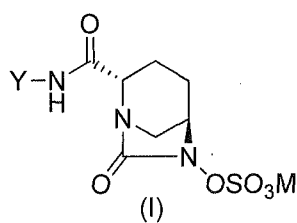


counter these new β -lactamases – particularly ineffective against class C producing organisms, newly emerged extended-spectrum β -lactamases (ESBLs) and carbapenemases like IMP, VIM, OXA, KPC, and NDM. Thus there is a need for broad-spectrum β -lactamase inhibitor to combat over 900 β -lactamases including the newly emerged β -lactamases.

5 Recently, certain diazabicyclic compounds have been disclosed in WO 2009/091856 which is hereby incorporated by reference in its entirety. In addition, a number of diazabicyclic heterocycles have been disclosed in the following patents as β -lactamase inhibitors: US 2003/0199541 A1, US 2004/0157826 A1, US 2004/0097490 A1, US 2005/0020572 A1, US 2006/7112592 B2, US 2006/0189652 A1, US 2008/7439253 B2, US 2009/0018329 A1, EP
10 1307457 B1, EP 1537117 B1, WO 2002/100860 A2, WO 2002/10172 A1, WO 2003/063864 A2, WO 2004/052891 A1, WO 2004/022563 A1, WO 2008/142285 A1, WO 2009/090320 A1, US 2010/0092443 A1, WO 2010/126820 A2, US 2012/0165533 A1.

The compounds of the present invention are new and the structural features are significantly distinct from the compounds described in the patent references cited above.

15 In one aspect, the present invention provides a compound of formula (I):



wherein:

M is hydrogen or a pharmaceutically acceptable salt-forming cation;

Y is OR¹;

20 R¹ is a radical selected from the group consisting of:

(1) C₁₋₆ straight or branched chain alkyl which is optionally substituted;

(2) C₃₋₇ cycloalkyl which is optionally substituted;

(3) C₄₋₇ saturated heterocycles containing at least one heteroatom selected from O, N and S wherein the said heterocycle is optionally substituted, the ring S is optionally oxidized to S(O) or S(O)₂ and the free ring N atom may optionally take a substituent;

(4) Heterocyclyl (C₁₋₆) alkyl wherein the said heterocycle has the same definition as defined in (3), and the said heterocycle is optionally substituted;

(5) C₅₋₇ membered saturated heterocycles optionally fused with a C₃₋₇ membered cycloalkyl group to form a bicyclic ring system where the bicyclic ring system so formed is fused either through two adjacent carbon atoms or through a N atom shared by both the rings and the other end of the cycloalkyl chain is attached to the adjacent carbon atom of the molecule, each ring of the said bicyclic ring system independently optionally substituted;

(6) C₅₋₇ membered saturated heterocycles optionally fused with another C₅₋₇ saturated heterocycle to form a bicyclic ring system where the bicyclic ring system so formed is fused either through two adjacent carbon atoms or through a N atom shared by both the rings, each ring of the said bi-cyclic ring system independently optionally substituted;

(7) C₃₋₇ cycloalkyl which is optionally fused with a C₅₋₇ membered saturated heterocycle containing at least one heteroatom selected from O, N and S, the said bicyclic ring optionally substituted;

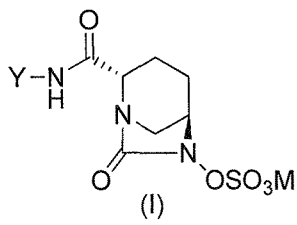
(8) Bridged bicyclic ring system having optionally one or two heteroatoms selected from O, N and S, the bicyclic ring system optionally substituted either at the carbon atom or at the free N atom present in the ring;

(9) C₅₋₇ membered saturated heterocycles optionally fused with C₅₋₇ membered heteroaryl ring where the bicyclic ring system so formed is fused either through two adjacent carbon atoms or through N atom shared by both the rings;

(10) C₅₋₇ membered saturated heterocycles optionally fused to a C₃₋₆ membered ring system through a common carbon atom to form a spiro system optionally containing one heteroatom selected from O, N and S that is present in the spiro ring where the ring S is optionally oxidized to S(O) or S(O)₂ and the free N atom present in either ring may optionally take a substituent; and

(11) C₅₋₇ membered heteroaryl (C₁₋₆) alkyl which is optionally substituted, or a deuterated compound of any such compound.

