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# Octahydropyrrolo[1,2-*a*]pyrazine Derivatives of Carbapenem as Antibacteria Antibiotics

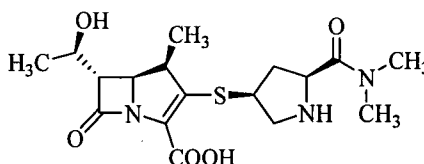
## 1. Field of The Invention

The present invention belongs to the pharmaceutical filed and specifically relates to Octahydropyrrolo[1,2-*a*]pyrazine Derivatives of Carbapenem as Antibacteria Antibiotics, or its pharmaceutically acceptable salts, or its readily hydrolyzed ester, or its solvate, or its stereoisomer and intermediates, thereof, to the processes for preparing the same, to the pharmaceutical compositions containing such compounds, and to the use of these compounds in the manufacture of a medicament for the treatment and / or prophylaxis of infectious disease.

## 2. Background of The Invention

Carbapenems have drawn wide attention due to their broad anti-bacterial spectrum, potent anti-bacterial activity and stability towards  $\beta$ -lactamase. The carbapenem currently in use at clinic include Imipenem, Panipenem, Meropenem, Ertapenem, Bioapenem, Doripenem and Tebipenem.

European patent application EP0126587 published Meropenem (structure below), which is a 1 $\beta$ -methyl carbapenem, active to gram-positive bacteria, and gram-negative bacteria. It is especially potent against gram-negative bacteria, stable against DHP-I enzyme, can be used as a single therapy.



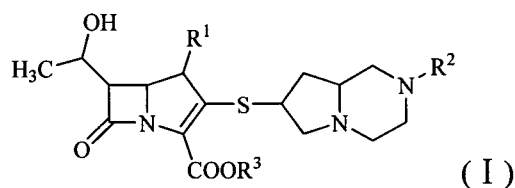
There are more and more drug-resistant bacteria emerging due partially to antibiotics abuses, additionally, most of the carbapenems on the market have a human elimination half-life of about 1 hour, require multiple daily doses, and are less tolerable. Therefore, it is important to develop more potent, stable, and long half-life carbapenem to meet clinical needs.

## 3. Disclosure of The Invention

The present invention provides Octahydropyrrolo[1,2-*a*]pyrazine Derivatives of Carbapenem as Antibacteria Antibiotics, or its pharmaceutically acceptable salts, or its readily hydrolyzed ester, or its solvate, or its stereoisomer:



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Wherein

$R^1$  is hydrogen or  $C_{1-6}$  alkyl;

$R^2$  is

(1) hydrogen,

(2)  $C_{1-6}$  alkyl,  $C_{2-8}$  alkenyl or  $C_{2-8}$  alkynyl, which is optionally substituted by one to three  $X^1$ ,

$X^1$  is independently selected from halogen, carboxyl, hydroxyl, amino, cyano, nitro,  $C_{1-6}$  alkoxy, halogenated  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkyl amino, bis-( $C_{1-6}$  alkyl)amine,  $C_{1-6}$  alkyl carbonyl,  $C_{1-6}$ alkyl carboxyl,  $C_{1-6}$  alkoxy carbonyl, carbamoyl,  $C_{1-6}$  alkyl carbamoyl, bis-( $C_{1-6}$  alkyl) carbamoyl, amino sulfonyl,  $C_{1-6}$  alkyl amino sulfonyl, bis-( $C_{1-6}$  alkyl) amino sulfonyl,  $C_{1-6}$  alkyl sulfonyl amino,  $C_{1-6}$  alkyl sulfonyl,  $C_{1-6}$  alkyl carbonyl amino, guanidino,  $C_{3-8}$  cycloalkyl, aryl or heterocyclic,

$C_{3-8}$  cycloalkyl, aryl or heterocyclic of said  $X^1$  can be further substituted by the following substituents: halogen, carboxyl, hydroxyl, amino, cyano, nitro,  $C_{1-6}$  alkyl, carboxy  $C_{1-6}$  alkyl, hydroxy  $C_{1-6}$  alkyl, amino  $C_{1-6}$  alkyl, halogenated  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, halogenated  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkoxy  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl amino, bis-( $C_{1-6}$  alkyl) amino, bis-( $C_{1-6}$  alkyl) amino  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl carbonyl,  $C_{1-6}$ alkyl carboxyl,  $C_{1-6}$  alkoxy carbonyl, carbamoyl, carbamoyl  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl carbamoyl, bis-( $C_{1-6}$  alkyl) carbamoyl, amino sulfonyl, amino sulfonyl  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl amino sulfonyl, bis-( $C_{1-6}$  alkyl) amino sulfonyl,  $C_{1-6}$  alkyl sulfonyl amino,  $C_{1-6}$  alkyl sulfonyl,  $C_{1-6}$  alkyl carbonyl amino or guanidino,

(3)  $C_{3-8}$  cycloalkyl, aryl or heterocyclic which is optionally substituted by one to three  $X^2$ ,

$X^2$  is independently selected from halogen, carboxyl, hydroxyl, amino, cyano, nitro,  $C_{1-6}$  alkyl, carboxy  $C_{1-6}$  alkyl, hydroxy  $C_{1-6}$  alkyl, amino  $C_{1-6}$  alkyl, halogenated  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, halogenated  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkoxy  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl amino, bis-( $C_{1-6}$  alkyl) amino, bis-( $C_{1-6}$  alkyl) amino  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl carbonyl,  $C_{1-6}$ alkyl carboxyl,  $C_{1-6}$  alkoxy carbonyl, carbamoyl, carbamoyl  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl carbamoyl, bis-( $C_{1-6}$  alkyl) carbamoyl, amino sulfonyl, amino sulfonyl  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl amino sulfonyl, bis-( $C_{1-6}$  alkyl) amino sulfonyl,  $C_{1-6}$  alkyl sulfonyl amino,  $C_{1-6}$  alkyl sulfonyl,  $C_{1-6}$  alkyl amino carbonyl or guanidino,

(4) -CO-Y,

Y is C<sub>1-6</sub> alkyl which is optionally substituted by one to three Y<sup>1</sup>, or C<sub>3-8</sub> cycloalkyl, aryl or heterocyclic which is optionally substituted by one to three Y<sup>2</sup>,

Y<sup>1</sup> represents the above defined X<sup>1</sup> and Y<sup>2</sup> represents the above defined X<sup>2</sup>,

(5) -S(O)<sub>m</sub>-Z, m is 1 or 2,

Z is amino, C<sub>1-6</sub> alkyl amino, bis-(C<sub>1-6</sub> alkyl)amino, or C<sub>1-6</sub> alkyl which is optionally substituted by one to three Y<sup>1</sup>, or C<sub>3-8</sub> cycloalkyl, aryl or heterocyclic which is optionally substituted by one to three Y<sup>2</sup>,

Y<sup>1</sup> represents the above defined X<sup>1</sup> and Y<sup>2</sup> represents the above defined X<sup>2</sup>; and

R<sup>3</sup> is hydrogen or the carboxyl protecting group.

**In another preferred embodiment, wherein**

R<sup>1</sup> is C<sub>1-4</sub> alkyl;

R<sup>2</sup> is

(1) hydrogen,

(2) C<sub>1-4</sub> alkyl, which is optionally substituted by one to three X<sup>1</sup>,

X<sup>1</sup> is independently selected from halogen, carboxyl, hydroxyl, amino, C<sub>1-4</sub> alkoxy, halogenated C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkyl amino, bis-(C<sub>1-4</sub> alkyl)amine, C<sub>1-4</sub> alkyl carbonyl, carbamoyl, amino sulfonyl, guanidino, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl or 3-7 membered heterocyclic,

C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl or 3-7 membered heterocyclic of the said X<sup>1</sup> can be further substituted by the following substituents: halogen, C<sub>1-4</sub> alkyl, halogenated C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, halogenated C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkyl amino, bis-(C<sub>1-4</sub> alkyl) amino, C<sub>1-4</sub> alkyl carbonyl, carbamoyl, carbamoyl C<sub>1-4</sub> alkyl, amino sulfonyl, amino sulfonyl C<sub>1-4</sub> alkyl, or guanidino,

(3) C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl or 3-7 membered heterocyclic which is optionally substituted by one to three X<sup>2</sup>,

X<sup>2</sup> is independently selected from halogen, amino, C<sub>1-4</sub> alkyl, halogenated C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, halogenated C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkyl amino, bis-(C<sub>1-4</sub> alkyl) amino, bis-(C<sub>1-4</sub> alkyl) amino C<sub>1-6</sub> alkyl, C<sub>1-4</sub> alkyl carbonyl, carbamoyl, carbamoyl C<sub>1-4</sub> alkyl, amino sulfonyl, amino sulfonyl C<sub>1-4</sub> alkyl, or guanidino,

(4) -CO-Y,

Y is C<sub>1-4</sub> alkyl which is optionally substituted by one to three Y<sup>1</sup>, or C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl or 3-7 membered heterocyclic which is optionally substituted by one to three Y<sup>2</sup>,

Y<sup>1</sup> represents the above defined X<sup>1</sup> and Y<sup>2</sup> represents the above defined X<sup>2</sup>,

(5) -S(O)<sub>m</sub>-Z, m is 1 or 2,

Z is amino, C<sub>1-4</sub> alkyl amino, bis-(C<sub>1-4</sub> alkyl)amino, or C<sub>1-4</sub> alkyl which is optionally substituted by one to three Y<sup>1</sup>, or C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl or 3-7 membered heterocyclic which is optionally substituted by one to three Y<sup>2</sup>,

Y<sup>1</sup> represents the above defined X<sup>1</sup> and Y<sup>2</sup> represents the above defined X<sup>2</sup>; and  
R<sup>3</sup> is hydrogen.

**In another preferred embodiment, wherein**

R<sup>1</sup> is methyl;

R<sup>2</sup> is

(1) hydrogen,

(2) C<sub>1-4</sub> alkyl, which is optionally substituted by one to three X<sup>1</sup>,

X<sup>1</sup> is independently selected from halogen, carboxyl, hydroxyl, amino, C<sub>1-4</sub> alkoxy, halogenated C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkyl amino, bis-(C<sub>1-4</sub> alkyl)amine, carbamoyl, amino sulfonyl, phenyl, pyridyl, piperidiny, piperazinyl or morpholinyl,

The phenyl, pyridyl, piperidiny, piperazinyl or morpholinyl of the said X<sup>1</sup> can be further substituted by the following substituents: halogen, C<sub>1-4</sub> alkyl, halogenated C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, halogenated C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkyl amino, bis-(C<sub>1-4</sub> alkyl) amino, C<sub>1-4</sub> alkyl carbonyl, carbamoyl, carbamoyl C<sub>1-4</sub> alkyl, or amino sulfonyl,

(3) phenyl, pyridyl, piperidiny, piperazinyl, morpholinyl, tetrahydrofuranyl, thiazole, 4,5-dihydro-thiazolyl, or cyclopropyl group which is optionally substituted by one to three X<sup>2</sup>,

X<sup>2</sup> is independently selected from halogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkyl amino, bis-(C<sub>1-4</sub> alkyl) amino, carbamoyl, carbamoyl C<sub>1-4</sub> alkyl, amino sulfonyl,

(4) -CO-Y,

Y is C<sub>1-4</sub> alkyl which is optionally substituted by one to three Y<sup>1</sup>, or phenyl, pyridyl, piperidiny, piperazinyl, morpholinyl, pyrrolidinyl, furanyl, thiazolyl or 4,5-dihydro-thiazolyl which is optionally substituted by one to three Y<sup>2</sup>,

Y<sup>1</sup> is independently selected from amino, C<sub>1-4</sub> alkyl amino, bis-(C<sub>1-4</sub> alkyl) amino,

carbamoyl, guanidino, phenyl, pyridyl, piperidinyl, morpholinyl or pyrrolidinyl,

$Y^2$  is independently selected from halogen, amino,  $C_{1-4}$  alkyl,  $C_{1-4}$  alkyl amino, bis-( $C_{1-4}$  alkyl) amino, carbamoyl, carbamoyl  $C_{1-4}$  alkyl or amino sulfonyl,

(5)  $-S(O)_m-Z$ ,  $m$  is 1 or 2,

$Z$  is amino,  $C_{1-4}$  alkyl amino, bis-( $C_{1-4}$  alkyl)amino, or  $C_{1-4}$  alkyl which is optionally substituted by one to three  $Y^1$ , or phenyl, pyridyl, piperidinyl, piperazinyl, morpholinyl or pyrrolidinyl which is optionally substituted by one to three  $Y^2$ ,

$Y^1$  and  $Y^2$  represents the above defined; and

$R^3$  is hydrogen.

**In another preferred embodiment, wherein**

$R^1$  is methyl;

$R^2$  is

(1) hydrogen,

(2) methyl, ethyl, isopropyl, which is optionally substituted by one to three  $X^1$ ,

$X^1$  is independently selected from halogen, hydroxyl, dimethylamine, phenyl or pyridyl,

The phenyl or pyridyl of the said  $X^1$  can be further substituted by the following substituents: halogen, methyl, carbamoyl, carbamoyl methyl, or amino sulfonyl,

(3) phenyl, pyridyl, tetrahydrofuranyl, thiazole, 4,5-dihydro-thiazolyl, or cyclopropyl group which is optionally substituted by one to three  $X^2$ ,

$X^2$  is independently selected from halogen, methyl, carbamoyl, amino sulfonyl,

(4)  $-CO-Y$ ,

$Y$  is methyl, ethyl or isopropyl which is optionally substituted by one to three  $Y^1$ , or phenyl, pyridyl, piperidinyl, piperazinyl, pyrrolidinyl which is optionally substituted by one to three  $Y^2$ ,

$Y^1$  is independently selected from dimethylamine, carbamoyl, guanidino, phenyl, pyridyl, piperidinyl, morpholinyl or pyrrolidinyl,

$Y^2$  is independently selected from halogen, methyl, carbamoyl, carbamoyl methyl or amino sulfonyl,

(5)  $-S(O)_m-Z$ ,  $m$  is 1 or 2,

$Z$  is amino, dimethylamino, dimethylamino methyl, methylpiperazine or morpholine methyl; and

R<sup>3</sup> is hydrogen.

**In another preferred embodiment, wherein**

R<sup>1</sup> is methyl;

R<sup>2</sup> is

(1) hydrogen,

(2) methyl, ethyl, or isopropyl, which is optionally substituted by one to two X<sup>1</sup>,

X<sup>1</sup> is independently selected from hydroxyl, or phenyl,

The said phenyl of X<sup>1</sup> can be further substituted by halogen, methyl, carbamoyl, or amino sulfonyl,

(3) -CO-Y,

Y is methyl, ethyl or isopropyl, which is optionally substituted by one to two Y<sup>1</sup>, or phenyl, pyridyl, piperidinyl, which is optionally substituted by one to two Y<sup>2</sup>,

Y<sup>1</sup> is independently selected from dimethylamine, guanidino, phenyl, pyridyl, or morpholinyl,

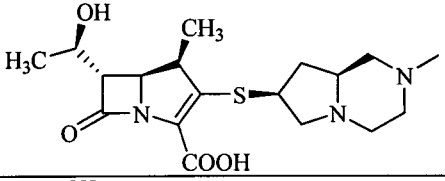
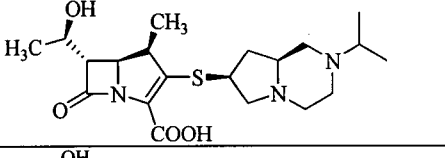
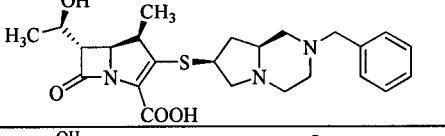
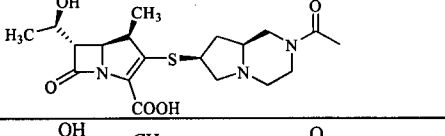
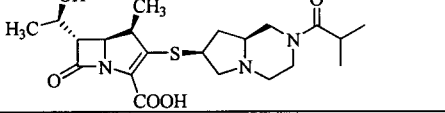
Y<sup>2</sup> is independently selected from halogen, methyl, carbamoyl, or amino sulfonyl,

(4) -S(O)<sub>m</sub>-Z, m is 1 or 2,

Z is amino, or dimethylamino; and

R<sup>3</sup> is hydrogen.

**Table 1 The compounds of present invention**

| No. | Structural Formula                                                                  | Chemical Name                                                                                                                                                                                                                     |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1   |  | (4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> )-6-[( <i>R</i> )-1-hydroxyethyl]-4-methyl-3-[(7 <i>S</i> ,8 <i>aS</i> )-2-methyloctahydropyrrolo[1,2- <i>a</i> ]pyrazin-7-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid      |
| 2   |  | (4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> )-6-[( <i>R</i> )-1-hydroxyethyl]-3-[(7 <i>S</i> ,8 <i>aS</i> )-2-Isopropyl-octahydropyrrolo[1,2- <i>a</i> ]pyrazin-7-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid  |
| 3   |  | (4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> )-3-[(7 <i>S</i> ,8 <i>aS</i> )-2-benzyl-octahydropyrrolo[1,2- <i>a</i> ]pyrazin-7-ylthio]-6-[( <i>R</i> )-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid     |
| 4   |  | (4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> )-3-[(7 <i>S</i> ,8 <i>aS</i> )-2-acetyloctahydropyrrolo[1,2- <i>a</i> ]pyrazin-7-ylthio]-6-[( <i>R</i> )-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid      |
| 5   |  | (4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> )-6-[( <i>R</i> )-1-hydroxyethyl]-3-[(7 <i>S</i> ,8 <i>aS</i> )-2-isobutyryl-octahydropyrrolo[1,2- <i>a</i> ]pyrazin-7-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid |

|    |  |                                                                                                                                                                                                                                                       |
|----|--|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6  |  | (4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> )-3-[(7 <i>S</i> ,8 <i>aS</i> )-2-benzoyloctahydropyrrolo[1,2- <i>a</i> ]pyrazin-7-ylthio]-6-[( <i>R</i> )-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid                         |
| 7  |  | (4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> )-6-[( <i>R</i> )-1-hydroxyethyl]-4-methyl-7-oxo-3-[(7 <i>S</i> ,8 <i>aS</i> )-2-picolinoyloctahydropyrrolo[1,2- <i>a</i> ]pyrazin-7-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid                      |
| 8  |  | (4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> )-6-[( <i>R</i> )-1-hydroxyethyl]-4-methyl-7-oxo-3-[(7 <i>S</i> ,8 <i>aS</i> )-2-(4-sulfamoylbenzoyl)octahydropyrrolo[1,2- <i>a</i> ]pyrazin-7-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid            |
| 9  |  | (4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> )-6-[( <i>R</i> )-1-hydroxyethyl]-4-methyl-7-oxo-3-[(7 <i>S</i> ,8 <i>aS</i> )-2-sulfamoyloctahydropyrrolo[1,2- <i>a</i> ]pyrazin-7-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid                       |
| 10 |  | (4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> )-6-[( <i>R</i> )-1-hydroxyethyl]-4-methyl-7-oxo-3-[(7 <i>S</i> ,8 <i>aS</i> )-2-(4-sulfamoylbenzyl)octahydropyrrolo[1,2- <i>a</i> ]pyrazin-7-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid             |
| 11 |  | (4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> )-3-[(7 <i>S</i> ,8 <i>aS</i> )-2-(2-guanidinoacetyl)octahydropyrrolo[1,2- <i>a</i> ]pyrazin-7-ylthio]-6-[( <i>R</i> )-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid             |
| 12 |  | (4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> )-3-[(7 <i>S</i> ,8 <i>aS</i> )-2-(2-(dimethylamino)acetyl)octahydro-pyrrolo[1,2- <i>a</i> ]pyrazin-7-ylthio]-6-[( <i>R</i> )-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid      |
| 13 |  | (4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> )-3-[(7 <i>S</i> ,8 <i>aS</i> )-2-(2-(dimethylamino)propionyl)octahydropyrrolo[1,2- <i>a</i> ]pyrazin-7-ylthio]-6-[( <i>R</i> )-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid    |
| 14 |  | (4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> )-6-[( <i>R</i> )-1-hydroxyethyl]-4-methyl-3-[(7 <i>S</i> ,8 <i>aS</i> )-2-(2-morpholinoacetyl)octahydropyrrolo[1,2- <i>a</i> ]pyrazin-7-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid            |
| 15 |  | (4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> )-6-[( <i>R</i> )-1-hydroxyethyl]-4-methyl-3-[(7 <i>S</i> ,8 <i>aS</i> )-2-(1-methylpiperidine-4-carbonyl)octahydropyrrolo[1,2- <i>a</i> ]pyrazin-7-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid |
| 16 |  | (4 <i>R</i> ,5 <i>S</i> ,6 <i>S</i> )-6-[( <i>R</i> )-1-hydroxyethyl]-3-[(7 <i>S</i> ,8 <i>aS</i> )-2-(2-hydroxyethyl)octahydropyrrolo[1,2- <i>a</i> ]pyrazin-7-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid                |

The term “C<sub>1-6</sub>alkyl”, as used hereinbefore, refers to linear, branched groups derived from removing one hydrogen from hydrocarbons 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-ethylpropyl, 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, et al. the term “C<sub>1-4</sub>alkyl” refers to the above examples that contain 1 to 4 carbon(s), for example, methyl, ethyl,

n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl.

