dosage form.

10. A method of the treatment and/or prevention of infectious diseases comprising a compound of any of claims 1 to 7, or its pharmaceutically acceptable salt or its stereoisomers.