In another aspect, the present invention provides a compound of formula (I):



wherein:

M is hydrogen or a pharmaceutically acceptable salt-forming cation;

Y is NR²R³;

R² is hydrogen or optionally substituted C₁₋₆ lower alkyl;

R³ is a radical selected from any of following groups consisting of:

(1) C₁₋₆ straight or branched chain alkyl which is optionally substituted;

(2) C₃₋₇ cycloalkyl which is optionally substituted;

(3) C₄₋₇ saturated heterocycles containing at least one heteroatom selected from O, N and S wherein the said heterocycle is optionally substituted, the ring S is optionally oxidized to S(O) or S(O)₂ and the free ring N atom may optionally take a substituent;

(4) C₁₋₆ straight or branched chain alkyl carbonyl which is optionally substituted;

(5) C₃₋₇ cycloalkyl carbonyl which is optionally substituted;

(6) C₄₋₇ membered saturated heterocyclyl carbonyl containing at least one heteroatom selected from O, N and S wherein the said heterocycle is optionally substituted, the ring S is optionally oxidized to S(O) or S(O)₂ and the free ring N atom may optionally take a substituent;

(7) C₃₋₇ membered saturated heterocyclyl (C₁₋₆) alkyl carbonyl wherein the said heterocycle has the same definition as defined in (6), and the free ring N atom may optionally take a substituent;

(8) C₆₋₁₀ aryl carbonyl which is optionally substituted;

(9) C₆₋₁₀ aryl (C₁₋₆) alkyl carbonyl which is optionally substituted;

(10) C₅₋₆ membered heteroaryl carbonyl containing at least one heteroatom selected from O, S and N wherein the heteroaryl is optionally substituted;

(11) C₅₋₆ heteroaryl (C₁₋₆) alkyl carbonyl wherein the said heteroaryl has the same definition as defined in (10);

(12) CF₃CO-, CH₃SO₂-, NH₂CO-, and NH₂SO₂- ;

(13) C₆₋₁₀ aryl which is optionally substituted;

(14) C₅₋₆ membered heteroaryl which is optionally substituted;

(15) or R² and R³ together may form an optionally substituted ring system and the said ring may contain another heteroatom selected from O, N, and S;

or a deuterated compound of any such compound.

In yet another aspect, the present invention provides use of an antibacterially effective amount of a compound as described herein in the manufacture of a medicament for treating a bacterial infection in a mammal in need thereof.

In yet another aspect, the present invention provides a pharmaceutical composition containing as an active ingredient, at least one compound as described herein.

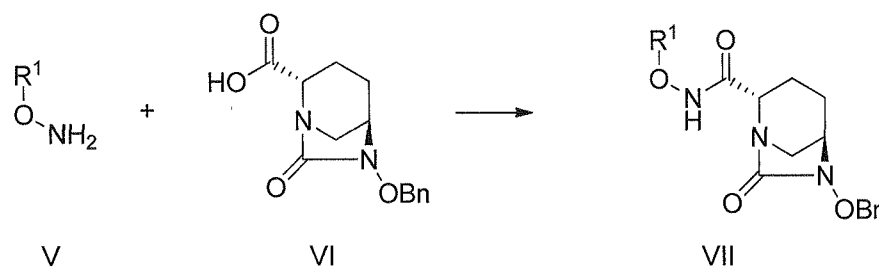
In yet another aspect, the present invention provides use of an effective amount of a compound as described herein in manufacture of a medicament for treating bacterial infection in a mammal in need thereof, wherein said medicament is to be administered into the mammal in combination with an effective amount of at least one β -lactam antibiotic, at least one salt of a β -lactam antibiotic, at least one hydrate of a β -lactam antibiotic or at least one prodrug of a β -lactam antibiotic.

In yet another aspect, the present invention provides use of an effective amount of a compound as described herein in the manufacture of a medicament for treating bacterial infection in a mammal in need thereof, wherein said medicament is to be administered into the mammal in combination with an effective amount of at least one antibiotic, at least one salt of an antibiotic, at least one hydrate of an antibiotic or at least one prodrug of an antibiotic.