The term "C<sub>3-8</sub> cycloalkyl", as used hereinbefore, refers to the cycloalkanes of 3 to 8 carbons atom membered size, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctanyl, methylcyclopropane, dimethylcyclopropane, methylcyclobutane, dimethylcyclobutane, methylcyclopentane, dimethylcyclopentane, methylcyclohexane, dimethylcyclohexane, and so on. The term "C<sub>3-6</sub>cycloalkyl" refer respectively 3 to 6 carbon atom cycloalkane in above-mentioned examples.

The term "C<sub>2-8</sub> alkenyl" , as used hereinbefore, refers straight or branched chain or cyclic alkenyl containing 2 to 8 carbon atom with double bond(s), such as vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 1,3-butadienyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 1,3-pentadienyl, 1,4-pentadienyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1,4-hexadienyl, cyclopentenyl, 1,3-cyclopentadienyl, cyclohexenyl, 1,4-cyclohexadienyl, cycloheptenyl, 1,4-cycloheptadienyl, cyclooctenyl, 1,5-cyclooctadienyl and so on.

The term "C<sub>2-8</sub> alkynyl", as used hereinbefore, refers straight or branched chain containing 2 to 8 carbon atom with triple bond(s), such as acetylenyl, propynyl, 2-butylnyl, 2-pentylnyl, 3-pentylnyl, 4-methyl-2-pentylnyl, 2-hexynyl, 3-hexynyl, 5-methyl-2-hexynyl, 2-heptynyl, 5-methyl-2-heptynyl, 2-octynyl, 3-octynyl and so on.

The term "C<sub>1-6</sub> alkoxy" , as used hereinbefore, refers to the term "C<sub>1-6</sub> alkyl" structure through the oxygen atom connected with other groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, secondary butoxy, pentyloxy, isopentyloxy, hexyloxy and so on. The terms "C<sub>1-4</sub> alkoxy" refer respectively to in above-mentioned specific examples 1 to 4 atoms.

The term "halo", as used hereinbefore, include fluorine, chlorine, bromine, and iodine.

The term "halogenated C<sub>1-6</sub> alkyl", "halogenated C<sub>1-6</sub> alkoxy" as used hereinbefore, is one or more hydrogen atoms of C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy substituted by one or more halo. The C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, and halo are denotes as hereinbefore.

The term "hydroxy C<sub>1-6</sub> alkyl", "carboxy C<sub>1-6</sub> alkyl", "amino C<sub>1-6</sub> alkyl", "C<sub>1-6</sub> alkoxy C<sub>1-6</sub> alkyl", as used hereinbefore, is one or more hydrogen atoms of C<sub>1-6</sub> alkyl independently substituted by one or more hydroxy, carboxy, amino or C<sub>1-6</sub> alkoxy. The C<sub>1-6</sub> alkyl and C<sub>1-6</sub> alkoxy are denotes as hereinbefore.

The term "aryl", as used hereinbefore, refers to aromatic rings, include "carbocyclic aryl" and "heteroaryl".

The term "carbocyclic aryl" have no heteroatom, examples include but are not limited to, phenyl, naphthalenyl, anthracenyl, and phenanthrenyl.

The term "heteroaryl" refers to 5 to 20 membered cyclic group containing one or more heteroatoms except carbons, the heteroatoms means nitrogen, oxygen, sulfur, and so on. The "heteroaryl" refers to 5 to 10 ring atoms containing one or more heteroatoms (called 5-10 membered heteroaryl) is preferred, examples include but are not limited to, furan, thiophene, pyrrole, imidazole, pyrazole, triazole, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine, benzofuran, isobenzofuran, benzothiophene, indole, isoindole, quinoline, isoquinoline, naphthyridine, acridine. The term "5-6 membered heteroaryl", refer respectively to in above-mentioned specific examples 5 to 6 membered atoms.

The term "heterocyclic" refers to 3 to 14 membered cyclic group containing one or more heteroatoms (called 3-14 membered heteroaryl), include saturated heterocyclic and unsaturated heterocyclic. The "heterocyclic" refers to 3 to 7 ring membered cyclic group containing one or more heteroatoms (called 3-7 membered heterocyclic) is preferred. The examples include but are not limited to, aziridine, azetidine, pyrrolidine, 2,5-dihydro-pyrrole, 2H-pyrrole, 3H-pyrrole, piperidine, dihydropyridine, tetrahydropyridine, oxirane, oxetane, dihydropyran, pyran, azepine, oxepine, thiirane, thietane, tetrahydrothiophene, thiepane, dioxolane, dioxepane, imidazolidine, pyrazolidine, imidazoline, piperazine, tetrahydro-oxazole, dihydro-oxazole, tetrahydro-isoxazole, dihydro-isoxazole, tetrahydro-oxazine, dihydro-oxazine, oxazine, thiazoline, thiazolidine, morpholine, thiomorpholine.

The term "carboxyl protecting group", as used hereinbefore, refers to a protecting group which can be conventionally used to substitute the acidic proton of a carboxylic acid. Examples of caboxyl protecting group include, but are not limited to, methoxymethyl, methylthiomethyl, tetrahydropyranyl, tetrahydrofuranyl, methoxyethylmethyl, benzyloxymethyl, phenacyl, allyl, p-bromophenacyl,  $\alpha$ -methylphenacyl, p-methoxyphenacyl, diacylmethyl, N-phthalimidomethyl, methyl, ethyl, diphenyl methyl, 2,2,2-trichloroethyl, 2-haloethyl,  $\omega$ -chloroalkyl, 2-(trimethylsilyl)ethyl, 2-methylthioethyl, 2-(p-nitrothiophenyl)ethyl, 2-(p-methylthiophenyl)ethyl, 1-methyl-1-phenylethyl, t-butyl, cyclopentyl, cyclohexyl, di-o-nitrophenylmethyl, 9-fluorenylmethyl, 2-(9,10-dioxo)fluorenylmethyl, 5-dithiophenyl, benzyl, 2,4,6-trimethylbenzyl, p-bromobenzyl, o-nitrobenzyl, p-nitrobenzyl, p-methoxybenzyl, piperonyl, 4-pyridinylmethyl, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, isopropyldimethylsilyl, phenyldimethylsilyl,

t-butyl, phenyl, 2-pyridyl, N-hydroxypiperidinyl, N-bydroxysuccinimido, N-hydroxyphthalimido, N-hydroxybenzotriazolyl, O-acyloxime, 2,4-dinitrothiophenyl, 2-alkyl-1,3-oxazoline, 4-alkyl-5-oxo-1,3-oxazolidinyl, 5-alkyl-4-oxo-1,3-dioxane, triethylstannyl, tri-n-butylstannayl, N,N'-diisopropylhydrazide, and so on.

The abbreviations in the present invention are defined as follows:

Bn: benzyl

Boc: t-butoxycarbonyl

PNB: p-nitrobenzyl

TEA : triethylamine

TFA: trifluoroacetyl

THF: tetrahydrofuranyl

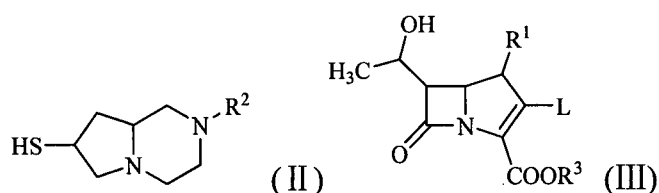
DCM: CH<sub>2</sub>Cl<sub>2</sub>

DEAD: (C<sub>2</sub>H<sub>5</sub>OOCN)<sub>2</sub>

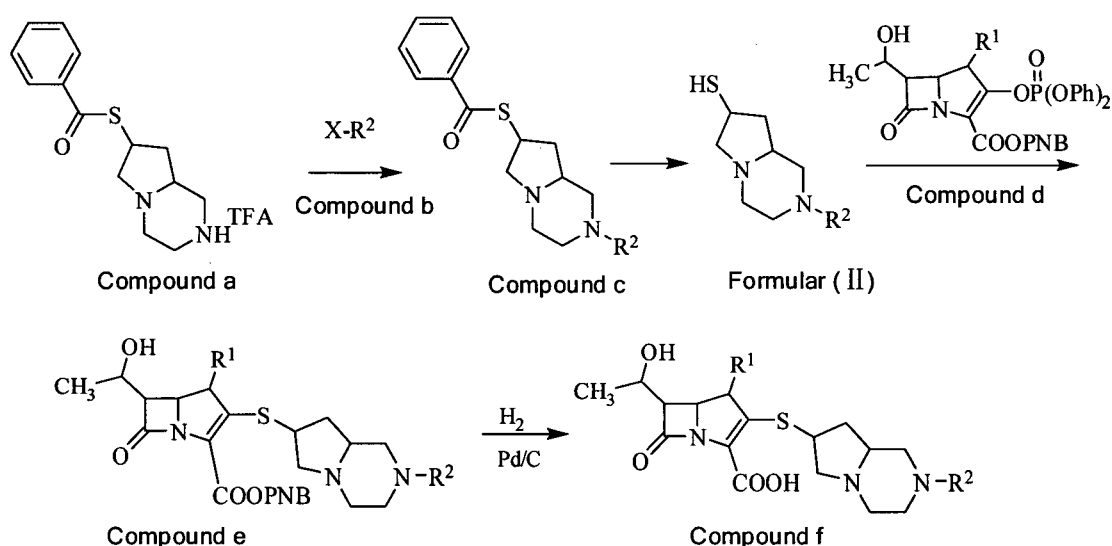
DIEA: diisopropylethylamine

Pd/C: Palladium on Carbon

The present invention provides the method of preparation of compounds of formular ( I ) by nucleophilic substitution reaction of compound of formular ( II ), or its pharmaceutically acceptable salts, or its readily hydrolyzed ester, or its solvate, or its stereoisomer with compound of formular (III), or its pharmaceutically acceptable salts, or its readily hydrolyzed ester, or its solvate, or its stereoisomer:



The method of preparation is generalized in the following scheme:



### Step 1 Preparation of Compound c

In a solution of Compound a in  $\text{CH}_2\text{Cl}_2$  was treated with TEA and Compound b. The resulting mixture was stirred at ambient temperature for overnight. The reaction mixture was washed with saturated brine, the organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give crude product of Compound c.

### Step 2 Preparation of compound of formular (II)

The crude Compound c from Step 1 was dissolved in methanol and treated with methanolic KOH solution. The resulting mixture was stirred at ambient temperature. Upon completion of the reaction, the reaction mixture was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure to give compounds of formular (II).

### Step 3 Preparation of Compound e

In a dried reaction flask, compound of formular (II) was dissolved in acetonitrile and was treated with Compound d and DIEA. The resulting mixture was stirred at ambient temperature for overnight. The reaction mixture was extracted with ethyl acetate and washed with water. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give crude product of Compound e.

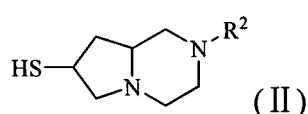
### Step 4 Synthesis of Compound f

The crude product from Step 3 in a mixture of tetrahydrofuran and water was treated with Pd/C. The result black suspension was stirred at ambient temperature under hydrogen atmosphere. Upon completion, the catalyst was removed by filtration and the filtered cake was washed with tetrahydrofuran and de-ionized water. The combined filtrate was extracted with ethyl acetate. The aqueous layer was purified by Prep. HPLC and the product fractions was combined and lyophilized.

to give Compound f.

Wherein  $R^1$ ,  $R^2$  and  $R^3$  are defined as above, L represents suitable leaving group. The synthesis of Compound a see example 1 (Step 1 to 8). X in Compound b represents halogen such as fluorine, chlorine, bromine, iodine or other replaceable group such as acid chloride.

This invention further claims compounds of formula ( I ), or its pharmaceutically acceptable salts, or its readily hydrolyzed ester, or its solvate, or its stereoisomer and the preparation of intermediates as described in formula ( II ), or its pharmaceutically acceptable salts, or its readily hydrolyzed ester, or its solvate, or its stereoisomer:



Wherein,  $R^2$  is defined as above.

The invention further claims the following pharmaceutically acceptable salts of formula ( I ) which contain alkali metal salts, such as sodium, potassium, lithium salt, etc.; alkaline earth metal salts, such as calcium, magnesium salt, etc.; other metal salts, such as aluminum, iron, zinc, copper, nickel, cobalt salt; inorganic alkali salts, such as ammonium salt; organic salts, such as tert-octyl amine, dibenzyl amine, morpholine, glucosamine, phenylglycine alkyl ester, ethylenediamine, N-methyl glucosamine, guanidine, diethylamine, triethylamine, dicyclohexyl ammonium, N,N'-dibenzyl ethylenediamine, chloroprocaine, procaine, diethanolamine, N-benzyl-phenylethyl amine, piperazine, tetramethyl ammonium, tris (hydroxymethyl) amino methane; halide salts, such as hydrofluoric acid salt, hydrochloric acid salt, hydrobromide, hydrogen iodate, etc.; inorganic salts, such as nitrate, perchlorate, sulfate, phosphate, etc.; lower alkyl sulfonate such as mesylate, triflate salt, ethanesulfonate, etc.; aryl sulfonates, such as benzene sulfonate, toluene sulfonate salt; organic acid, such as acetate, malate, fumarate, succinate, citrate, tartrate, oxalate, maleate, etc.; amino acid salts, such as glycine, trimethyl glycine, arginine, ornithine, glutamate, aspartate salt.

The term "readily hydrolyzed ester", as used hereinbefore, refers to an ester that is pharmaceutically acceptable and can be hydrolyzed to the corresponding carboxyl acid in vivo. It is obvious to those skilled in the art that a hydrolysable ester of a compound of the present invention can be formed at free carboxyl or hydroxyl of the said compound by using conventional methods.

The invention further claims "solvates" of formula ( I ), where "solvate" is referred to a compound crystal in which a solvent molecule is added to the crystal lattice during the

crystallization process. If the solvent is water, solvates are known as hydrates; If the solvent is an organic solvent, the solvates are known as organic solvates.

The invention further claims the “stereoisomers” of formula ( I ), including all of enantiomers, diastereomeric isomers, racemic isomers, cis and trans isomers, tautomers, geometric isomers, epimers and mixtures thereof.

The present invention further provides that a said compound, or its pharmaceutically acceptable salts, or its readily hydrolyzed ester, or its solvate, or its stereoisomer, can be formulated by any known method of the field into any formulation that is pharmaceutically or clinically acceptable and given to a patient in need of treatment through a variety of administration methods, such as oral, and ex-gastrointestinal, and so on.

When administered orally, it can be formulated into conventional solid dosage forms, for example, tablets, capsules, pills, granules, and so on. When the compound is administered ex-gastrointestinally, it can be formulated into dosage forms for injection, for example, solution ready for injection, sterile power for injection, concentrated solution for injection, and so on. Such formulations can be manufactured with conventional methods in contemporary pharmaceutical manufacturing, depending on the properties of compounds, the formulation can include either no or certain additives.

The present invention also provides the use of compounds described hereinbefore in the manufacture of a medicament for the treatment and / or prophylaxis of infectious diseases. These compounds have potent activities against broad spectrum of bacteria, including gram-positive bacteria, gram-negative bacteria, aerobic bacteria, anaerobic bacteria, and clinical pathogens. They can be used to treat and / or prophylaxis diseases caused by pathogenic microorganisms, such as respiratory and urinary tract infections.

**The compounds said hereinbefore, when compared to those disclosed in the most related prior art, have the following advantages:**

(1) The compounds said hereinbefore display excellent anti-bacterial activity and low toxicities, they could be used safely to treat and / or prevent various infectious diseases in mammals including human caused by pathogenic microorganisms.

(2) The compounds said hereinbefore have strong activities against broad spectrum of bacteria, including gram-positive, gram-negative bacteria, and other clinical pathogens.

(3) The compounds said hereinbefore are stable against  $\beta$ -lactamase and renal

dehydropeptidase-I (DHP-I), and could be used as a single therapy.

(4) The compounds said hereinbefore have long elimination half-life, post-antibiotic effect, and long-lasting anti-bacterial activities, therefore it is more convenient to apply clinically.

(5) The compounds said hereinbefore are relatively easy to synthesize, with high purity, high yield, and consistent quality, suitable for large-scale industrial production.

#### **Example 1 Anti-bacterial spectrum and *in vitro* Activities**

##### **Test Bacteria:**

Staphylococcus aureus, Methicillin-resistant Staphylococcus Epidermidis(MRSE), Methicillin Sensitive Staphylococcus Epidermidis(MSSE), Enterococcus faecali, Enterococcus faecom, Streptococcus pneumoniae, Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus viridans, Klebsiella pneumoniae (non-enzyme producing strain) , Klebsiella oxytoca(non-enzyme producing strain), Salmonella , Morganella morganii;

These bacteria are all purchased from Beijing Fuwai Hospital of Cardiovascular Diseases, Shanghai Renji Hospital, Xijing Hospital Affiliated to the Fourth Military Medical University.

##### **Test Compounds:**

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;

Meropenem, Etapenem: Purchased form commercial sources;

##### **Test Methods:**

**Agar dilution method**, see reference Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard-Seventh Edition. CLSI Document M7-A7. Vol26, no.2, Wayne, PA: Clinical and Laboratory Standards Institute, 2006.

##### **Experimental Results and conclusions:**

**Table 2 Comparison of *in vitro* Anti-Bacterial Activities**

| Bacteria                                               | MIC <sub>90</sub> (μg/mL) |          |            |
|--------------------------------------------------------|---------------------------|----------|------------|
|                                                        | Meropenem                 | Etapenem | Compound 1 |
| Enterococcus faecalis                                  | 4                         | 8        | 2          |
| MRSE                                                   | 2                         | 2        | 2          |
| Klebsiella oxytoca<br>(non-enzyme producing strain)    | 0.125                     | 0.25     | 0.06       |
| Salmonella                                             | 0.125                     | 0.25     | 0.125      |
| Klebsiella pneumoniae<br>(non-enzyme producing strain) | 0.015                     | 0.06     | 0.015      |
| Morganella morganii                                    | 0.125                     | 0.25     | 0.125      |

|                          |       |       |       |
|--------------------------|-------|-------|-------|
| Streptococcus agalactiae | 0.008 | 0.015 | 0.008 |
| Streptococcus pneumoniae | 0.25  | 0.25  | 0.125 |

**Table 3 Comparison of *in vitro* Anti-Bacterial Activities**

| Bacteria                 | MIC ( $\mu\text{g/mL}$ ) |          |            |              |            |
|--------------------------|--------------------------|----------|------------|--------------|------------|
|                          | Meropenem                | Etapenem | Compound 2 | Compound 6   | Compound 7 |
| Enterococcus faecali     | 2                        | 8        | 1          | 1            | 2          |
| Streptococcus pneumoniae | 0.008                    | 0.008    | 0.004      | $\leq 0.002$ | 0.004      |

**Table 4 Comparison of *in vitro* Anti-Bacterial Activities**

| Bacteria                 | MIC ( $\mu\text{g/mL}$ ) |          |            |            |            |
|--------------------------|--------------------------|----------|------------|------------|------------|
|                          | Meropenem                | Etapenem | Compound 4 | Compound 5 | Compound 8 |
| Streptococcus agalactiae | 0.03                     | 0.06     | 0.06       | 0.06       | 0.06       |
| Streptococcus pneumoniae | 0.25                     | 0.5      | 0.125      | 0.125      | 0.125      |
| Streptococcus viridans   | 0.06                     | 0.5      | 0.06       | 0.06       | 0.06       |

**Table 5 Comparison of *in vitro* Anti-Bacterial Activities**

| Bacteria                 | MIC ( $\mu\text{g/mL}$ ) |          |            |            |             |
|--------------------------|--------------------------|----------|------------|------------|-------------|
|                          | Meropenem                | Etapenem | Compound 3 | Compound 9 | Compound 16 |
| MRSE                     | 0.5                      | 2        | 0.5        | —          | —           |
| Streptococcus agalactiae | 0.03                     | 0.25     | 0.03       | —          | —           |
| Enterococcus faecom      | 0.25                     | 0.25     | —          | 0.125      | —           |
| Staphylococcus aureus    | 0.125                    | —        | —          | —          | 0.125       |
| Streptococcus pneumoniae | 0.06                     | —        | —          | —          | 0.06        |

**Table 6 Comparison of *in vitro* Anti-Bacterial Activities**

| Bacteria                 | MIC ( $\mu\text{g/mL}$ ) |          |             |             |             |
|--------------------------|--------------------------|----------|-------------|-------------|-------------|
|                          | Meropenem                | Etapenem | Compound 12 | Compound 13 | Compound 14 |
| Enterococcus faecali     | 2                        | 8        | 1           | —           | —           |
| MSSE                     | 0.06                     | 0.25     | 0.125       | —           | —           |
| Streptococcus pyogenes   | 0.008                    | 0.015    | 0.015       | —           | —           |
| Streptococcus agalactiae | 0.03                     | 0.06     | —           | 0.03        | 0.06        |

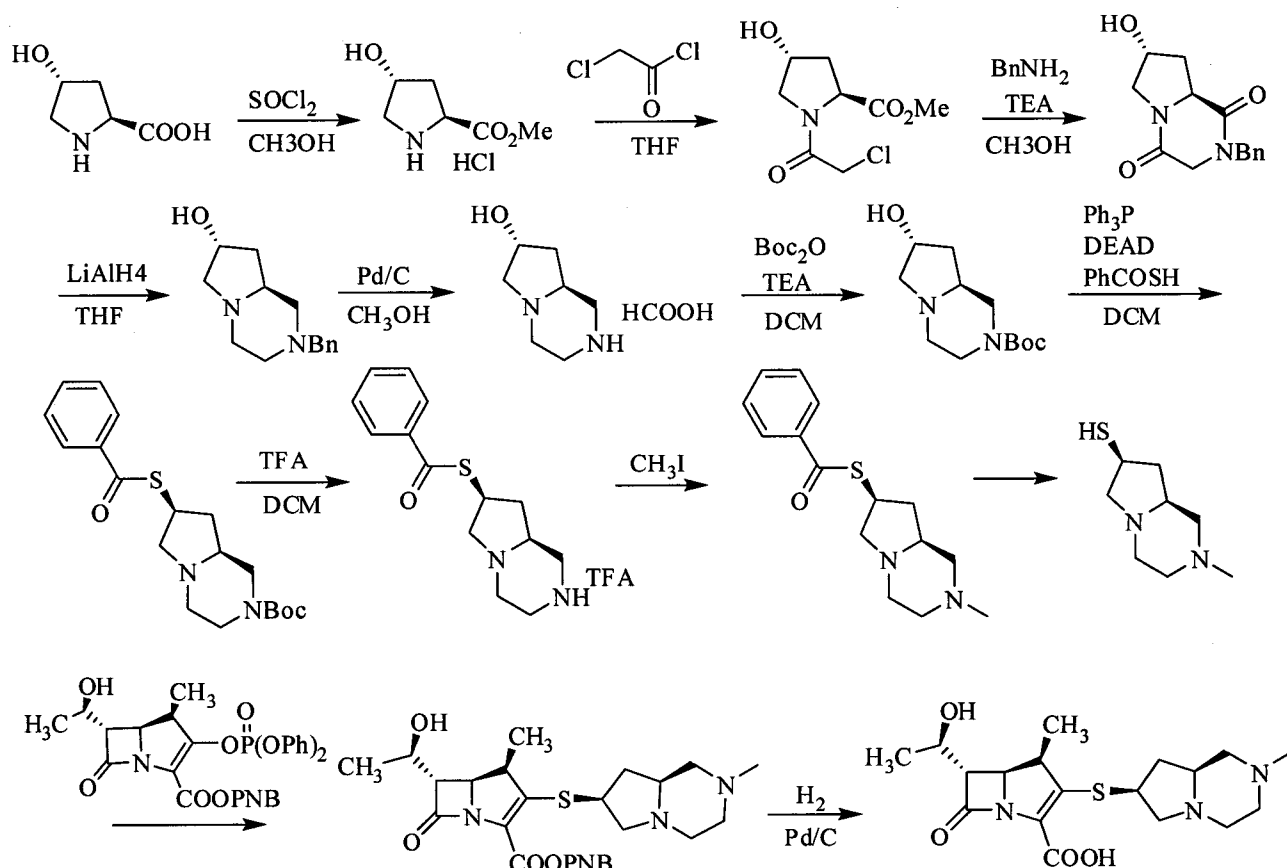
As shown in Tables 2 to 6, the compounds of the invention demonstrate superior or equivalent antibacterial activities against bacteria tested, when compared with meropenem, they are more effective than ertapenem.

#### 4. Examples

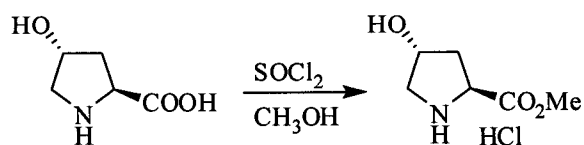
The present invention will be further illustrated with the following examples. However

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 (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-3-[(7*S*,8*aS*)-2-methyl-octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (Compound 1)**

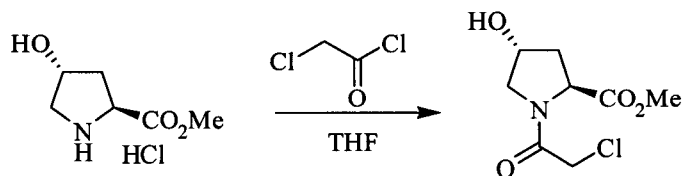


**Setp 1 Preparation of (2*S*,4*R*)-methyl 4-hydroxypyrrolidine-2-carboxylate hydrochloride**



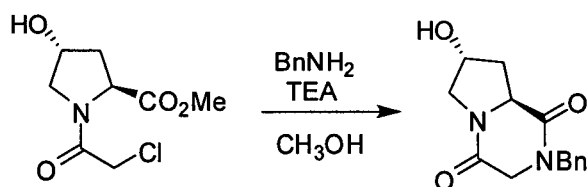
To a solution of (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylic acid (250.4 g, 1.91 mol) in 1.5 L of anhydrous methanol at 0 °C was treated dropwise with thionyl chloride (250.0 g, 2.1 mol). The resulting mixture was heated to reflux for 2 hours. The solvent and excess thionyl chloride was removed under reduced pressure to afford 312.4 g of desired product (90.0% yield).

**Setp 2 Preparation of methyl (2*S*,4*R*)-1-(2-chloroacetyl)-4-hydroxypyrrolidine-2-carboxylate**



To a solution of (2*S*,4*R*)-methyl 4-hydroxypyrrolidine-2-carboxylate hydrochloride (312.4 g, 1.72 mol) in 3.5 L of anhydrous THF at 0 °C in an ice-bath was slowly added chloroacetyl chloride (213.4 g, 1.89 mol). The resulting mixture was heated to reflux for 2 hours. The solvent and excess chloroacetyl chloride was removed under reduced pressure to give desired product 350.2 g (91.9% yield).

**Setp 3 Preparation of (7*R*,8*aS*)-2-benzyl-7-hydroxyhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione**



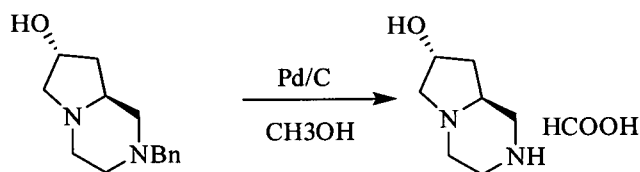
To a solution of (2*S*,4*R*)-methyl 1-(2-chloroacetyl)-4-hydroxypyrrolidine-2-carboxylate (350.2 g, 1.58 mol) in 1.5 L of methanol was sequentially treated with benzylamine (338.6 g, 3.16 mol) and TEA (159.7 g, 1.58 mol). The resulting mixture was heated to reflux for 3 hours. After removing the solvent under reduced pressure, the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic extract was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was further recrystallized from CH<sub>2</sub>Cl<sub>2</sub> to give product 320.2 g (77.8% yield).

**Setp 4 Preparation of (7*R*,8*aS*)-2-benzyl-7-hydroxyhexahydropyrrolo[1,2-*a*]pyrazine-7-ol**



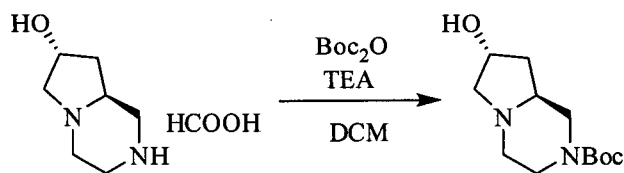
(7*R*,8*aS*)-2-benzyl-7-hydroxyhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (320.2 g, 1.23 mol) was added in portions to a refluxing solution of lithium aluminum hydride (186.7 g, 4.92 mol) in 6.0 L of anhydrous THF. The resulting mixture was maintained at refluxing temperature for another 2 hours. After cooling to 0 °C, the excess lithium aluminum hydride was carefully quenched with water. The reaction mixture was filtered and the filtered cake was washed several times with THF. The combined THF solution was concentrated under reduced pressure and the residue was recrystallized from ethyl acetate to afford desired product 143.8 g (52.8% yield).

### Setp 5 Preparation of (7*R*,8*aS*)-octahydropyrrolo[1,2-*a*]pyrazin-7-ol formate



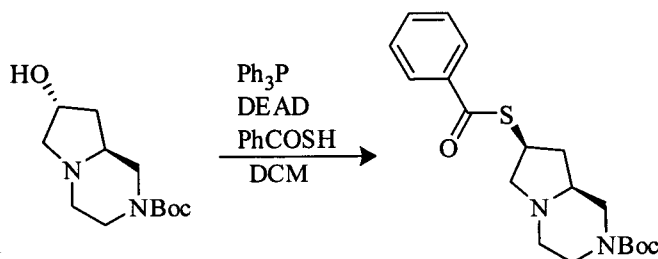
To a solution of (7*R*,8*aS*)-2-benzyl-octahydropyrrolo[1,2-*a*]pyrazin-7-ol (143.8 g, 0.65 mol) in methanol (1.0L) was sequentially added Palladium-on carbon (35.2 g) and formic acid (33.1g, 0.72 mol). The resulting black suspension was stirred at 40 °C for 10 hours under hydrogen pressure (1 atm). The catalyst was removed by filtering through a short pad of Celite and the filtered cake was rinsed with additional methanol. The filtrate was concentrated under reduced pressure to give product 120.4 g (98.5% yield) which was used directly in next step without further purification.

### Setp 6 Preparation of (7*R*,8*aS*)-*tert*-butyl 7-hydroxyhexahydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxylate



To a solution of (7*R*,8*aS*)-octahydropyrrolo[1,2-*a*]pyrazin-7-ol formate (120.4 g, 0.64 mol) in 600 mL of CH<sub>2</sub>Cl<sub>2</sub> was cooled to -10 °C in a salt-ice bath and treated with TEA (135.5 g, 1.34 mol). After stirring for 10 min, di-*tert*-butyl dicarbonate (138.2 g, 0.64 mol) was added to the reaction mixture. The reaction mixture was stirred at -10 °C for 4 hours. The reaction mixture was washed twice with saturated NaHCO<sub>3</sub> solution and one time with brine. The resulting mixture was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give product 135.7 g (87.5% yield).

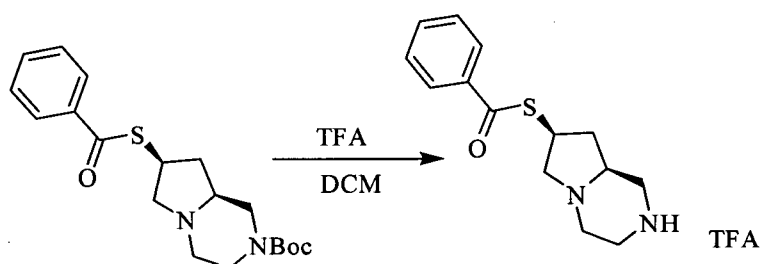
### Setp 7 Preparation of (7*S*,8*aS*)-*tert*-butyl 7-(benzoylthio)hexahydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxylate



Triphenylphosphine (264.9 g, 1.02 mol) in 700 mL of CH<sub>2</sub>Cl<sub>2</sub> was cooled to -10 °C and stirred for 15 min. The resulting solution was treated with DEAD (175.9 g, 1.01 mol) and stirred for 1 hour

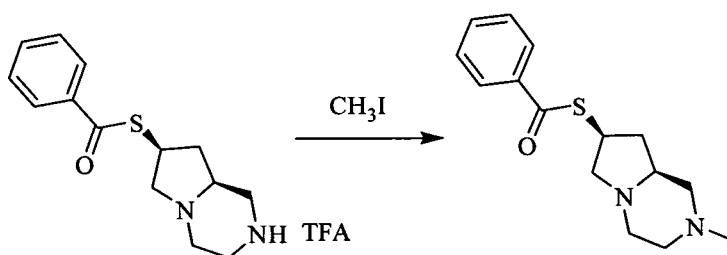
followed by adding thiobenzoic acid (138.8 g, 1.01 mol). The resulting mixture was stirred for additional 1 hour and treated dropwise with (7*R*,8*aS*)-*tert*-butyl 7-hydroxy-hexahydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxylate (135.7 g, 0.56 mol) in 300 mL of CH<sub>2</sub>Cl<sub>2</sub>. The reaction mixture was stirred at -10 °C for 6 hours. The solvent was removed under reduced pressure and the residue was extracted with ethyl acetate. The extract was concentrated and the residue was purified by flash column chromatography on silica gel to give product 137.7 g (67.8% yield).

**Setp 8 Preparation of *S*-(7*S*,8*aS*)-octahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate**



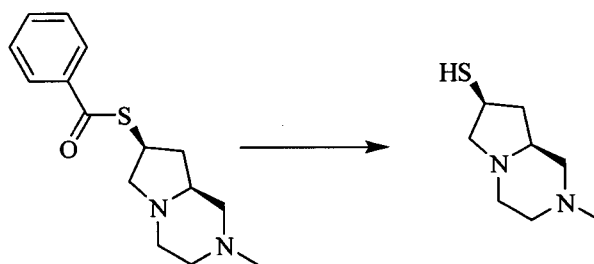
A solution of (7*S*,8*aS*)-*tert*-butyl 7-(benzoylthio)hexahydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxylate (137.7 g, 0.38 mol) in CH<sub>2</sub>Cl<sub>2</sub> (600 mL) was cooled to 0 °C and treated with trifluoroacetic acid (173.3 g, 1.52 mol). The resulting mixture was stirred at 0 °C for 4 hours. The reaction mixture was triturated with diethyl ether and the resulting precipitate was collected by filtration to afford product 89.8 g (86.8% yield).

**Setp 9 Preparation of *S*-(7*S*,8*aS*)-2-methyloctahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate**



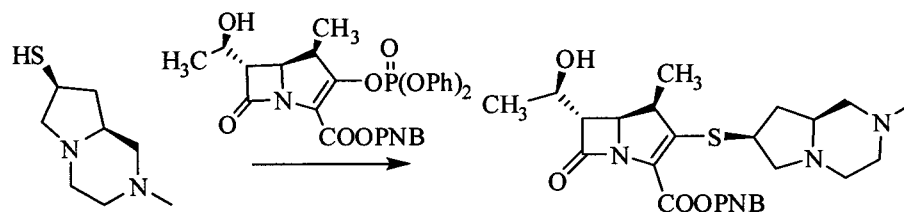
To a solution of *S*-(7*S*,8*aS*)-octahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate (3.59 g, 10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) at 0 °C was treated with TEA (2 g, 20 mmol) and iodomethane (1.42 g, 10 mmol). The resulting mixture was stirred at 0 °C for overnight. The reaction mixture was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to afford crude product which was used directly in next step without further purification.

**Setp 10 Preparation of (7*S*,8*aS*)-2-methyloctahydropyrrolo[1,2-*a*]pyrazine-7-thiol**



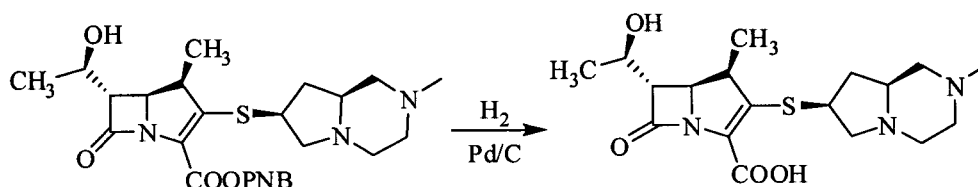
The crude product of previous step was dissolved in methanol and was added to a saturated methanolic KOH solution at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was adjusted to pH=6 to 7 with 1N HCl solution. Methanol was removed and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give product 0.82 g (48%).

**Setp 11 Preparation of 4-nitrobenzyl (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-3-[(7*S*,8*aS*)-2-methyloctahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate**



In a dried reaction flask, 0.52 g of (7*S*,8*aS*)-2-methyloctahydropyrrolo[1,2-*a*]pyrazine-7-thiol (3 mmol) was dissolved in acetonitrile. To this solution was added 4-nitrobenzyl (4*R*,5*R*,6*S*)-3-(diphenoxyphosphoryloxy)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (1.78 g, 3 mmol) and DIEA (0.39 g, 3 mmol). The reaction mixture was stirred at ambient temperature for overnight. The reaction mixture was extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filterd and concentrated under reduced pressure to give crude product 1.39 g (90% yield) which was used directly in next step without further purification.

**Setp 12 Preparation of (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-3-[(7*S*,8*aS*)-2-methyloctahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid**

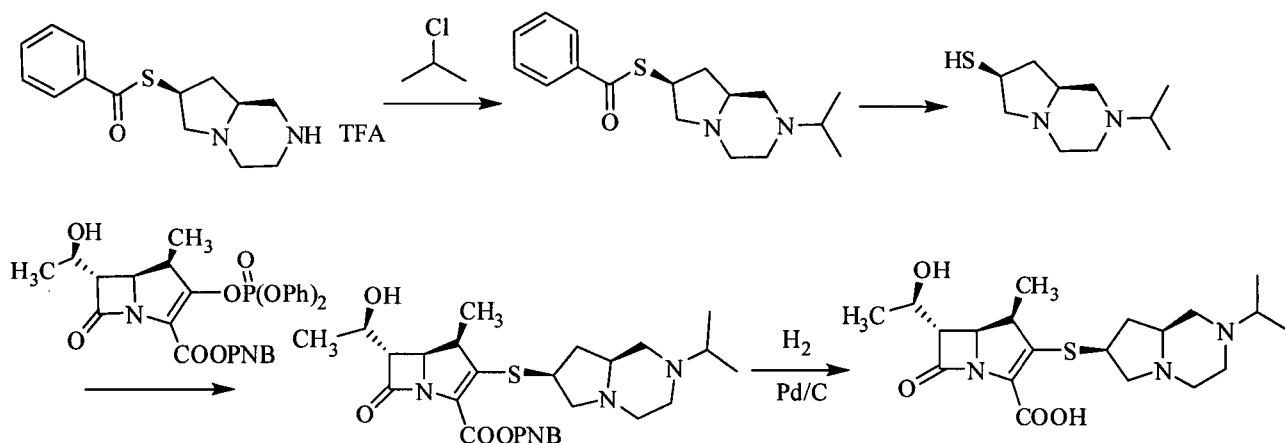


The crude product (3.0 g, 6 mmol) from step 11 was dissolved in a 1:1 mixture of THF and water (20 mL) and 10% Pd/C was added. The resulting black suspension was stirred at ambient temperature under hydrogen pressure for 2 hours. The catalyst was filtered off and rinsed with THF and de-ionized water. The combined filtrate was extracted with ethyl acetate. The product in aqueous layer was purified by prep. HPLC and the product fractions was freeze-dried to give solid product (21 mg, 1% yield).

Formula:  $C_{18}H_{27}N_3O_4S$  Mol.Wt: 381.49 LC-MS: 382 ( $M+H^+$ )

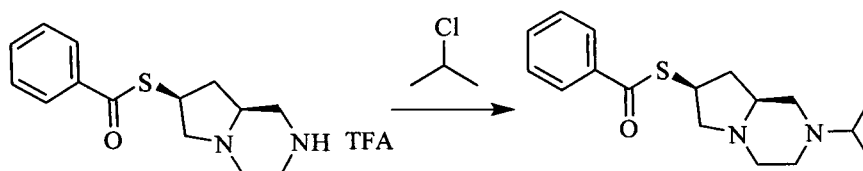
$^1H$  NMR (400MHz,  $D_2O$ ) 4.13 (t, 1H), 4.07 (dd, 1H), 3.67 (t, 1H), 3.29 (dd, 1H), 3.21 (t, 1H), 2.88-2.94 (m, 3H), 2.76 (m, 1H), 2.57 (dd, 1H), 2.28-2.34 (m, 1H), 2.17-2.22 (m, 6H), 1.96 (t, 1H), 1.14-1.22 (m, 4H), 1.08 (d, 3H, ).

**Example 2 Preparation of (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-3-[(7*S*,8*aS*)-2-Isopropyl-octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (Compound 2)**



**Setp 1-8 Procedures were same as step 1-8 in Example 1.**

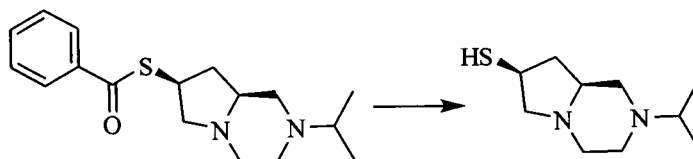
**Setp 9 Preparation of *S*-(7*S*,8*aS*)-2-isopropyloctahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate**



To a solution of *S*-(7*S*,8*aS*)-octahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate (3.59 g, 10 mmol) in  $CH_2Cl_2$  (100 mL) was treated with TEA (2 g, 20 mmol) and 2-chloropropane (0.785 g, 10 mmol). The resulting mixture was stirred at 0 °C for overnight. The reaction mixture was washed with brine, dried over anhydrous  $Na_2SO_4$ , filtered and concentrated under reduced pressure. The

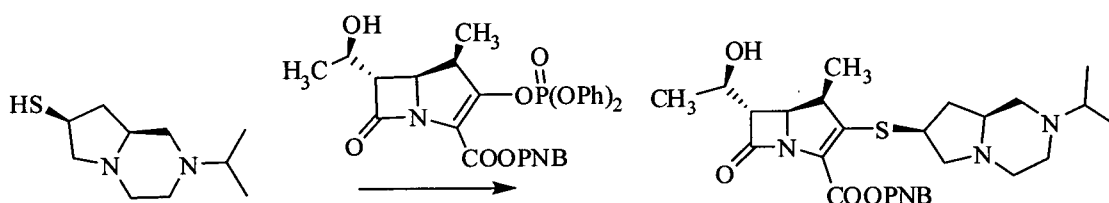
crude residue was used directly in next step without further purification.