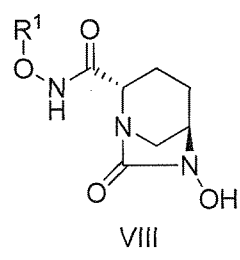
In yet another aspect, the present invention provides a molecular complex comprising a compound as described herein and at least one solvent.

In yet another aspect, the present invention provides a process for preparing a compound as described herein, wherein $M = H$, and wherein the process comprises:

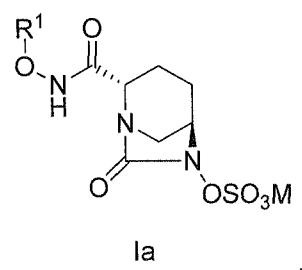
[A] Reacting substituted hydroxylamine (V) with an acid (VI) in presence of a coupling agent selected from the group consisting of EDCI, HOBT-DCC and PyBop to provide an intermediate of formula (VII);



[B] Removing the benzyl protecting group of the intermediate (VII) with a source of hydrogen in presence of Pd catalyst to provide debenzylated product (VIII);



[C] Contacting compound (VIII) with a sulfating agent in the presence of solvent to obtain compound of formula (Ia)



Detailed description of the invention

In one aspect, the present invention relates to new, low molecular weight diazabicyclic compounds (some of which have potent broad-spectrum β -lactamase inhibitory activity and others do not have such activity) that when used in combination with a β -lactam antibiotic or with other non β -lactam antibiotics enhance the activity of the antibiotic against class A, Class B, class C, and class D enzyme producing organisms and thereby enhance the antibacterial properties. The compounds are therefore useful in the treatment of bacterial infections in humans or animals either alone or in combination with β -lactam antibiotics and/or with other non β -lactam antibiotics.

In accordance with the present invention, there are provided (A) new compounds of general formula (I), (B) pharmaceutically acceptable salts of the compounds of formula (I), (C) pharmaceutically acceptable solvates of the compounds of formula (I) and of their salts, and

(2*S*,5*R*)-*N*-[2-(1*H*-imidazol-5-yl)ethoxy]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide

(2*S*,5*R*)-*N*-[1-(1*H*-imidazol-5-yl)ethoxy]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide

(2*S*,5*R*)-*N*-[(1-methyl-1*H*-pyrrol-2-yl)methoxy]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide

(2*S*,5*R*)-*N*-(1,2-oxazol-3-ylmethoxy)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide

(2*S*,5*R*)-7-oxo-6-(sulfooxy)-*N*-(1*H*-1,2,4-triazol-3-ylmethoxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide

(2*S*,5*R*)-*N*-[(5-methylpyrazin-2-yl)methoxy]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide

(2*S*,5*R*)-*N*-[(2-aminocyclopropyl)oxy]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide

(2*S*,5*R*)-*N*-(morpholin-2-ylmethoxy)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide

(2*S*,5*R*)-*N*-[2-(azetidin-3-yloxy)ethoxy]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide

(2*S*,5*R*)-7-oxo-*N*-[2-(pyrrolidin-3-yloxy)ethoxy]-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide

(2*S*,5*R*)-7-oxo-*N*-[2-(piperidin-3-yloxy)ethoxy]-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide

or a deuterated compound of any such compound.

5. ~~A method of treating a bacterial infection comprising administering to a mammal in need thereof~~ Use of an antibacterially effective amount of a compound as recited in claim 1 in the manufacture of a medicament for treating a bacterial infection in a mammal in need thereof.