**Setp 10 Preparation of (7*S*,8*aS*)-2-isopropyloctahydropyrrolo[1,2-*a*]pyrazine-7-thiol**



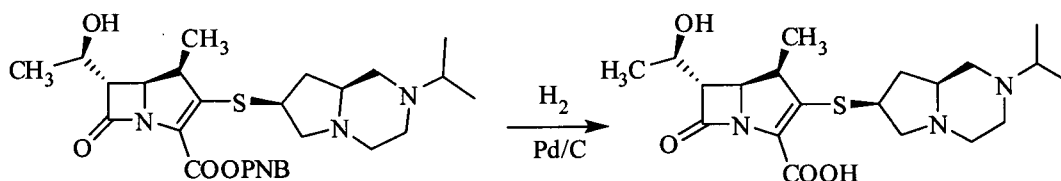
The crude product of previous step was dissolved in methanol and was added to a saturated methanolic KOH solution at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was adjusted to pH=6 to 7 with 1N HCl solution. Methanol was removed and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give product 0.84 g (42%).

**Setp 11 Preparation of 4-nitrobenzyl (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-3-[(7*S*,8*aS*)-2-isopropyloctahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate**



In a dried reaction flask, 0.60 g of (7*S*,8*aS*)-2-isopropyloctahydropyrrolo[1,2-*a*]pyrazine-7-thiol (3 mmol) was dissolved in acetonitrile. To this solution was added 4-nitrobenzyl (4*R*,5*R*,6*S*)-3-(diphenoxyphosphoryloxy)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (1.78 g, 3 mmol) and DIEA (0.39 g, 3 mmol). The reaction mixture was stirred at ambient temperature for overnight. The reaction mixture was extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product 1.30 g (80% yield) which was used directly in next step without further purification.

**Setp 12 Preparation of (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-3-[(7*S*,8*aS*)-2-isopropyloctahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid**



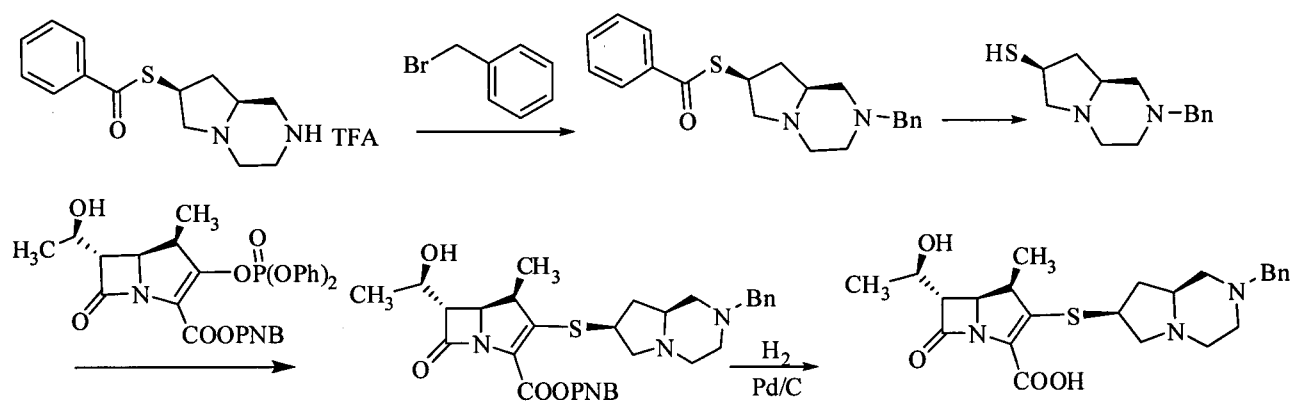
The crude product (2.0 g, 3.68 mmol) from step 11 of Example 2 was dissolved in a 1:1

mixture of THF and water (20 mL) and 10% Pd/C (1 g) was added. The resulting black suspension was stirred at ambient temperature under hydrogen pressure for 2 hours. The catalyst was filtered off and rinsed with THF and de-ionized water. The combined filtrate was extracted with ethyl acetate. The product in aqueous layer was purified by prep. HPLC and the product fractions was freeze-dried to give solid product (70 mg, 4.6% yield).

Formula:  $C_{20}H_{31}N_3O_4S$  Mol.Wt: 409.54 LC-MS: 410(M+H<sup>+</sup>)

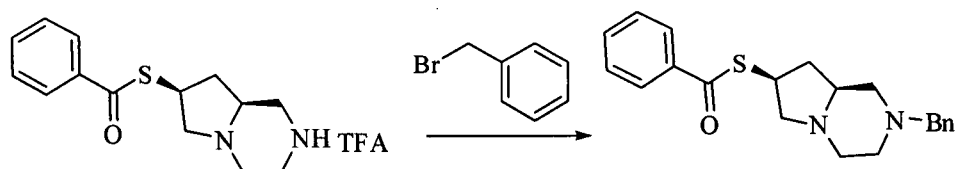
<sup>1</sup>H NMR (400MHz, D<sub>2</sub>O) 4.05-4.15 (m, 2H), 3.73 (t, 1H), 3.54 (d, 1H), 3.37-3.47 (m, 2H), 3.29 (dd, 1H), 3.14-3.23 (m, 2H), 2.94-3.01 (m, 2H), 2.78 (t, 1H), 2.65-2.69 (m, 1H), 2.40-2.48 (m, 3H), 1.22-1.31 (m, 7H), 1.17 (d, 3H), 1.08 (d, 3H).

**Example 3 Preparation of (4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-benzyl-octahydropyrrolo[1,2-*a*]-pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (Compound 3)**



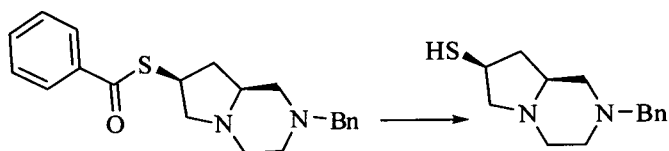
**Setp 1-8** Procedures were same as step 1-8 in Example 1.

**Setp 9 Preparation of *S*-(7*S*,8*aS*)-2-benzyl-octahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate**



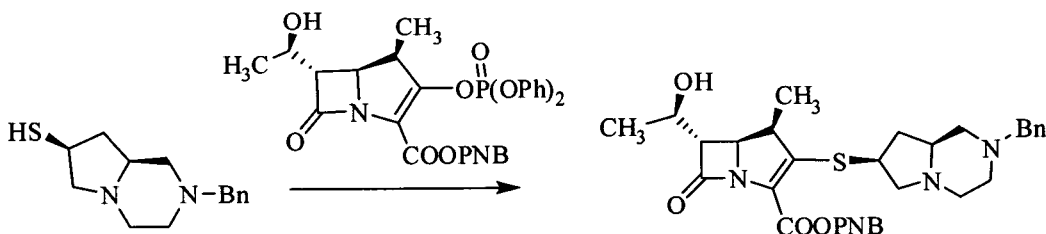
To a solution of *S*-(7*S*,8*aS*)-octahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate (3.59 g, 10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was treated with TEA (2 g, 20 mmol) and benzyl bromide (1.71 g, 10 mmol). The resulting mixture was stirred at 0 °C for overnight. The reaction mixture was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude residue was used directly in next step without further purification.

**Setp 10 Preparation of (7*S*,8*aS*)-2-benzyl-octahydropyrrolo[1,2-*a*]pyrazine-7-thiol**



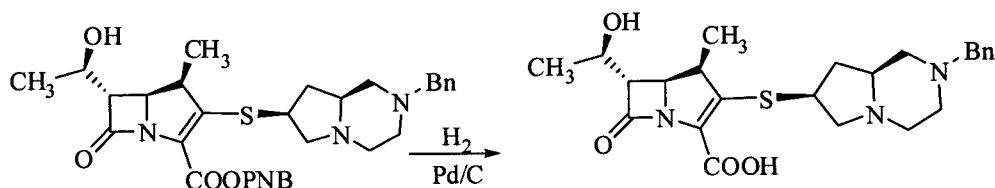
The crude product of previous step was dissolved in methanol and was added to a saturated methanolic KOH solution at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was adjusted to pH=6 to 7 with 1N HCl solution. Methanol was removed and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give product (7*S*,8*aS*)-2-benzyl-octahydropyrrolo[1,2-*a*]pyrazine-7-thiol (1.31 g, 53%).

**Setp 11 Preparation of 4-nitrobenzyl (4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-benzyl-octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate**



In a dried reaction flask, 0.74 g of (7*S*,8*aS*)-2-benzyl-octahydropyrrolo[1,2-*a*]pyrazine-7-thiol (3 mmol) was dissolved in acetonitrile. To this solution was added 4-nitrobenzyl (4*R*,5*R*,6*S*)-3-(diphenoxyphosphoryloxy)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (1.78 g, 3 mmol) and DIEA (0.39 g, 3 mmol). The reaction mixture was stirred at ambient temperature for overnight. The reaction mixture was extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product 1.56 g (88% yield) which was used directly in next step without further purification.

**Setp 12 Preparation of (4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-benzyl-octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid**



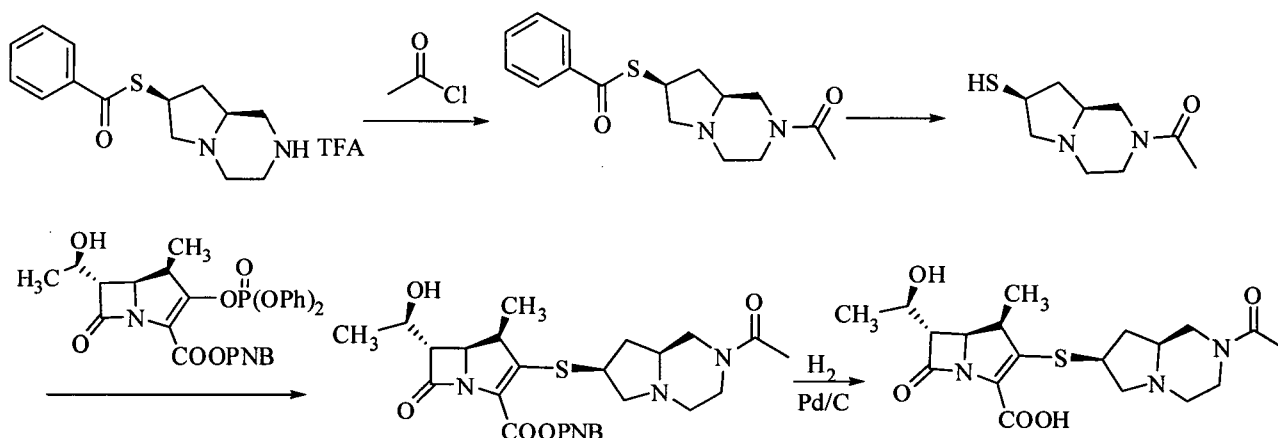
The crude product (0.59 g, 1.0 mmol) from step 11 of Example 3 was dissolved in a 1:1 mixture of THF and water (20 mL) and 10% Pd/C (1 g) was added. The resulting black suspension

was stirred at ambient temperature under hydrogen pressure for 2 hours. The catalyst was filtered off and rinsed with THF and de-ionized water. The combined filtrate was extracted with ethyl acetate. The product in aqueous layer was purified by prep. HPLC and the product fractions was freeze-dried to give solid product (70 mg, 4.6% yield).

Formula:  $C_{24}H_{31}N_3O_4S$  Mol.Wt: 457.59 LC-MS: 458(M+H<sup>+</sup>)

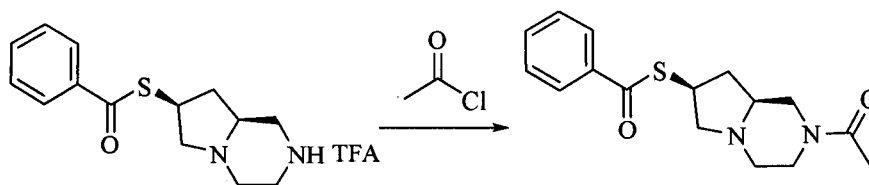
<sup>1</sup>H NMR (400MHz, DLC-MSO-d<sub>6</sub>) 7.24-7.33 (m, 5H),  $\delta$  5.01(s,1H), 4.11-4.12(m, 1H), 4.09-4.10 (m, 1H), 3.91-3.95 (m, 1H), 3.45-3.56 (d,  $J=13.2$ Hz, 2H), 3.23-3.27 (m, 1H), 3.15-3.17 (m, 1H), 3.15-3.17 (m, 1H), 3.15-3.17 (m, 1H), 2.85-2.91 (m, 3H), 2.70-2.72(m, 1H), 2.50-2.52 (m, 1H), 2.11-2.15 (m, 1H), 2.07-2.11 (m, 3H), 1.79-1.82 (m, 1H), 1.07-1.48 (m, 6H).

**Example 4 Preparation of (4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-acetyloctahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (Compound 4)**



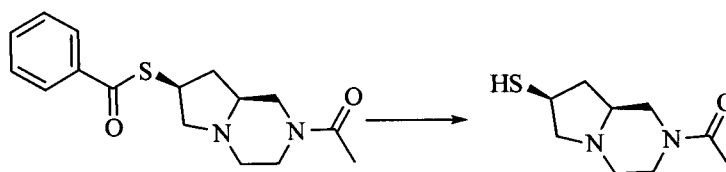
**Setp 1-8 Procedures were same as step 1-8 in Example 1.**

**Setp 9 Preparation of *S*-(7*S*,8*aS*)-2-acetyloctahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate**



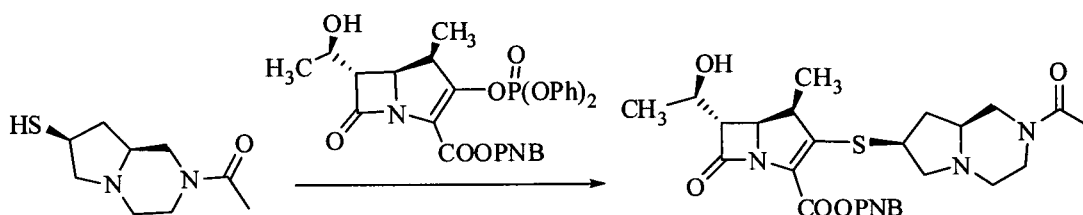
To a solution of *S*-(7*S*,8*aS*)-octahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate (3.59 g, 10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was treated with TEA (2 g, 20 mmol) and acetyl chloride (0.78 g, 10 mmol). The resulting mixture was stirred at 0 °C for 2 hours. The reaction mixture was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude residue was used directly in next step without further purification.

**Setp 10 Preparation of 1-[(7*S*,8*aS*)-7-mercaptohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]ethanone**



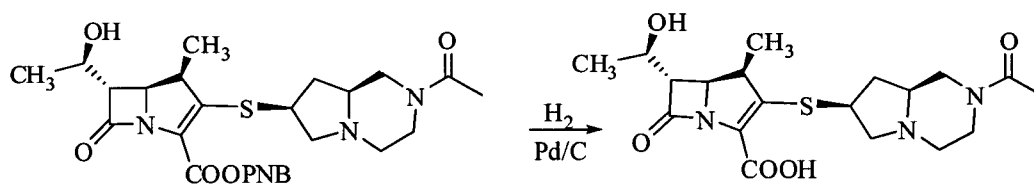
The crude product of previous step was dissolved in methanol and was added to a saturated methanolic KOH solution at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was adjusted to pH=6 to 7 with 1N HCl solution. Methanol was removed and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give product 1-[(7*S*,8*aS*)-7-mercaptohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]ethanone (1.06 g, 53%).

**Setp 11 Preparation of 4-nitrobenzyl (4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-acetyloctahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate**



In a dried reaction flask, 0.6 g of (7*S*,8*aS*)-2-acetyloctahydropyrrolo[1,2-*a*]pyrazine-7-thiol (3 mmol) was dissolved in acetonitrile. To this solution was added 4-nitrobenzyl (4*R*,5*R*,6*S*)-3-(diphenoxyphosphoryloxy)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (1.78 g, 3 mmol) and DIEA (0.39 g, 3 mmol). The reaction mixture was stirred at ambient temperature for overnight. The reaction mixture was extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product 1.43 g (88% yield) which was used directly in next step without further purification.

**Setp 12 Preparation of (4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-acetyloctahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid**



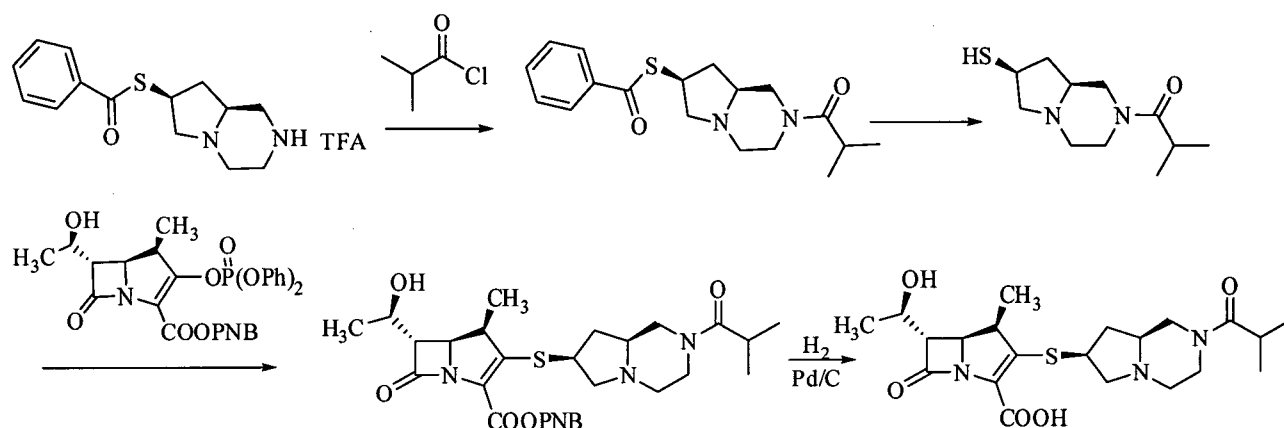
The crude product (0.7 g, 1.28 mmol) from step 11 of Example 4 was dissolved in a 1:1 mixture of THF and water (20 mL) and 10% Pd/C (0.3 g) was added. The resulting black suspension was stirred at ambient temperature under hydrogen pressure for 2 hours. The catalyst was filtered off and rinsed with THF and de-ionized water. The combined filtrate was extracted with ethyl acetate. The product in aqueous layer was purified by prep. HPLC and the product fractions was freeze-dried to give solid product (47 mg, 9.0% yield).

Due to the amide bond on the octahydropyrrolo[1,2-*a*]-pyrazine ring, <sup>1</sup>H NMR exhibits two conformers.

Formula: C<sub>19</sub>H<sub>27</sub>N<sub>3</sub>O<sub>5</sub>S Mol.Wt: 409.50 LC-MS: 410(M+H<sup>+</sup>)

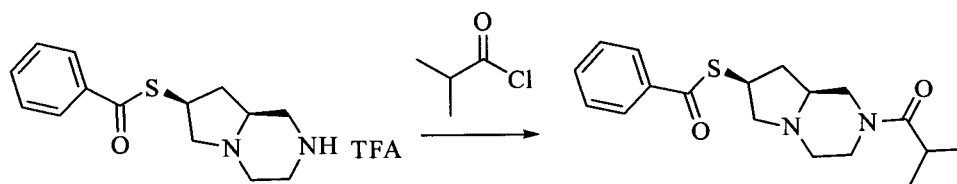
<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ 4.42 (d, 0.5H), δ 4.27 (d, 0.5H), δ 4.07-4.15 (m, 2H), δ 3.97 (d, 0.5H), δ 3.81 (d, 0.5H), δ 3.67-3.71 (m, 1H), δ 3.31 (d, 1H), δ 3.17-3.24 (m, 1.5H), δ 2.90-2.99 (m, 2.5H), δ 2.72 (t, 0.5H), δ 2.61 (t, 1H), δ 2.48 (t, 0.5H), δ 2.33-2.39 (m, 1H), δ 2.10-2.22 (m, 1H), δ 2.03-2.13 (m, 1H), δ 2.04 (d, 3H), δ 1.17-1.27 (m, 4H), δ 1.09 (d, 3H).

**Example 5 Preparation of (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-3-[(7*S*,8*aS*)-2-isobutyryl-octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (Compound 5)**



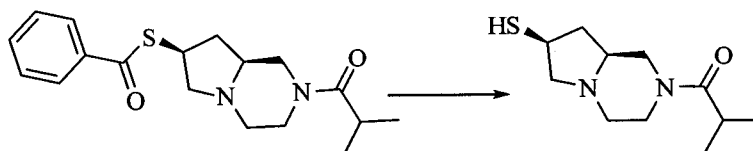
**Step 1-8 Procedures were same as step 1-8 in Example 1.**

**Step 9 Preparation of *S*-(7*S*,8*aS*)-2-isobutyryloctahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate**



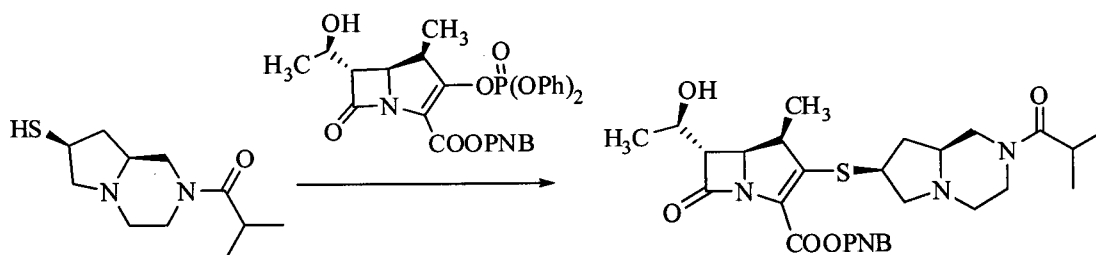
To a solution of *S*-(7*S*,8*aS*)-octahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate (3.59 g, 10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was treated with TEA (2 g, 20 mmol) and isobutyryl chloride (1.07 g, 10 mmol). The resulting mixture was stirred at 0 °C for 2 hours. The reaction mixture was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude residue was used directly in next step without further purification.

**Setp 10 Preparation of 1-[(7*S*,8*aS*)-7-mercaptohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-2-methylpropan-1-one**



The crude product of previous step was dissolved in methanol and was added to a saturated methanolic KOH solution at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was adjusted to pH=6 to 7 with 1N HCl solution. Methanol was removed and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give product (1.41 g, 62%).

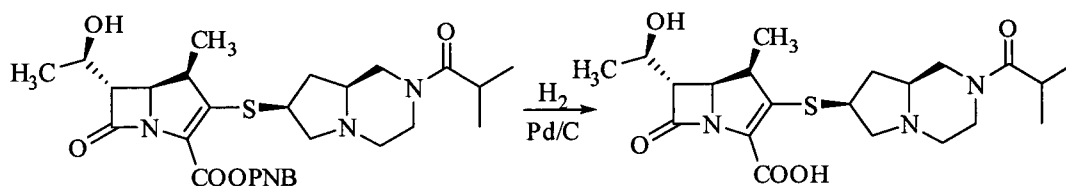
**Setp 11 Preparation of 4-nitrobenzyl (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-3-[(7*S*,8*aS*)-2-isobutyryloctahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate**



In a dried reaction flask, 0.68 g of 1-[(7*S*,8*aS*)-7-mercaptohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-2-methylpropan-1-one (3 mmol) was dissolved in acetonitrile. To this solution was added 4-nitrobenzyl (4*R*,5*R*,6*S*)-3-(diphenoxyposphoryloxy)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate (1.78 g, 3 mmol) and DIEA (0.39 g, 3 mmol). The reaction mixture was stirred at ambient temperature for overnight. The reaction mixture was

extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give crude product 1.51 g (88% yield) which was used directly in next step without further purification.

**Setp 12 Preparation of (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-3-[(7*S*,8*aS*)-2-isobutyryloctahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid**



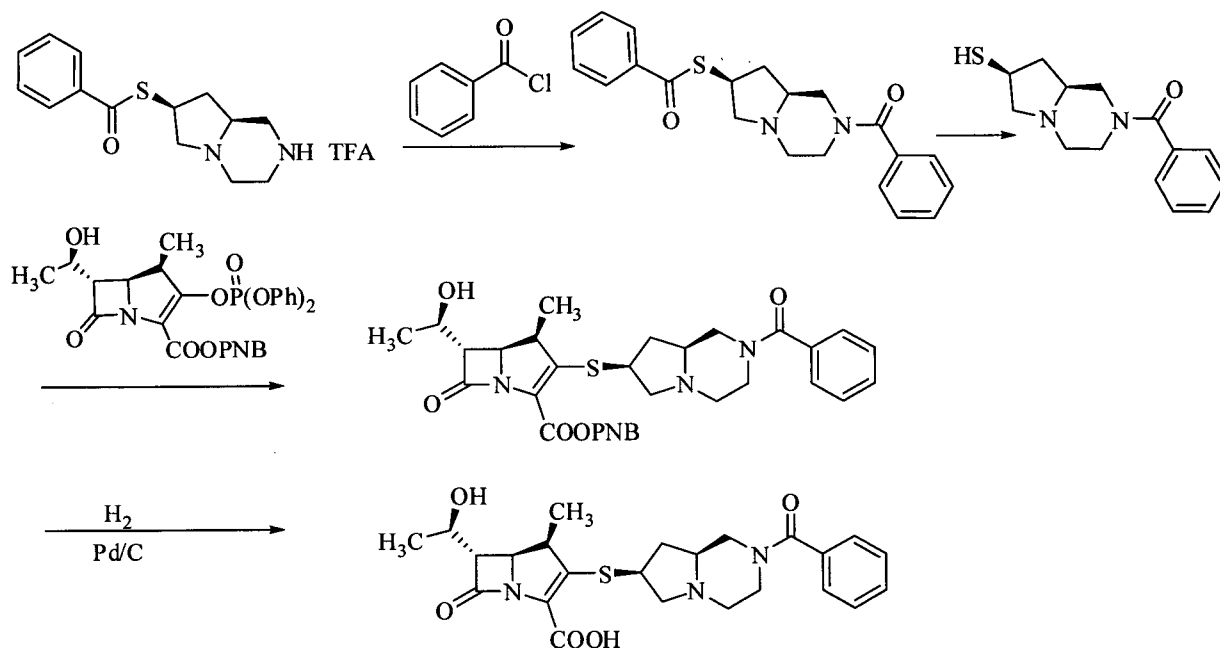
The crude product (2.0 g, 3.5 mmol) from step 11 of Example 5 was dissolved in a 1:1 mixture of THF and water (20 mL) and 10% Pd/C (1.0 g) was added. The resulting black suspension was stirred at ambient temperature under hydrogen pressure for 2 hours. The catalyst was filtered off and rinsed with THF and de-ionized water. The combined filtrate was extracted with ethyl acetate. The product in aqueous layer was purified by prep. HPLC and the product fractions was freeze-dried to give solid product 52 mg (3.4% yield).

Due to the amide bond on the octahydropyrrolo[1,2-*a*]-pyrazine ring,  $^1\text{H}$  NMR exhibits two conformers.

Formula:  $\text{C}_{21}\text{H}_{31}\text{N}_3\text{O}_5\text{S}$  Mol.Wt: 437.55 LC-MS: 438( $\text{M}+\text{H}^+$ )

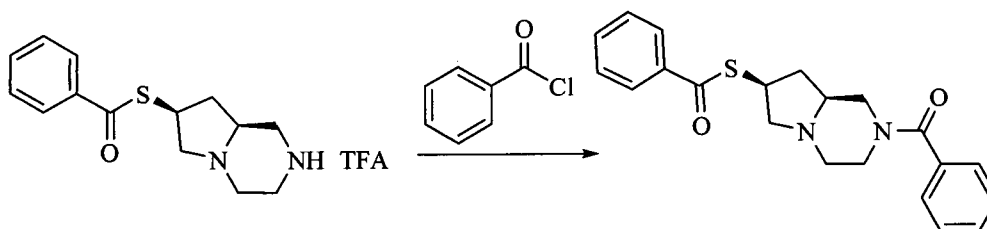
$^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ )  $\delta$  4.44 (d, 0.5H),  $\delta$  4.31 (d, 0.5H),  $\delta$  4.04-4.14 (m, 2.5H),  $\delta$  3.96 (d, 0.5H),  $\delta$  3.65-3.67 (m, 1 H),  $\delta$  3.27 (dd, 1H),  $\delta$  3.16-3.21 (m, 1.5H),  $\delta$  2.86-2.96 (m, 3.5H),  $\delta$  2.67 (t, 0.5H),  $\delta$  2.58 (t, 1H),  $\delta$  2.44 (t, 0.5H),  $\delta$  2.31-2.38 (m, 1H),  $\delta$  2.12-2.26 (m, 1H),  $\delta$  2.04-2.08 (m, 1H),  $\delta$  1.15-1.24 (m, 4H),  $\delta$  1.07 (d, 3H),  $\delta$  0.91-0.96 (m, 6H).

**Example 6 Preparation of (4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-benzoyloctahydropyrrolo[1,2-*a*]-pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (Compound 6)**



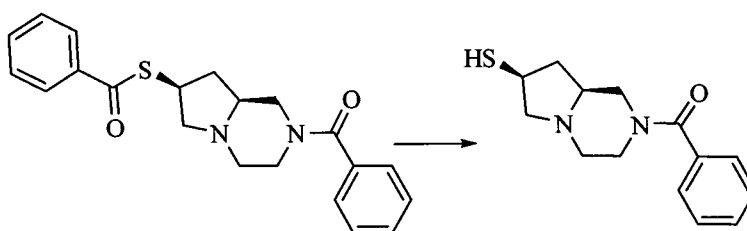
**Setp 1-8** Procedures were same as step 1-8 in Example 1.

**Setp 9** Preparation of *S*-(7*S*,8*aS*)-2-benzoyloctahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate



To a solution of *S*-(7*S*,8*aS*)-octahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate (3.59 g, 10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was treated with TEA (2 g, 20 mmol) and benzoyl chloride (1.4 g, 10 mmol). The resulting mixture was stirred at 0 °C for 2 hours. The reaction mixture was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude residue was used directly in next step without further purification.

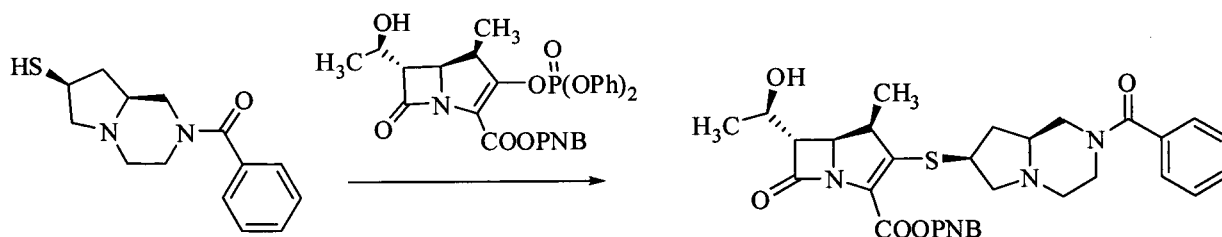
**Setp 10** Preparation of [(7*S*,8*aS*)-7-mercaptohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl](phenyl)methanone



The crude product of previous step was dissolved in methanol and was added to a saturated methanolic KOH solution at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. The reaction

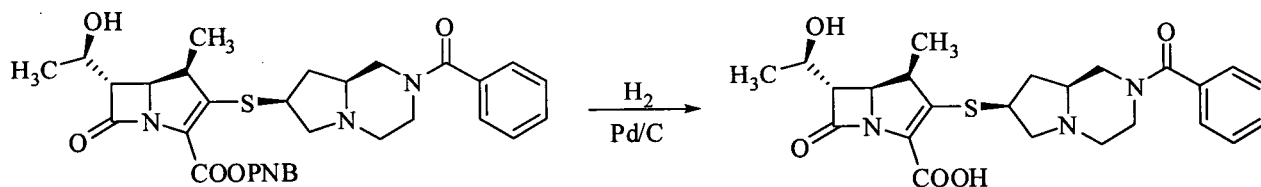
mixture was adjusted to pH=6 to 7 with 1N HCl solution. Methanol was removed and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give product (1.86 g, 71%).

**Setp 11 Preparation of 4-nitrobenzyl (4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-benzoyloctahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate**



In a dried reaction flask, 0.78 g of ((7*S*,8*aS*)-7-mercaptohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)(phenyl)methanone (3 mmol) was dissolved in acetonitrile. To this solution was added 4-nitrobenzyl (4*R*,5*R*,6*S*)-3-(diphenoxyphosphoryloxy)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate (1.78 g, 3 mmol) and DIEA (0.39 g, 3 mmol). The reaction mixture was stirred at ambient temperature for overnight. The reaction mixture was extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product 1.32 g (73% yield) which was used directly in next step without further purification.

**Setp 12 Preparation of (4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-benzoyloctahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid**



The crude product (0.8 g, 1.32 mmol) from step 11 of Example 6 was dissolved in a 1:1 mixture of THF and water (20 mL) and 10% Pd/C (0.4 g) was added. The resulting black suspension was stirred at ambient temperature under hydrogen pressure for 2 hours. The catalyst was filtered off and rinsed with THF and de-ionized water. The combined filtrate was extracted with ethyl acetate. The product in aqueous layer was purified by prep. HPLC and the product fractions was freeze-dried to give solid product 55 mg (8.7% yield).

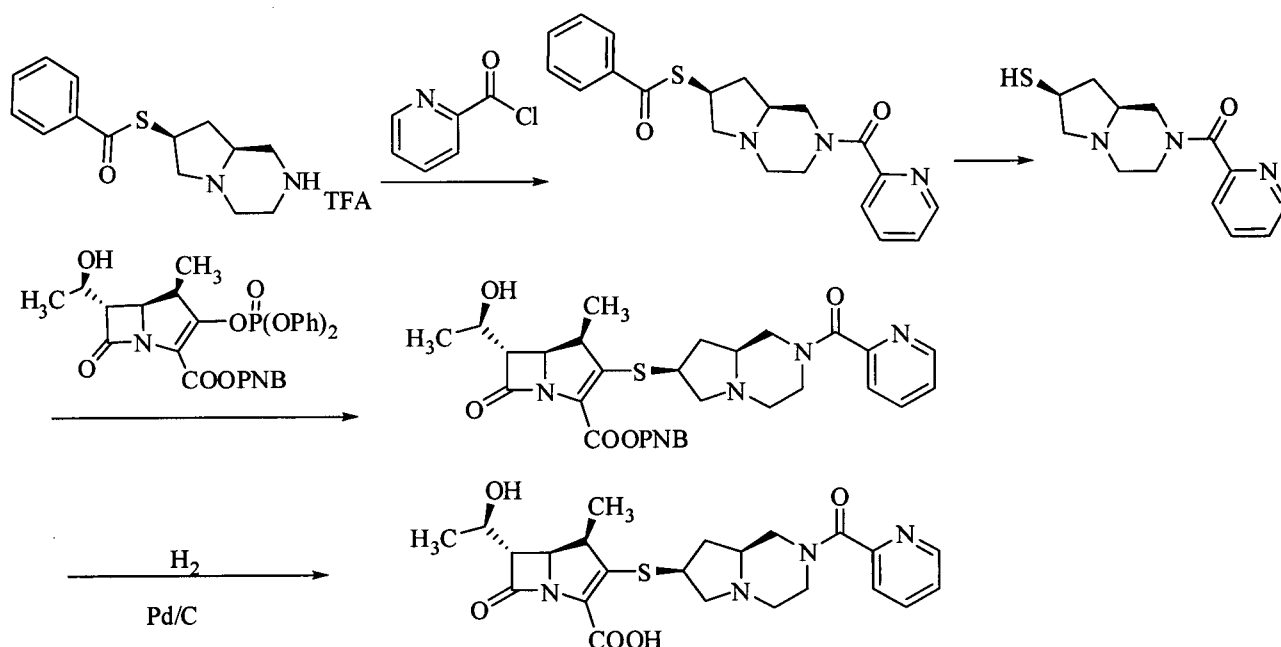
Due to the amide bond on the octahydropyrrolo[1,2-*a*]pyrazine ring, <sup>1</sup>H NMR exhibits two

conformers.

Formula: C<sub>24</sub>H<sub>29</sub>N<sub>3</sub>O<sub>5</sub>S Mol.Wt: 471.57 LC-MS: 472(M+H<sup>+</sup>)

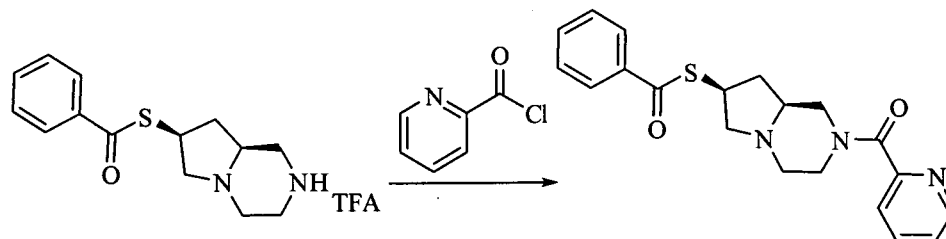
<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) 7.39-7.45 (m, 3H), 7.31-7.34 (m, 2H), 4.58 (d, 0.5H), 4.44 (d, 0.5H), 4.13 (t, 1H), 4.07 (dd, 1H), 3.61-3.74 (m, 2H), 3.28-3.32 (m, 1H), 2.93-3.20 (m, 2.5H), 2.86 (d, 0.5H), 2.82 (d, 0.5H), 2.68 (t, 0.5H), 2.62 (t, 1H), 2.39 (m, 0.5H), 2.14-2.27 (m, 2.5H), 1.25-1.35 (m, 0.5H), 1.18 (d, 3H), 1.05-1.11 (m, 3.5H).

**Example 7 Preparation of (4R,5S,6S)-6-[(R)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(7S,8aS)-2-picolinoyloctahydropyrrolo[1,2-a]pyrazin-7-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (Compound 7)**



**Setp 1-8** Procedures were same as step 1-8 in Example 1.

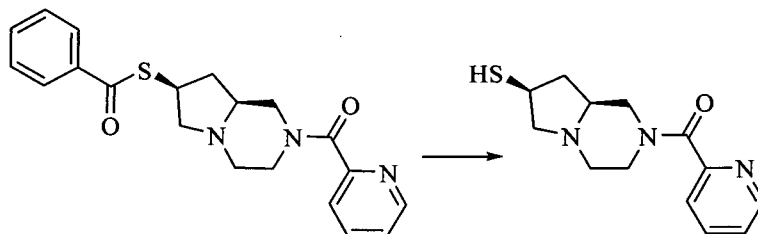
**Setp 9 Preparation of S-(7S,8aS)-2-picolinoyloctahydropyrrolo[1,2-a]pyrazin-7-yl benzothioate**



To a solution of S-(7S,8aS)-octahydropyrrolo[1,2-a]pyrazin-7-yl benzothioate (3.59 g, 10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was treated with TEA (2 g, 20 mmol) and benzoyl chloride (1.4 g, 10 mmol). The resulting mixture was stirred at 0 °C for 2 hours. The reaction mixture was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude

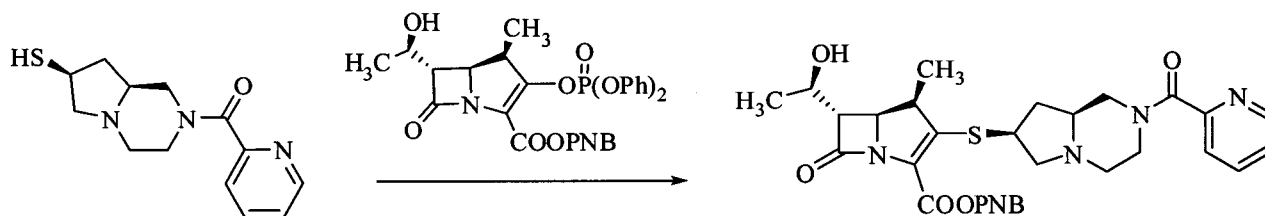
residue was used directly in next step without further purification.

**Setp 10 Preparation of [(7*S*,8*aS*)-7-mercaptohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl](pyridin-2-yl)methanone**



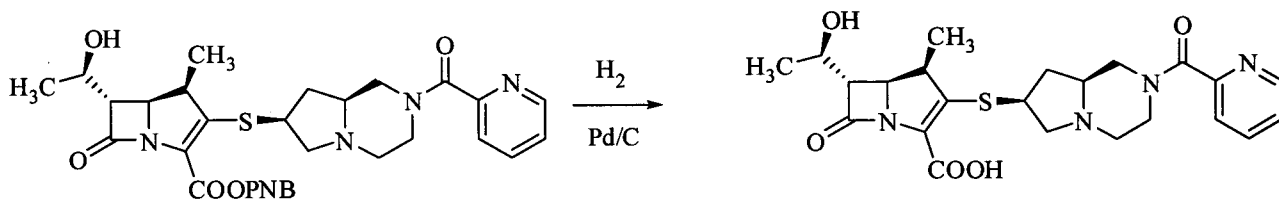
The crude product of previous step was dissolved in methanol and was added to a saturated methanolic KOH solution at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was adjusted to pH=6 to 7 with 1N HCl solution. Methanol was removed and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give product (2.23 g, 85%).

**Setp 11 Preparation of 4-nitrobenzyl (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(7*S*,8*aS*)-2-picolinoyloctahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate**



In a dried reaction flask, 0.79 g of [(7*S*,8*aS*)-7-mercaptohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl](pyridin-2-yl)methanone (3 mmol) was dissolved in acetonitrile. To this solution was added 4-nitrobenzyl (4*R*,5*R*,6*S*)-3-(diphenoxyphosphoryloxy)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate (1.78 g, 3 mmol) and DIEA (0.39 g, 3 mmol). The reaction mixture was stirred at ambient temperature for overnight. The reaction mixture was extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product 1.33 g (73% yield) which was used directly in next step without further purification.