6. A pharmaceutical composition containing as an active ingredient, at least one compound as recited in claim 1.
7. ~~A method of treating bacterial infection, comprising administering to a mammal in need thereof a combination of (i) Use of an effective amount of a compound as recited in claim 1 in manufacture of a medicament for treating bacterial infection in a mammal in need thereof, wherein said medicament is to be administered into the mammal in combination with and (ii)-an effective amount of at least one β -lactam antibiotic, at least one salt of a β -lactam antibiotic, at least one hydrate of a β -lactam antibiotic or at least one prodrug of a β -lactam antibiotic.~~
8. ~~A method of treating bacterial infection, comprising administering to a mammal in need thereof a combination of (i) Use of an effective amount of a compound as recited in claim 1 in the manufacture of a medicament for treating bacterial infection in a mammal in need thereof, wherein said medicament is to be administered into the mammal in combination with and (ii)-an effective amount of at least one antibiotic, at least one salt of an antibiotic, at least one hydrate of an antibiotic or at least one prodrug of an antibiotic.~~
9. A molecular complex comprising a compound as recited in claim 1 and at least one solvent.
10. A process for preparing a compound recited in claim 1, wherein M = H, and wherein the process comprises:
- [A] Reacting substituted hydroxylamine (V) with an acid (VI) in presence of a coupling agent selected from the group consisting of EDCI, HOBt-DCC and PyBop to provide an intermediate of formula (VII);

(2S,5R)-N'-[(2S)-2-aminopropanoyl]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carbohydrazide

(2S,5R)-N'-[(2S)-2-aminopropanoyl]-N'-methyl-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carbohydrazide

(2S,5R)-N'-[3-(dimethylamino)propanoyl]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carbohydrazide

(2S,5R)-N'-[(3,3-difluorocyclobutyl)carbonyl]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carbohydrazide

(2S,5R)-N'-[(3-aminocyclobutyl)carbonyl]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carbohydrazide

(2S,5R)-N'-[[3-(methylamino)cyclobutyl]carbonyl]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carbohydrazide

(2S,5R)-N'-[[3-(dimethylamino)cyclobutyl]carbonyl]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carbohydrazide,

or a deuterated compound of any such compound.

15. ~~A method of treating a bacterial infection comprising administering to a mammal in need thereof~~ Use of an antibacterially effective amount of a compound as recited in claim 11 in the manufacture of a medicament for treating a bacterial infection in a mammal in need thereof.

16. A pharmaceutical composition containing as an active ingredient, at least one compound as recited in claim 11.

17. ~~A method of treating bacterial infection, comprising administering to a mammal in need thereof a combination of (i)~~ Use of an effective amount of a compound as recited in claim 11 in the manufacture of a medicament for treating bacterial infection in a mammal in need thereof, wherein said medicament is to be administered in combination with and (ii)
an effective amount of at least one β -lactam antibiotic, at least one salt of a

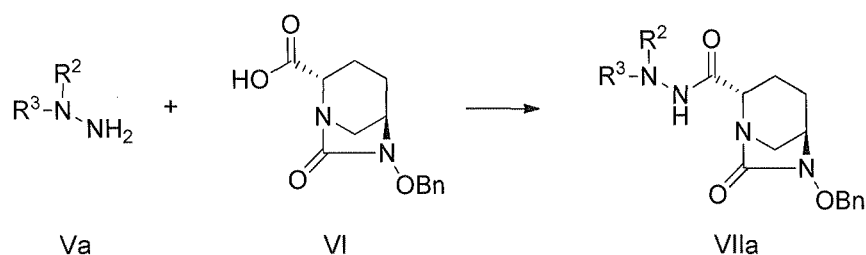
β -lactam antibiotic, at least one hydrate of a β -lactam antibiotic or at least one prodrug of a β -lactam antibiotic.

18. ~~A method of treating bacterial infection, comprising administering to a mammal in need thereof a combination of (i) Use of an effective amount of a compound as recited in claim 11 in the manufacture of a medicament for treating bacterial infection in a mammal in need thereof, wherein said medicament is to be administered in combination with and (ii)~~
an effective amount of at least one antibiotic, at least one salt of an antibiotic, at least one hydrate of an antibiotic or at least one prodrug of an antibiotic.

19. A molecular complex comprising a compound as recited in claim 11 and at least one solvent.

20. A process for preparing a compound recited in claim 11, wherein M = H, and wherein the process comprises:

[A] Reacting substituted hydrazine (Va) with an acid (VI) in presence of a coupling agent selected from the group consisting of EDCI or HOBT-DCC and PyBop to provide an intermediate of formula (VIIa),



[B] Removing the benzyl protecting group of the intermediate (VIIa) with a source of hydrogen in presence of Pd catalyst to provide the debenzylated product (VIIIa),