**Setp 12 Preparation of (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(7*S*,8*aS*)-2-picolinoyloctahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid**



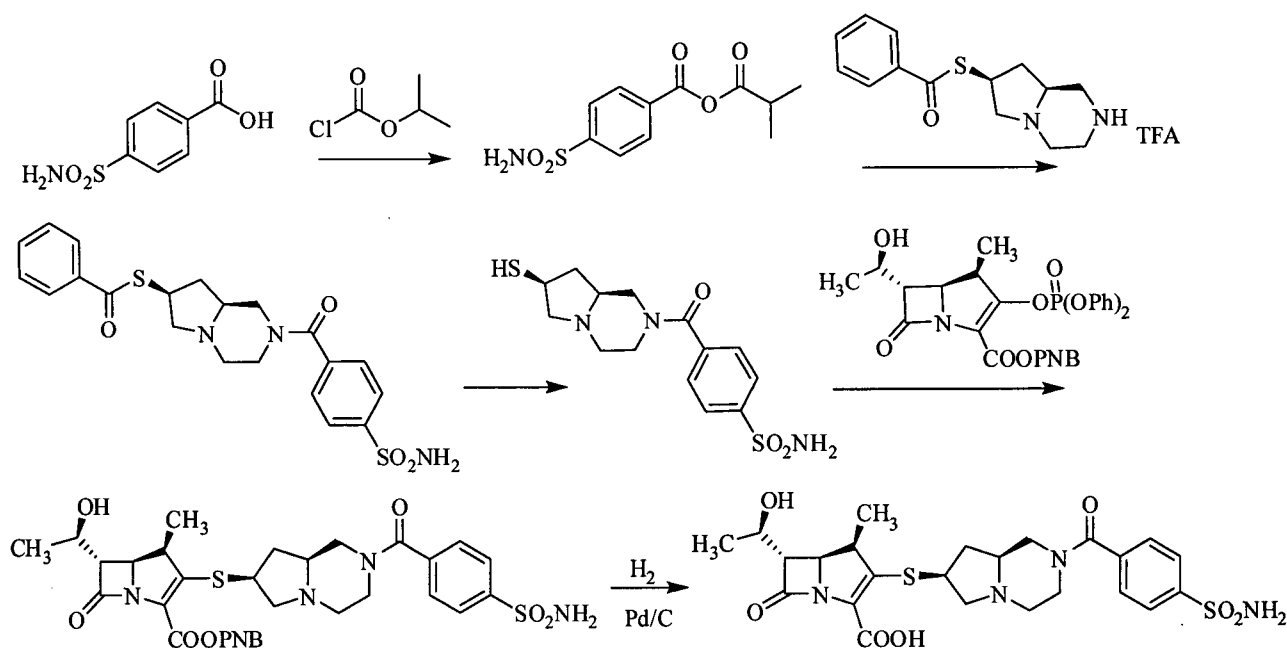
The crude product (0.8 g, 1.32 mmol) from step 11 of Example 7 was dissolved in a 1:1 mixture of THF and water (20 mL) and 10% Pd/C (0.4 g) was added. The resulting black suspension was stirred at ambient temperature under hydrogen pressure for 2 hours. The catalyst was filtered off and rinsed with THF and de-ionized water. The combined filtrate was extracted with ethyl acetate. The product in aqueous layer was purified by prep. HPLC and the product fractions was freeze-dried to give solid product 50 mg (8.2% yield).

Due to the amide bond on the octahydropyrrolo[1,2-*a*]-pyrazine ring, <sup>1</sup>H NMR exhibits two conformers.

Formula: C<sub>23</sub>H<sub>28</sub>N<sub>4</sub>O<sub>5</sub>S Mol.Wt: 472.56 LC-MS: 473(M+H<sup>+</sup>)

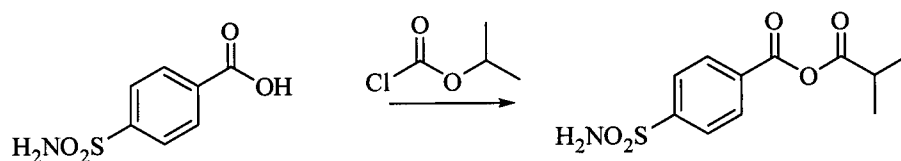
<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) 8.46 (d, 1H), 7.89 (t, 1H), 7.40-7.47 (m, 2H), 4.58 (d, 0.5H), 4.41 (d, 0.5H), 4.04-4.13 (m, 2H), 3.61-3.71 (m, 1.5H), 3.46 (d, 0.5H), 3.26-3.30 (m, 1H), 3.13-3.22 (m, 1.5H), 2.90-3.07 (m, 2.5H), 2.69 (d, 0.5H), 2.59 (t, 0.5H), 2.58-2.65 (m, 1H), 2.39-2.43 (m, 0.5H), 2.12-2.26 (m, 2.5H), 1.23-1.32 (m, 0.5H), 1.16 (d, 3H), 1.04-1.10 (m, 3.5H).

**Example 8 Preparation of (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(7*S*,8*aS*)-2-(4-sulfamoylbenzoyl)octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (Compound 8)**



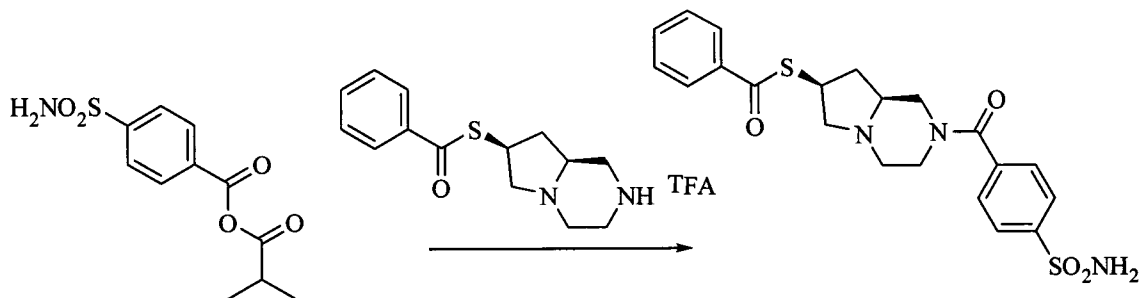
**Step 1-8 Procedures were same as step 1-8 in Example 1.**

### Setp 9 Preparation of isobutyric 4-sulfamoylbenzoic anhydride



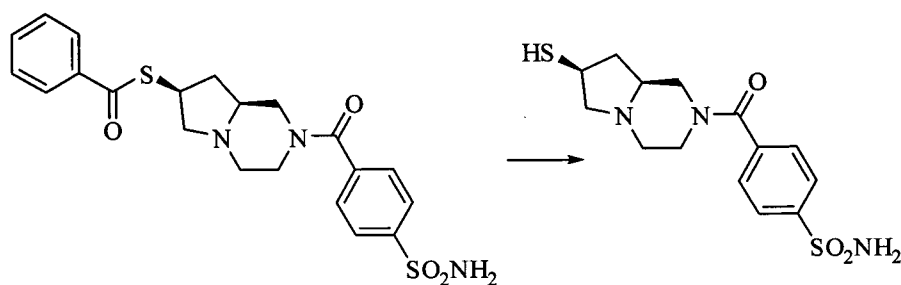
To a solution of 4-sulfamoylbenzoic acid (11.2 g, 56 mmol) in  $\text{CH}_2\text{Cl}_2$  was cooled to  $-10^\circ\text{C}$  and treated with TEA (12.5 g, 124 mmol) followed by dropwise addition of isobutylchloroformate (11.5 g, 93 mmol). The resulting mixture was stirred for 2 hours at  $-10^\circ\text{C}$ . The reaction mixture was washed with water and the organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give product 7.28 g (48% yield).

### Setp 10 Preparation of *S*-(7*S*,8*aS*)-2-(4-sulfamoylbenzoyl)octahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate



To a solution of *S*-(7*S*,8*aS*)-octahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate (3.59 g, 10 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) was treated with TEA (2 g, 20 mmol) and isobutyric 4-sulfamoylbenzoic anhydride (2.71 g, 10 mmol). The resulting mixture was stirred at  $0^\circ\text{C}$  for 2 hours. The reaction mixture was washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The crude residue was used directly in next step without further purification.

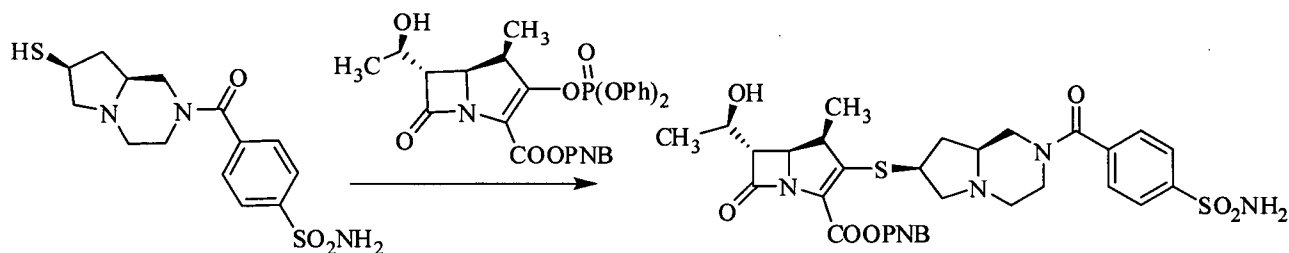
### Setp 11 Preparation of 4-[(7*S*,8*aS*)-7-mercaptooctahydropyrrolo[1,2-*a*]pyrazine-2-carbonyl]benzenesulfonamide



The crude product of previous step was dissolved in methanol and was added to a saturated methanolic KOH solution at  $0^\circ\text{C}$ . The reaction mixture was stirred at  $0^\circ\text{C}$  for 2 hours. The reaction

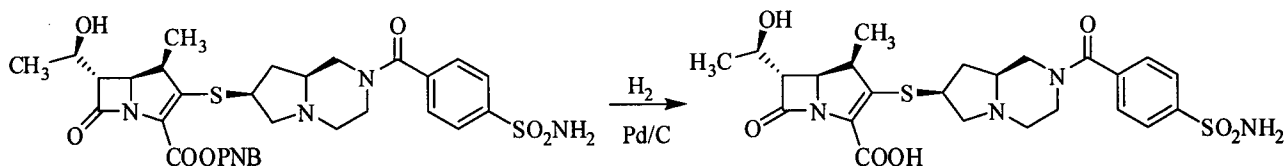
mixture was adjusted to pH=6 to 7 with 1N HCl solution. Methanol was removed and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give product (2.45 g, 72%).

**Setp 12 Preparation of 4-nitrobenzyl (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(7*S*,8*aS*)-2-(4-sulfamoylbenzoyl)octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate**



In a dried reaction flask, 0.79 g of 4-[(7*S*,8*aS*)-7-mercaptooctahydropyrrolo[1,2-*a*]pyrazine-2-carbonyl]benzenesulfonamide (3 mmol) was dissolved in acetonitrile. To this solution was added 4-nitrobenzyl (4*R*,5*R*,6*S*)-3-(diphenoxyphosphoryloxy)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (1.78 g, 3 mmol) and DIEA (0.39 g, 3 mmol). The reaction mixture was stirred at ambient temperature for overnight. The reaction mixture was extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product 1.54 g (75% yield) which was used directly in next step without further purification.

**Setp 13 Preparation of (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(7*S*,8*aS*)-2-(4-sulfamoylbenzoyl)octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid**



The crude product (0.9 g, 1.4 mmol) from step 12 of Example 8 was dissolved in a 1:1 mixture of THF and water (20 mL) and 10% Pd/C (0.4 g) was added. The resulting black suspension was stirred at ambient temperature under hydrogen pressure for 2 hours. The catalyst was filtered off and rinsed with THF and de-ionized water. The combined filtrate was extracted with ethyl acetate. The product in aqueous layer was purified by prep. HPLC and the product fractions was freeze-dried to give solid product 50 mg (8.0% yield).

Due to the amide bond on the octahydropyrrolo[1,2-*a*]-pyrazine ring, <sup>1</sup>H NMR exhibits two

conformers.

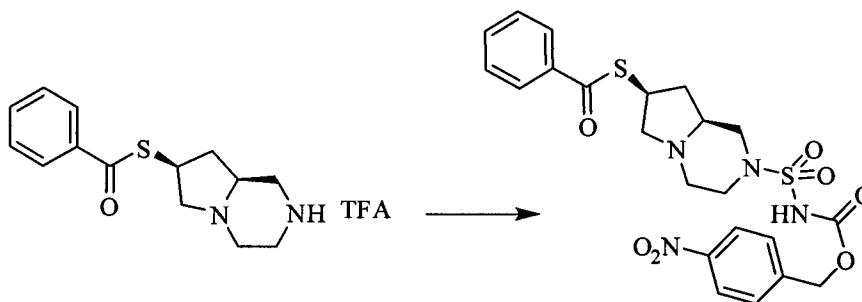
Formula: C<sub>24</sub>H<sub>30</sub>N<sub>4</sub>O<sub>7</sub>S<sub>2</sub> Mol.Wt: 550.65 LC-MS: 551(M+H<sup>+</sup>)

<sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ 7.88 (d, 2H), δ 7.51 (dd, 2H), δ 4.58 (d, 0.5H), δ 4.42 (d, 0.5H), δ 4.03-4.12 (m, 2H), δ 3.62-3.68 (m, 1.5H), δ 3.48 (d, 0.5H), δ 3.26-3.30 (m, 1H), δ 3.14-3.22 (m, 1.5H), δ 2.91-3.08 (m, 2.5H), δ 2.68 (d, 0.5H), δ 2.59 (t, 0.5H), δ 2.58-2.65 (m, 1H), δ 2.37-2.41 (m, 0.5H), δ 2.14-2.28 (m, 2.5H), δ 1.23-1.32 (m, 0.5H), δ 1.18 (d, 3H), δ 1.04-1.09 (m, 3.5H).

**Example 9 Preparation of (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(7*S*,8*aS*)-2-sulfamoyloctahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (Compound 9)**

**Setp 1-8** Procedures were same as step 1-8 in Example 1.

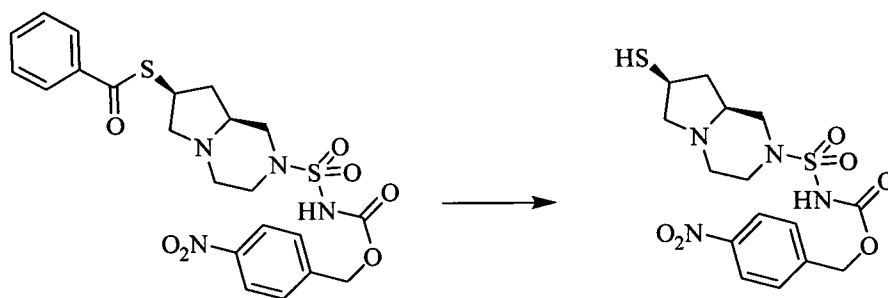
**Setp 9** Preparation of *S*-(7*S*,8*aS*)-2-[N-[(4-nitrobenzyloxy)carbonyl]sulfamoyl]octahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate



To a solution of 4-nitrobenzyl alcohol (2.73 g, 17.9 mmol) in acetonitrile was cooled to 0 °C and dropwise treated with a CH<sub>2</sub>Cl<sub>2</sub> solution of chlorosulfonyl isocyanate (2.5 g, 17.9 mmol). The resulting mixture was stirred at 0 °C for 1 hour and used directly in next reaction with purification.

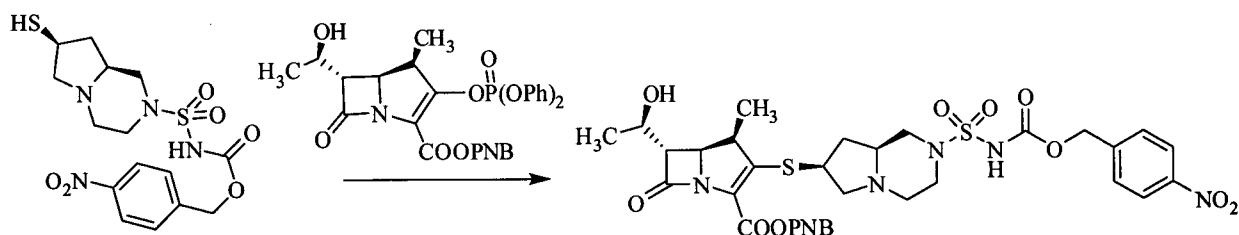
The above solution was slowly added to a solution of *S*-(7*S*,8*aS*)-octahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate (4.27 g, 11.9 mmol) and TEA (5 mL, 35.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The resulting mixture was stirred at 0 °C for 2 hours and at ambient temperature for additional 10 hours. The reaction mixture was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel to afford product 2.18 g (35.2% yield).

**Setp 10** Preparation of 4-nitrobenzyl (7*S*,8*aS*)-7-mercaptohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-ylsulfonylcarbamate



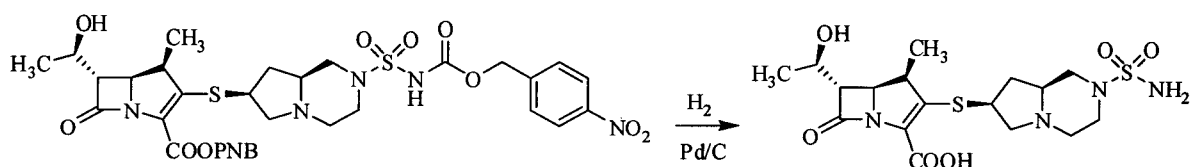
*S*-(7*S*,8*aS*)-2-[*N*-[(4-nitrobenzyloxy)carbonyl]sulfamoyl]octahydropyrrolo- [1,2-*a*]pyrazin-7-yl benzothioate (2.18 g, 4.19 mmol) was dissolved in methanol and was added to a saturated methanolic KOH solution at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was adjusted to pH=6 to 7 with 1N HCl solution. Methanol was removed and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give product (1.25 g, 72%).

**Setp 11 Preparation of 4-nitrobenzyl (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-3-[(7*S*,8*aS*)-2-[*N*-[(4-nitrobenzyloxy)carbonyl]sulfamoyl]octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate**



In a dried reaction flask, 2.725 g of 4-nitrobenzyl (7*S*,8*aS*)-7-mercaptohexahydropyrrolo- [1,2-*a*]pyrazin-2(1*H*)-ylsulfonylcarbamate (6.55 mmol) and DIEA (2.17 g, 13 mmol) was dissolved in acetonitrile. To this solution was added 4-nitrobenzyl (4*R*,5*R*,6*S*)-3-(diphenoxyphosphoryloxy)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (4.28 g, 7.21 mmol). The reaction mixture was stirred at ambient temperature for 72 hours under nitrogen atmosphere. The reaction mixture was extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product 1.4 g (28% yield) which was used directly in next step without further purification.

**Setp 12 Preparation of (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(7*S*,8*aS*)-2-sulfamoyloctahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid**



The product (1.4 g, 1.84 mmol) from step 11 of Example 9 was dissolved in a 1:1 mixture of THF and water (20 mL) and 10% Pd/C (0.4 g) was added. The resulting black suspension was stirred at ambient temperature under hydrogen pressure for 2 hours. The catalyst was filtered off and rinsed with THF and de-ionized water. The combined filtrate was extracted with ethyl acetate. The product in aqueous layer was purified by prep. HPLC and the product fractions was freeze-dried to give solid product 280 mg (35% yield).

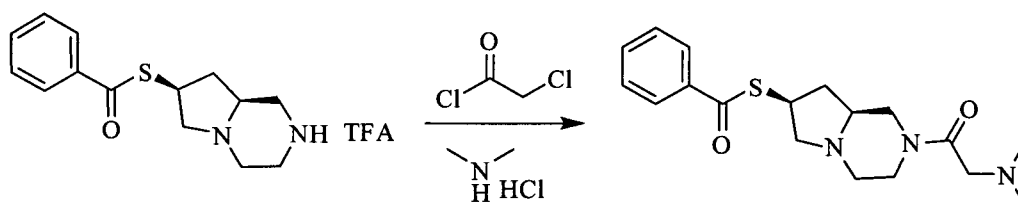
Formula:  $C_{17}H_{26}N_4O_6S_2$  Mol.Wt: 446.54 LC-MS: 447(M+H<sup>+</sup>)

<sup>1</sup>HMR: (400 MHz, DLC-MSO-d<sub>6</sub>)  $\delta$ : 6.74 (s, 2H), 4.92 (s, 1H), 3.84-3.91 (m, 2H), 3.46 (d, 2H), 2.87-2.97 (m, 3H), 2.62-2.67 (m, 1H), 2.23-2.33 (m, 2H), 2.03-2.09 (m, 2H), 1.1 (d, 3H), 1.0 (d, 3H).

**Example 10 Preparation of (4R,5S,6S)-3-[(7S,8aS)-2-[2-(dimethylamino)acetyl]octahydro-pyrrolo[1,2-a]pyrazin-7-ylthio]-6-[(R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (Compound 12)**

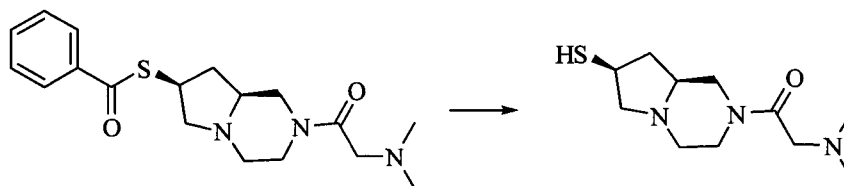
**Step 1-8** Procedures were same as step 1-8 in Example 1.

**Step 9 Preparation of *S*-(7S,8aS)-2-[2-(dimethylamino)acetyl]octahydro-pyrrolo[1,2-a]-pyrazin-7-yl benzothioate**

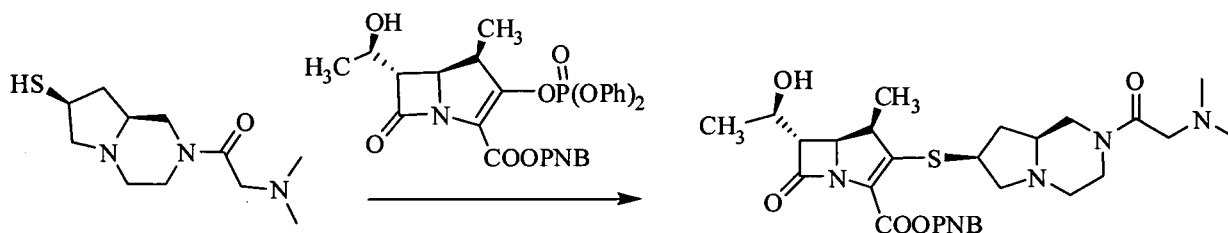


To a solution of *S*-(7S,8aS)-octahydro-pyrrolo[1,2-a]pyrazin-7-yl benzothioate (4.27 g, 11.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) was treated with TEA (5 mL, 35.7 mmol) and chloroacetyl chloride (1.35 g, 11.9 mmol). The resulting mixture was stirred at ambient temperature for overnight. To the reaction mixture was added dimethylamine hydrochloride salt (0.97 g, 11.9 mmol) and TEA (1.7 mL, 11.9 mmol). The resulting mixture was heated to reflux and stirred until the reaction completed. The reaction mixture was washed with saturated aqueous NaHCO<sub>3</sub> solution and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give product 1.70 g (41.2%).

**Step 10 Preparation of 2-(dimethylamino)-1-[(7S,8aS)-7-mercaptohexahydro-pyrrolo-**

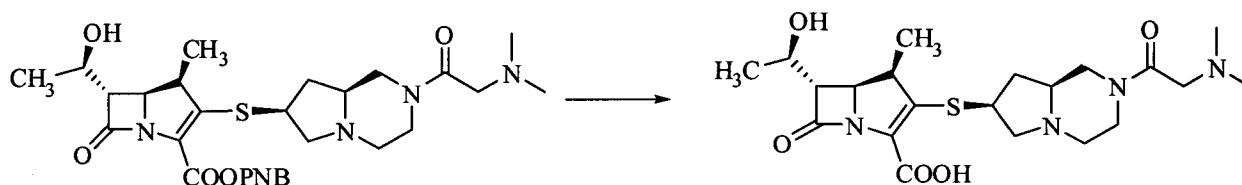
**[1,2-*a*]pyrazin-2(1*H*)-yl]ethanone**

To a solution of *S*-(7*S*,8*aS*)-2-[2-(dimethylamino)acetyl]octahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate (1.70 g, 4.9 mmol) in methanol was added to a saturated methanolic KOH solution at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was adjusted to pH=6 to 7 with 1N HCl solution. Methanol was removed and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give product (0.99 g, 83%).

**Step 11 Preparation of 4-nitrobenzyl (4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-[2-(dimethylamino)acetyl]octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate**

In a dried reaction flask, 0.97 g of 2-(dimethylamino)-1-[(7*S*,8*aS*)-7-mercaptohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]ethanone (4.0 mmol) and DIEA (1.03 g, 8 mmol) was dissolved in acetonitrile (100 mL). To this solution was added 4-nitrobenzyl (4*R*,5*R*,6*S*)-3-(diphenoxyphosphoryloxy)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate (2.38 g, 4 mmol). The reaction mixture was stirred at ambient temperature for 24 hours under nitrogen atmosphere. The reaction mixture was extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product 1.62 g (69% yield) which was used directly in next step without further purification.

**Step 12 Preparation of (4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-[2-(dimethylamino)acetyl]octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid**



The product (1.62 g, 2.76 mmol) from step 11 of Example 10 was dissolved in a 1:1 mixture of THF and water (20 mL) and 10% Pd/C (0.4 g) was added. The resulting black suspension was stirred at ambient temperature under hydrogen pressure for 2 hours. The catalyst was filtered off and rinsed with THF and de-ionized water. The combined filtrate was extracted with ethyl acetate. The product in aqueous layer was purified by prep. HPLC and the product fractions was freeze-dried to give solid product 287 mg (23% yield).

Due to the amide bond on the octahydropyrrolo[1,2-*a*]-pyrazine ring, <sup>1</sup>H NMR exhibits two conformers.

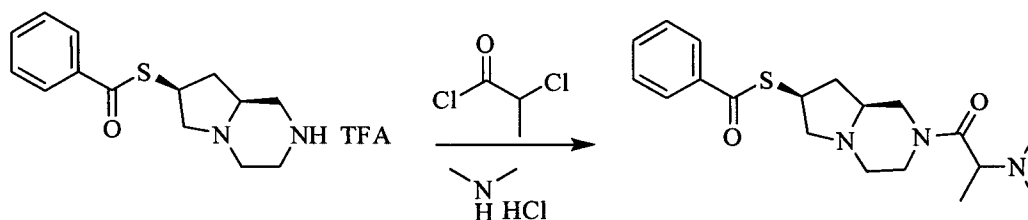
Formula: C<sub>21</sub>H<sub>32</sub>N<sub>4</sub>O<sub>5</sub>S Mol.Wt.: 452.57 LC-MS: 453(M+H<sup>+</sup>)

<sup>1</sup>HNMR: (400 MHz, D<sub>2</sub>O) δ: 4.39(d, 0.5H), 4.25(d, 0.5H), 4.09 (t, 1H), 4.04 (d, 1H), 3.84(d, 0.5H), 3.60-3.69 (m, 1.5H), 3.55(d, 2H), 3.27(d, 1H), 3.09-3.19 (m, 1.5H), 2.83-2.95(m, 2.5H), 2.69-2.75 (m, 0.5H) 2.57(t, 1H), 2.48 (t, 0.5H), 2.33-2.41(m, 7H), 2.06-2.31 (m, 2H), 1.14-1.18(m, 4H), 1.06 (d, 3H).

**Example 11 Preparation of (4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-[2-(dimethylamino)propionyl]octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (Compound 13)**

**Step 1-8** Procedures were same as step 1-8 in Example 1.

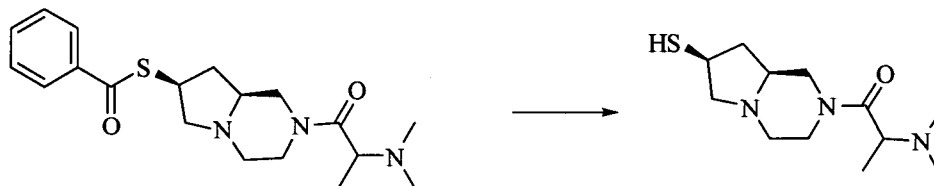
**Step 9** Preparation of *S*-(7*S*,8*aS*)-2-(2-(dimethylamino)propionyl)Octahydropyrrolo [1,2-*a*]-pyrazin-7-yl benzothioate



To a solution of *S*-(7*S*,8*aS*)-octahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate (4.27 g, 11.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) was treated with TEA (5 mL, 35.7 mmol) and 2-chloropropionyl chloride (1.51 g, 11.9 mmol). The resulting mixture was stirred at ambient temperature for overnight. To the reaction mixture was added dimethylamine hydrochloride salt (0.97 g, 11.9 mmol) in 20 mL of CH<sub>2</sub>Cl<sub>2</sub> and TEA (1.7 mL, 11.9 mmol). The resulting mixture was heated to reflux and

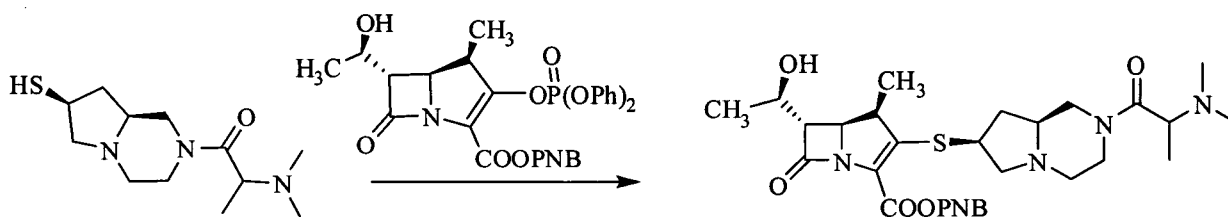
stirred until the reaction completed. The reaction mixture was washed with saturated aqueous  $\text{NaHCO}_3$  solution and brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give product 1.59 g (37.2% yield).

**Step 10 Preparation of 2-(dimethylamino)-1-((7*S*,8*aS*)-7-mercaptohexahydropyrrolo[1,2-*a*]-pyrazin-2(1*H*)-yl)propan-1-one**



*S*-(7*S*,8*aS*)-2-[2-(dimethylamino)propionyl]octahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate (1.59 g, 4.4 mmol) dissolved in methanol was added to a saturated methanolic KOH solution at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was adjusted to pH=6 to 7 with 1N HCl solution. Methanol was removed and the residue was extracted with  $\text{CH}_2\text{Cl}_2$ , dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to give product (0.91 g, 81%).

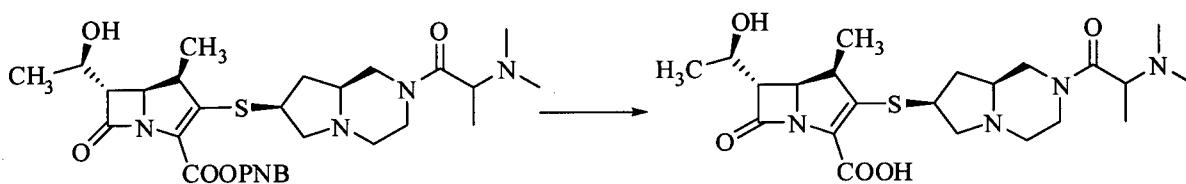
**Step 11 Preparation of 4-nitrobenzyl (4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-[2-(dimethylamino)propionyl]octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate**



In a dried reaction flask, 0.91 g of 2-(dimethylamino)-1-[(7*S*,8*aS*)-7-mercaptohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]ethanone (3.56 mmol) and DIEA (1.03 g, 8 mmol) was dissolved in acetonitrile (100 mL). To this solution was added 4-nitrobenzyl (4*R*,5*R*,6*S*)-3-(diphenoxyphosphoryloxy)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (2.11 g, 3.56 mmol). The reaction mixture was stirred at ambient temperature for 24 hours under nitrogen atmosphere. The reaction mixture was extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to give crude product 1.51 g (71% yield) which was used directly in next step without further purification.

**Step 12 Preparation of (4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-[2-(dimethylamino)propanoyl]**

**octahydro-pyrrolo[1,2-*a*]pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabi  
cyclo[3.2.0]hept-2-ene-2-carboxylic acid**



The product (1.51 g, 2.52 mmol) from step 11 of Example 11 was dissolved in a 1:1 mixture of THF and water (20 mL) and 10% Pd/C (0.4 g) was added. The resulting black suspension was stirred at ambient temperature under hydrogen pressure for 2 hours. The catalyst was filtered off and rinsed with THF and de-ionized water. The combined filtrate was extracted with ethyl acetate. The product in aqueous layer was purified by prep. HPLC and the product fractions was freeze-dried to give solid product 140 mg (12% yield).

Due to the amide bond on the octahydro-pyrrolo[1,2-*a*]-pyrazine ring, <sup>1</sup>H NMR exhibits two conformers.

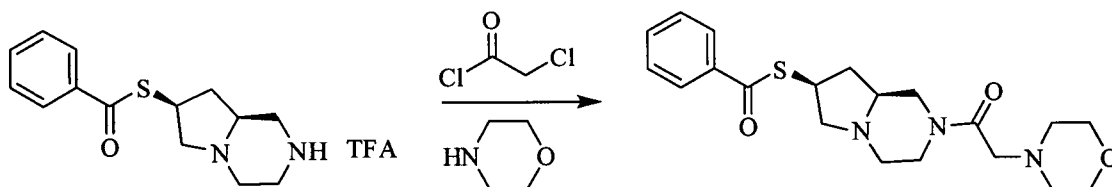
Formula: C<sub>22</sub>H<sub>34</sub>N<sub>4</sub>O<sub>5</sub>S Mol.Wt: 466.59 LC-MS: 467(M+H<sup>+</sup>)

<sup>1</sup>HNMR: (400 MHz, D<sub>2</sub>O) δ: 4.40-4.43(m, 0.5H), 4.29-4.36(m, 1.5H), 4.06-4.14(m, 2H), 3.85-3.95(m, 0.5H), 3.67-3.82(m, 1.5H), 3.29(d, 1H), 3.18-3.25(m, 1.5H), 2.96-3.02(m, 2.5H), 2.73-2.85(m, 6.5H), 2.59-2.63(m, 1.5H) 2.35-2.38(m, 1H) 2.12-2.21(m, 2H) 1.37-1.42(m, 3H) 1.13-1.26(m, 4H) 1.08(d, 3H)

**Example 12: Preparation of (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-3-[(7*S*,8*aS*)-2-(2-morpholinoacetyl)octahydro-pyrrolo[1,2-*a*]pyrazin-7-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (compound 14)**

**Step1-8** Procedures were same as step 1-8 in Example 1.

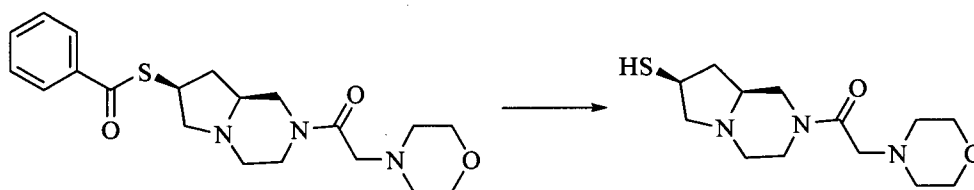
**Step 9** Preparation of *S*-(7*S*,8*aS*)-2-(2-morpholinoacetyl)octahydro-pyrrolo[1,2-*a*]pyrazin-7-yl benzothioate



To a solution of *S*-(7*S*,8*aS*)-octahydro-pyrrolo[1,2-*a*]pyrazin-7-yl benzothioate (4.27 g, 11.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) was treated with TEA (5 mL, 35.7 mmol) and 2-chloroacetyl chloride (1.35 g, 11.9 mmol) in 20 mL of CH<sub>2</sub>Cl<sub>2</sub>. The resulting mixture was stirred at ambient temperature

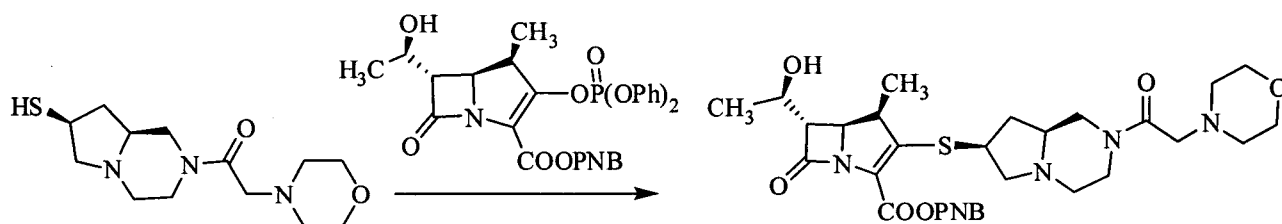
for overnight. To the reaction mixture was added morpholine (1.03 g, 11.9 mmol) in 20 mL of CH<sub>2</sub>Cl<sub>2</sub>. The resulting mixture was heated to reflux and stirred until the reaction completed. The reaction mixture was washed with saturated aqueous NaHCO<sub>3</sub> solution and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give product 2.40 g (56% yield).

**Step 10 Preparation of 1-[(7*S*,8*aS*)-7-mercaptohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]-2-morpholinoethanone**



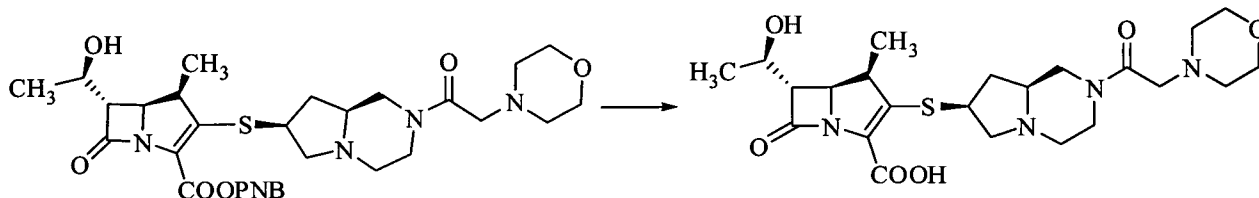
*S*-(7*S*,8*aS*)-2-(2-morpholinoacetyl)octahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate (2.60 g, 6.67 mmol) dissolved in methanol was added to a saturated methanolic KOH solution at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was adjusted to pH=6 to 7 with 1N HCl solution. Methanol was removed and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give product (1.29 g, 68%).

**Step 11 Preparation of 4-nitrobenzyl (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-3-[(7*S*,8*aS*)-2-(2-morpholinoacetyl)octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate**



In a dried reaction flask, 1.29 g of 1-[(7*S*,8*aS*)-7-mercaptohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]- 2-morpholinoethanone (4.52 mmol) and DIEA (1.03 g, 8 mmol) was dissolved in acetonitrile (100 mL). To this solution was added 4-nitrobenzyl (4*R*,5*R*,6*S*)-3-(diphenoxyphosphoryloxy)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate (2.69 g, 4.52 mmol). The reaction mixture was stirred at ambient temperature for 24 hours under nitrogen atmosphere. The reaction mixture was extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product 1.36 g (48% yield) which was used directly in next step without further purification.

**Step 12 Preparation of (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-3-[(7*S*,8*aS*)-2-(2-morpholinoacetyl)octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid**



The product (1.36 g, 2.16 mmol) from step 11 of Example 12 was dissolved in a 1:1 mixture of THF and water (20 mL) and 10% Pd/C (0.4 g) was added. The resulting black suspension was stirred at ambient temperature under hydrogen pressure for 2 hours. The catalyst was filtered off and rinsed with THF and de-ionized water. The combined filtrate was extracted with ethyl acetate. The product in aqueous layer was purified by prep. HPLC and the product fractions was freeze-dried to give solid product 171 mg (16% yield).

Due to the amide bond on the octahydropyrrolo[1,2-*a*]-pyrazine ring, <sup>1</sup>H NMR exhibits two conformers.

Formula: C<sub>23</sub>H<sub>34</sub>N<sub>4</sub>O<sub>6</sub>S Mol.Wt: 494.60 LC-MS: 495(M+H<sup>+</sup>)

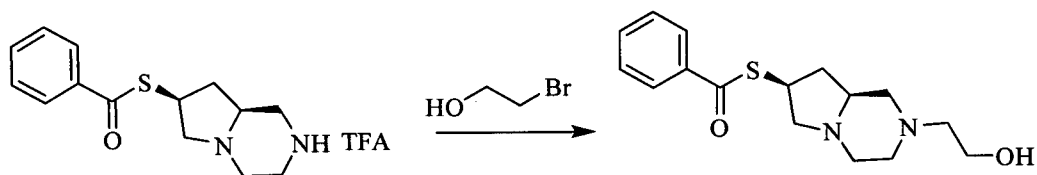
<sup>1</sup>HNMR: (400 MHz, D<sub>2</sub>O) δ: 4.40(d, 0.5H), 4.25(d, 0.5H), 4.03-4.11 (m, 2H), 3.93 (d, 0.5H), 3.75(d, 0.5H), 3.55-3.65 (m, 5H), 3.35-3.91(m, 2.5H), 3.17-3.26 (m, 1H), 3.05-3.15(m, 0.5H), 2.86-2.94 (m, 2.5H) 2.59-2.62 (m, 0.5H) 2.46-2.59(m, 6H) 2.34-2.45 (m, 1H) 2.11-2.21(m, 2H) 1.11-1.20 (m, 4H) 1.05 (d, 3H).

<sup>1</sup>HNMR: (400 MHz, D<sub>2</sub>O) δ: 4.40(d, 0.5H), 4.25(d, 0.5H), 4.03-4.11(m, 2H), 3.93(d, 0.5H), 3.75(d, 0.5H), 3.55-3.65(m, 5H), 3.35-3.91(m, 2.5H), 3.17-3.26(m, 1H), 3.05-3.15(m, 0.5H), 2.86-2.94(m, 2.5H), 2.59-2.62(m, 0.5H), 2.46-2.59(m, 6H), 2.34-2.45(m, 1H), 2.11-2.21(m, 2H), 1.11-1.20 (m, 4H), 1.05 (d, 3H).

**Example 13 Preparation of (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-3-[(7*S*,8*aS*)-2-(2-hydroxyethyl)octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (Compound 16)**

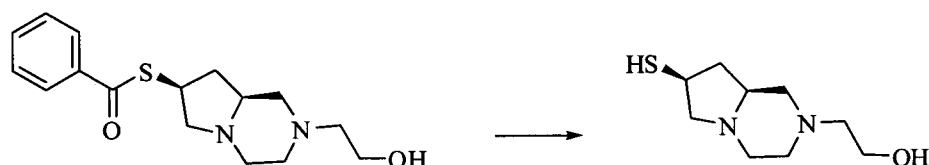
**Setp 1-8** Procedures were same as step 1-8 in Example 1.

**Step 9 Preparation of *S*-(7*S*,8*aS*)-2-(2-hydroxyethyl)octahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate**



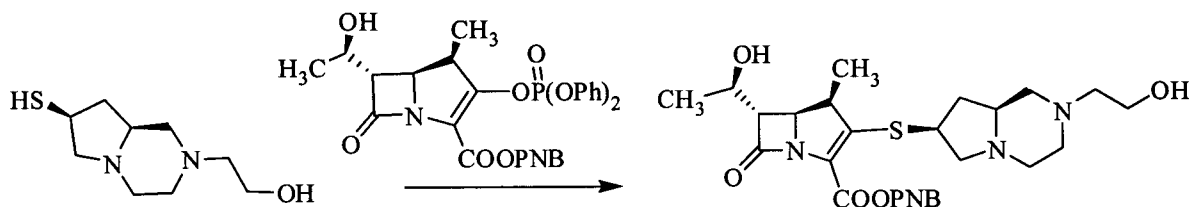
To a solution of *S*-(7*S*,8*aS*)-octahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate (4.27 g, 11.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) was treated with TEA (5 mL, 35.7 mmol) and 2-bromoethanol (1.35 g, 11.9 mmol). The resulting mixture was heated to reflux and stirred until the reaction completed. The reaction mixture was washed with saturated aqueous NaHCO<sub>3</sub> solution and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to give product 2.26 g (62% yield).

**Step 10 Preparation of 2-[(7*S*,8*aS*)-7-mercaptohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl] ethanol**



*S*-(7*S*,8*aS*)-2-(2-hydroxyethyl)octahydropyrrolo[1,2-*a*]pyrazin-7-yl benzothioate (2.26 g, 7.37 mmol) dissolved in methanol was added to a saturated methanolic KOH solution at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was adjusted to pH=6 to 7 with 1N HCl solution. Methanol was removed and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure to give product (0.77 g, 52%).

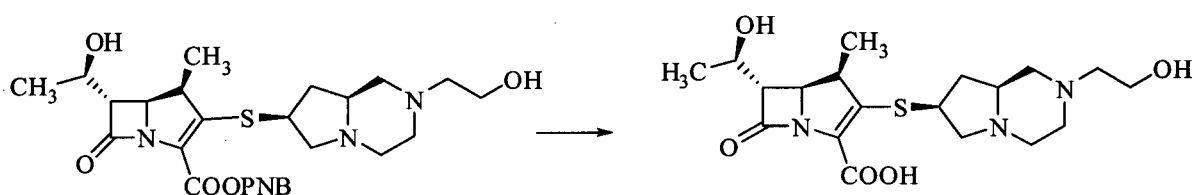
**Step 11 Preparation of 4-nitrobenzyl (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-3-[(7*S*,8*aS*)-2-(2-hydroxyethyl)octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate**



In a dried reaction flask, 0.77 g of 2-[(7*S*,8*aS*)-7-mercaptohexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl]ethanol (3.83 mmol) and DIEA (1.03 g, 8 mmol) was dissolved in acetonitrile (100 mL). To this solution was added 4-nitrobenzyl (4*R*,5*R*,6*S*)-3-(diphenoxyphosphoryloxy)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (MAP) (2.27 g, 4.83 mmol). The reaction mixture was stirred at ambient temperature for 24 hours

under nitrogen atmosphere. The reaction mixture was extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give crude product 1.23 g (59% yield) which was used directly in next step without further purification.

**Step12 Preparation of (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-3-[(7*S*,8*aS*)-2-(2-hydroxyethyl)-octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2- carboxylic acid**



The product (1.23 g, 2.25 mmol) from step 11 of Example 13 was dissolved in a 1:1 mixture of THF and water (20 mL) and 10% Pd/C (0.4 g) was added. The resulting black suspension was stirred at ambient temperature under hydrogen pressure for 2 hours. The catalyst was filtered off and rinsed with THF and de-ionized water. The combined filtrate was extracted with ethyl acetate. The product in aqueous layer was purified by prep. HPLC and the product fractions was freeze-dried to give solid product 101 mg (11% yield).

Formula: C<sub>19</sub>H<sub>29</sub>N<sub>3</sub>O<sub>5</sub>S Mol.Wt: 411.52 LC-MS: 412(M+H<sup>+</sup>)

<sup>1</sup>HNMR: (400 MHz, D<sub>2</sub>O) δ: 3.98-4.12 (m, 2H), 3.52-3.68 (m, 3H), 3.21-3.27 (m, 1H), 3.09-3.10 (m, 1H), 2.98 (d, 1H), 2.76-2.90 (m, 3H), 2.48-2.57 (m, 3H), 2.11-2.34 (m, 4H), 1.92-2.01 (m, 1H), 1.05-1.19 (m, 4H), 1.03 (d, 3H).

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

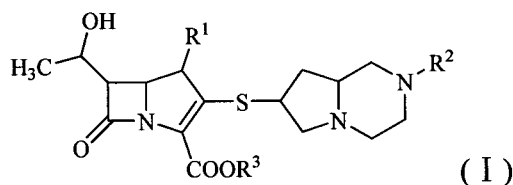
**Table 3 The compounds of present invention**

| NO. | Structural Formula | NO. | Structural Formula |
|-----|--------------------|-----|--------------------|
| 17  |                    | 31  |                    |
| 18  |                    | 32  |                    |

|    |  |    |  |
|----|--|----|--|
| 19 |  | 33 |  |
| 20 |  | 34 |  |
| 21 |  | 35 |  |
| 22 |  | 36 |  |
| 23 |  | 37 |  |
| 24 |  | 38 |  |
| 25 |  | 39 |  |
| 26 |  | 40 |  |
| 27 |  | 41 |  |
| 28 |  | 42 |  |
| 29 |  | 43 |  |
| 30 |  |    |  |

## CLAIMS

1. A compound of formula (I), or its pharmaceutically acceptable salts, or its readily hydrolyzed ester, or its solvate, or its stereoisomer thereof:



Wherein

$R^1$  is hydrogen or  $C_{1-6}$  alkyl;

$R^2$  is

(1) hydrogen,

(2)  $C_{1-6}$  alkyl,  $C_{2-8}$  alkenyl or  $C_{2-8}$  alkynyl, which is optionally substituted by one to three  $X^1$ ,

$X^1$  is independently selected from halogen, carboxyl, hydroxyl, amino, cyano, nitro,  $C_{1-6}$  alkoxy, halogenated  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkyl amino, bis-( $C_{1-6}$  alkyl)amine,  $C_{1-6}$  alkyl carbonyl,  $C_{1-6}$ alkyl carboxyl,  $C_{1-6}$  alkoxy carbonyl, carbamoyl,  $C_{1-6}$  alkyl carbamoyl, bis-( $C_{1-6}$  alkyl) carbamoyl, amino sulfonyl,  $C_{1-6}$  alkyl amino sulfonyl, bis-( $C_{1-6}$  alkyl) amino sulfonyl,  $C_{1-6}$  alkyl sulfonyl amino,  $C_{1-6}$  alkyl sulfonyl,  $C_{1-6}$  alkyl carbonyl amino, guanidino,  $C_{3-8}$  cycloalkyl, aryl or heterocyclic,

$C_{3-8}$  cycloalkyl, aryl or heterocyclic of said  $X^1$  can be further substituted by the following substituents: halogen, carboxyl, hydroxyl, amino, cyano, nitro,  $C_{1-6}$  alkyl, carboxy  $C_{1-6}$  alkyl, hydroxy  $C_{1-6}$  alkyl, amino  $C_{1-6}$  alkyl, halogenated  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, halogenated  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkoxy  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl amino, bis-( $C_{1-6}$  alkyl) amino, bis-( $C_{1-6}$  alkyl) amino  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl carbonyl,  $C_{1-6}$ alkyl carboxyl,  $C_{1-6}$  alkoxy carbonyl, carbamoyl, carbamoyl  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl carbamoyl, bis-( $C_{1-6}$  alkyl) carbamoyl, amino sulfonyl, amino sulfonyl  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl amino sulfonyl, bis-( $C_{1-6}$  alkyl) amino sulfonyl,  $C_{1-6}$  alkyl sulfonyl amino,  $C_{1-6}$  alkyl sulfonyl,  $C_{1-6}$  alkyl carbonyl amino or guanidino,

(3)  $C_{3-8}$  cycloalkyl, aryl or heterocyclic which is optionally substituted by one to three  $X^2$ ,

$X^2$  is independently selected from halogen, carboxyl, hydroxyl, amino, cyano, nitro,  $C_{1-6}$  alkyl, carboxy  $C_{1-6}$  alkyl, hydroxy  $C_{1-6}$  alkyl, amino  $C_{1-6}$  alkyl, halogenated  $C_{1-6}$  alkyl,  $C_{1-6}$  alkoxy, halogenated  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkoxy  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl amino, bis-( $C_{1-6}$  alkyl) amino, bis-( $C_{1-6}$  alkyl) amino  $C_{1-6}$  alkyl,  $C_{1-6}$  alkyl carbonyl,  $C_{1-6}$ alkyl carboxyl,  $C_{1-6}$  alkoxy

carbonyl, carbamoyl, carbamoyl C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyl carbamoyl, bis-(C<sub>1-6</sub> alkyl) carbamoyl, amino sulfonyl, amino sulfonyl C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkyl amino sulfonyl, bis-(C<sub>1-6</sub> alkyl) amino sulfonyl, C<sub>1-6</sub> alkyl sulfonyl amino, C<sub>1-6</sub> alkyl sulfonyl, C<sub>1-6</sub> alkyl amino carbonyl or guanidino,

(4) -CO-Y,

Y is C<sub>1-6</sub> alkyl which is optionally substituted by one to three Y<sup>1</sup>, or C<sub>3-8</sub> cycloalkyl, aryl or heterocyclic which is optionally substituted by one to three Y<sup>2</sup>,

Y<sup>1</sup> represents the above defined X<sup>1</sup> and Y<sup>2</sup> represents the above defined X<sup>2</sup>,

(5) -S(O)<sub>m</sub>-Z, m is 1 or 2,

Z is amino, C<sub>1-6</sub> alkyl amino, bis-(C<sub>1-6</sub> alkyl)amino, or C<sub>1-6</sub> alkyl which is optionally substituted by one to three Y<sup>1</sup>, or C<sub>3-8</sub> cycloalkyl, aryl or heterocyclic which is optionally substituted by one to three Y<sup>2</sup>,

Y<sup>1</sup> represents the above defined X<sup>1</sup> and Y<sup>2</sup> represents the above defined X<sup>2</sup>; and

R<sup>3</sup> is hydrogen or the carboxyl protecting group.

2. A compound claimed in claim 1, or its pharmaceutically acceptable salts, or its readily hydrolyzed ester, or its solvate, or its stereoisomer:

Wherein

R<sup>1</sup> is C<sub>1-4</sub> alkyl;

R<sup>2</sup> is

(1) hydrogen,

(2) C<sub>1-4</sub> alkyl, which is optionally substituted by one to three X<sup>1</sup>,

X<sup>1</sup> is independently selected from halogen, carboxyl, hydroxyl, amino, C<sub>1-4</sub> alkoxy, halogenated C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkyl amino, bis-(C<sub>1-4</sub> alkyl)amine, C<sub>1-4</sub> alkyl carbonyl, carbamoyl, amino sulfonyl, guanidino, C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl or 3-7 membered heterocyclic,

C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl or 3-7 membered heterocyclic of the said X<sup>1</sup> can be further substituted by the following substituents: halogen, C<sub>1-4</sub> alkyl, halogenated C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, halogenated C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkyl amino, bis-(C<sub>1-4</sub> alkyl) amino, C<sub>1-4</sub> alkyl carbonyl, carbamoyl, carbamoyl C<sub>1-4</sub> alkyl, amino sulfonyl, amino sulfonyl C<sub>1-4</sub> alkyl, or guanidino,

(3) C<sub>3-6</sub> cycloalkyl, phenyl, 5-6 membered heteroaryl or 3-7 membered heterocyclic which is

optionally substituted by one to three  $X^2$ ,

$X^2$  is independently selected from halogen, amino,  $C_{1-4}$  alkyl, halogenated  $C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy, halogenated  $C_{1-4}$  alkoxy,  $C_{1-4}$  alkyl amino, bis-( $C_{1-4}$  alkyl) amino, bis-( $C_{1-4}$  alkyl) amino  $C_{1-6}$  alkyl,  $C_{1-4}$  alkyl carbonyl, carbamoyl, carbamoyl  $C_{1-4}$  alkyl, amino sulfonyl, amino sulfonyl  $C_{1-4}$  alkyl, or guanidino,

(4) -CO-Y,

Y is  $C_{1-4}$  alkyl which is optionally substituted by one to three  $Y^1$ , or  $C_{3-6}$  cycloalkyl, phenyl, 5-6 membered heteroaryl or 3-7 membered heterocyclic which is optionally substituted by one to three  $Y^2$ ,

$Y^1$  represents the above defined  $X^1$  and  $Y^2$  represents the above defined  $X^2$ ,

(5) -S(O)<sub>m</sub>-Z, m is 1 or 2,

Z is amino,  $C_{1-4}$  alkyl amino, bis-( $C_{1-4}$  alkyl)amino, or  $C_{1-4}$  alkyl which is optionally substituted by one to three  $Y^1$ , or  $C_{3-6}$  cycloalkyl, phenyl, 5-6 membered heteroaryl or 3-7 membered heterocyclic which is optionally substituted by one to three  $Y^2$ ,

$Y^1$  represents the above defined  $X^1$  and  $Y^2$  represents the above defined  $X^2$ ; and

$R^3$  is hydrogen.

3. A compound claimed in claim 2, or its pharmaceutically acceptable salts, or its readily hydrolyzed ester, or its solvate, or its stereoisomer:

Wherein

$R^1$  is methyl;

$R^2$  is

(1) hydrogen,

(2)  $C_{1-4}$  alkyl, which is optionally substituted by one to three  $X^1$ ,

$X^1$  is independently selected from halogen, carboxyl, hydroxyl, amino,  $C_{1-4}$  alkoxy, halogenated  $C_{1-4}$  alkoxy,  $C_{1-4}$  alkyl amino, bis-( $C_{1-4}$  alkyl)amine, carbamoyl, amino sulfonyl, phenyl, pyridyl, piperidinyl, piperazinyl or morpholinyl,

The phenyl, pyridyl, piperidinyl, piperazinyl or morpholinyl of the said  $X^1$  can be further substituted by the following substituents: halogen,  $C_{1-4}$  alkyl, halogenated  $C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy, halogenated  $C_{1-4}$  alkoxy,  $C_{1-4}$  alkyl amino, bis-( $C_{1-4}$  alkyl) amino,  $C_{1-4}$  alkyl carbonyl, carbamoyl, carbamoyl  $C_{1-4}$  alkyl, or amino sulfonyl,

(3) phenyl, pyridyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, thiazole,

4,5-dihydro-thiazolyl, or cyclopropyl group which is optionally substituted by one to three  $X^2$ ,

$X^2$  is independently selected from halogen,  $C_{1-4}$  alkyl,  $C_{1-4}$  alkyl amino, bis-( $C_{1-4}$  alkyl) amino, carbamoyl, carbamoyl  $C_{1-4}$  alkyl, amino sulfonyl,

(4) -CO-Y,

Y is  $C_{1-4}$  alkyl which is optionally substituted by one to three  $Y^1$ , or phenyl, pyridyl, piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, furanyl, thiazolyl or 4,5-dihydro-thiazolyl which is optionally substituted by one to three  $Y^2$ ,

$Y^1$  is independently selected from amino,  $C_{1-4}$  alkyl amino, bis-( $C_{1-4}$  alkyl) amino, carbamoyl, guanidino, phenyl, pyridyl, piperidinyl, morpholinyl or pyrrolidinyl,

$Y^2$  is independently selected from halogen, amino,  $C_{1-4}$  alkyl,  $C_{1-4}$  alkyl amino, bis-( $C_{1-4}$  alkyl) amino, carbamoyl, carbamoyl  $C_{1-4}$  alkyl or amino sulfonyl,

(5) -S(O)<sub>m</sub>-Z, m is 1 or 2,

Z is amino,  $C_{1-4}$  alkyl amino, bis-( $C_{1-4}$  alkyl)amino, or  $C_{1-4}$  alkyl which is optionally substituted by one to three  $Y^1$ , or phenyl, pyridyl, piperidinyl, piperazinyl, morpholinyl or pyrrolidinyl which is optionally substituted by one to three  $Y^2$ ,

$Y^1$  and  $Y^2$  represents the above defined; and

$R^3$  is hydrogen.

4. A compound claimed in claim 3, or its pharmaceutically acceptable salts, or its readily hydrolyzed ester, or its solvate, or its stereoisomer:

Wherein

$R^1$  is methyl;

$R^2$  is

(1) hydrogen,

(2) methyl, ethyl, isopropyl, which is optionally substituted by one to three  $X^1$ ,

$X^1$  is independently selected from halogen, hydroxyl, dimethylamine, phenyl or pyridyl,

The phenyl or pyridyl of the said  $X^1$  can be further substituted by the following substituents: halogen, methyl, carbamoyl, carbamoyl methyl, or amino sulfonyl,

(3) phenyl, pyridyl, tetrahydrofuranyl, thiazole, 4,5-dihydro-thiazolyl, or cyclopropyl group which is optionally substituted by one to three  $X^2$ ,

$X^2$  is independently selected from halogen, methyl, carbamoyl, amino sulfonyl,

(4) -CO-Y,

Y is methyl, ethyl or isopropyl which is optionally substituted by one to three  $Y^1$ , or phenyl, pyridyl, piperidinyl, piperazinyl, pyrrolidinyl which is optionally substituted by one to three  $Y^2$ ,

$Y^1$  is independently selected from dimethylamine, carbamoyl, guanidino, phenyl, pyridyl, piperidinyl, morpholinyl or pyrrolidinyl,

$Y^2$  is independently selected from halogen, methyl, carbamoyl, carbamoyl methyl or amino sulfonyl,

(5)  $-S(O)_m-Z$ , m is 1 or 2,

Z is amino, dimethylamino, dimethylamino methyl, methylpiperazine or morpholine methyl; and

$R^3$  is hydrogen.

5. A compound claimed in claim 4, or its pharmaceutically acceptable salts, or its readily hydrolyzed ester, or its solvate, or its stereoisomer:

Wherein

$R^1$  is methyl;

$R^2$  is

(1) hydrogen,

(2) methyl, ethyl, or isopropyl, which is optionally substituted by one to two  $X^1$ ,

$X^1$  is independently selected from hydroxyl, or phenyl,

The said phenyl of  $X^1$  can be further substituted by halogen, methyl, carbamoyl, or amino sulfonyl,

(3)  $-CO-Y$ ,

Y is methyl, ethyl or isopropyl, which is optionally substituted by one to two  $Y^1$ , or phenyl, pyridyl, piperidinyl, which is optionally substituted by one to two  $Y^2$ ,

$Y^1$  is independently selected from dimethylamine, guanidino, phenyl, pyridyl, or morpholinyl,

$Y^2$  is independently selected from halogen, methyl, carbamoyl, or amino sulfonyl,

(4)  $-S(O)_m-Z$ , m is 1 or 2,

Z is amino, or dimethylamino; and

$R^3$  is hydrogen.

6. A compound claimed in claim 5, or its pharmaceutically acceptable salts, or its readily

hydrolyzed ester, or its solvate, or its stereoisomer, and the said compound is selected from the followings:

(4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-3-[(7*S*,8*aS*)-2-methyloctahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid,

(4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-3-[(7*S*,8*aS*)-2-Isopropyl-octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid,

(4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-benzyl-octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid,

(4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-acetyl-octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid,

(4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-3-[(7*S*,8*aS*)-2-isobutyryl-octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid,

(4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-benzoyl-octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid,

(4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(7*S*,8*aS*)-2-picolinoyl-octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid,

(4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(7*S*,8*aS*)-2-(4-sulfamoylbenzoyl)-octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid,

(4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(7*S*,8*aS*)-2-sulfamoyl-octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid,

(4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(7*S*,8*aS*)-2-(4-sulfamoylbenzyl)-octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid,

(4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-(2-guanidinoacetyl)-octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid,

(4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-(2-(dimethylamino)acetyl)-octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid,

(4*R*,5*S*,6*S*)-3-[(7*S*,8*aS*)-2-(2-(dimethylamino)propionyl)-octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-6-[(*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid,

(4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-3-[(7*S*,8*aS*)-2-(2-morpholinoacetyl)-octahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid,

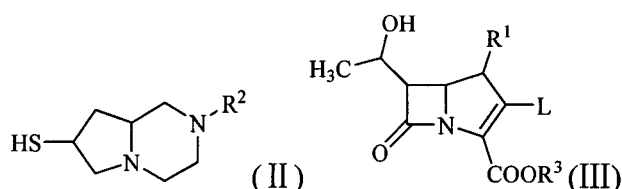
(4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-4-methyl-3-[(7*S*,8*aS*)-2-(1-methylpiperidine-4-carbonyl)-oct

ahydropyrrolo[1,2-*a*]pyrazin-7-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, and  
 (4*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-3-[(7*S*,8*aS*)-2-(2-hydroxy-ethyl)octahydropyrrolo[1,2-*a*]pyr  
 azin-7-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

7. A pharmaceutical dosage form comprising a compound claimed in claims 1-6, or its pharmaceutically acceptable salts, or its readily hydrolyzed ester, or its solvate, or its stereoisomer, characterized in that the said dosage form contains one or more pharmaceutical carriers.

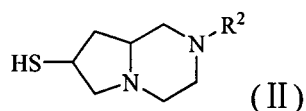
8. A method of the treatment or prevention of infectious diseases comprising a compound claimed in claims 1-6, or its pharmaceutically acceptable salts, or its readily hydrolyzed ester, or its solvate, or its stereoisomer.

9. A method of preparation of a compound of formula ( I ) comprising a nucleophilic substitution reactionin between an intermediate of formula ( II ) and an intermediate of formula (III)



Wherein,  $R^1$ ,  $R^2$  and  $R^3$  are defined as in claim 1 , and L is a leaving group.

10. A compound of formula ( II ), or its pharmaceutically acceptable salts, or its readily hydrolyzed ester, or its solvate, or its stereoisomer:



Wherein,  $R^2$  is defined as in claim 1.