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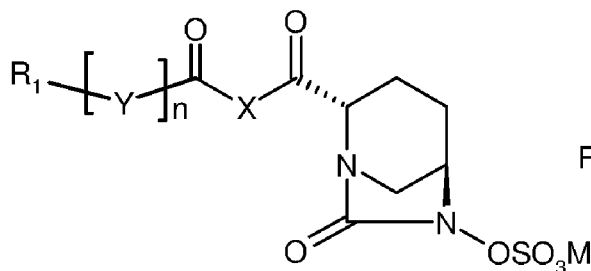
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(54) **Title:** NITROGEN CONTAINING BICYCLIC COMPOUNDS AND THEIR USE IN TREATMENT OF BACTERIAL INFECTIONS



Formula (I)

(57) **Abstract:** Compounds of Formula (I), their preparation, and use in preventing or treating a bacterial infection are disclosed.

NITROGEN CONTAINING BICYCLIC COMPOUNDS AND THEIR USE IN TREATMENT OF BACTERIAL INFECTIONS

RELATED PATENT APPLICATIONS

This application claims priority to Indian Patent Application No. 251/MUM/2015 filed on January 24, 2015, the disclosures of which are incorporated herein by reference in its entirety as if fully rewritten herein.

FIELD OF THE INVENTION

The invention relates to nitrogen containing bicyclic compounds, their preparation and their use in preventing or treating infections.

BACKGROUND OF INVENTION

Emergence of bacterial resistance to known antibacterial agents is becoming a major challenge in treating bacterial infections. One way forward to treat bacterial infections, and especially those caused by resistant bacteria, is to develop newer antibacterial agents that can overcome the bacterial resistance. Coates *et al.* (*Br. J. Pharmacol.* **2007**; 152(8), 1147-1154.) have reviewed novel approaches to developing new antibiotics. However, the development of new antibacterial agents is a challenging task. For example, Gwynn *et al.* (*Annals of the New York Academy of Sciences*, **2010**, 1213: 5-19) have reviewed the challenges in discovery of antibacterial agents.

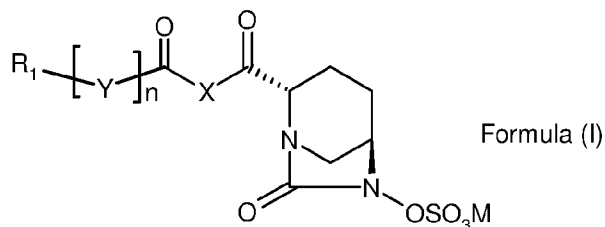
Several antibacterial agents have been described in the prior art (for example, see PCT International Application Nos. PCT/US2010/060923, PCT/EP2010/067647, PCT/US2010/052109, PCT/US2010/048109, PCT/GB2009/050609, PCT/FR01/02418, PCT/EP2009/056178, PCT/US2009/041200, PCT/IB2012/054290, PCT/IB2013/053092, PCT/IB2012/054296, PCT/IB2012/054706, PCT/JP2013/064971, PCT/IB2012/002675, PCT/US2013/034562 and PCT/US2013/034589). However, there remains a need for development of antibacterial agents for preventing and/or treating bacterial infections, including those caused by bacteria that are resistant to known antibacterial agents.

The inventors have now surprisingly discovered, nitrogen containing bicyclic compounds having antibacterial activity.

SUMMARY OF THE INVENTION

Accordingly, there are provided nitrogen containing bicyclic compounds, methods for preparation of these compounds, pharmaceutical compositions comprising these compounds, and methods for preventing or treating bacterial infection in a subject using these compounds.

In one general aspect, there are provided compounds of Formula (I):



or a stereoisomer or a pharmaceutically acceptable derivative thereof;

wherein:

X is: -NH- or -NH-NH-;

Y is: -CR₂R₃-, -NH-, -NHNH-, -ONH- or -O-;

provided that when X is -NH-NH-; Y is -NH- or -O-;

R₁ is:

- (a) hydrogen;
- (b) C₁-C₆ alkyl optionally substituted with one or more substituents independently selected from OR₂, NR₂R₃, SR₂, halogen, CN, COOR₂, CONR₂R₃, (CH₂)_mOR₂, (CH₂)_mNR₂R₃, cycloalkyl, heterocycloalkyl, aryl or heteroaryl;
- (c) cycloalkyl optionally substituted with one or more substituents independently selected from OR₂, NR₂R₃, SR₂, halogen, CN, COOR₂, CONR₂R₃, (CH₂)_mOR₂ or CH₂NR₂R₃;
- (d) aryl optionally substituted with one or more substituents independently selected from OR₂, NR₂R₃, SR₂, halogen, CN, COOR₂, CONR₂R₃, (CH₂)_mOR₂ or (CH₂)_mNR₂R₃;
- (e) heteroaryl optionally substituted with one or more substituents independently selected from OR₂, NR₂R₃, SR₂, halogen, CN, COOR₂, CONR₂R₃, (CH₂)_mOR₂ or (CH₂)_mNR₂R₃ or;
- (f) heterocycloalkyl optionally substituted with one or more substituents independently selected from OR₂, NR₂R₃, SR₂, halogen, CN, COOR₂, CONR₂R₃, (CH₂)_mOR₂ or (CH₂)_mNR₂R₃;

R₂ and R₃ are each independently:

- (a) hydrogen,
- (b) C₁-C₆ alkyl,
- (c) cycloalkyl,
- (d) aryl,
- (e) heteroaryl, or
- (f) heterocycloalkyl;
- (g) R₂ and R₃ are joined together to form three to seven membered ring optionally containing one or more heteroatoms selected from nitrogen, sulfur and oxygen.

m is 1 to 5;

n is 0 or 1;

M is hydrogen or a cation.

In one general aspect, there are provided pharmaceutical compositions comprising a compound of Formula (I), or a stereoisomer or a pharmaceutically acceptable derivative thereof.

In another general aspect, there is provided a method for preventing or treating a bacterial infection in a subject, said method comprising administering to said subject a pharmaceutically effective amount of a compound of Formula (I), or a stereoisomer or a pharmaceutically acceptable derivative thereof.

In another general aspect, there is provided a method for preventing or treating a bacterial infection in a subject, said method comprising administering to said subject a pharmaceutically

effective amount of a pharmaceutical composition comprising a compound of Formula (I), or a stereoisomer, or a pharmaceutically acceptable derivative thereof.

In yet another general aspect, there are provided pharmaceutical compositions comprising: (a) a compound of Formula (I), or a stereoisomer or a pharmaceutically acceptable derivative thereof, and (b) at least one antibacterial agent or a pharmaceutically acceptable derivative thereof.

In another general aspect, there is provided a method for preventing or treating a bacterial infection in a subject, said method comprising administering to said subject a pharmaceutically effective amount of a pharmaceutical composition comprising: (a) a compound of Formula (I), or a stereoisomer or a pharmaceutically acceptable derivative thereof, and (b) at least one antibacterial agent or a pharmaceutically acceptable derivative thereof.

In another general aspect, there is provided a method for preventing or treating a bacterial infection in a subject, said method comprising administering to said subject a pharmaceutically effective amount of: (a) a compound of Formula (I), or a stereoisomer or a pharmaceutically acceptable derivative thereof, and (b) at least one antibacterial agent or a pharmaceutically acceptable derivative thereof.

In one general aspect, there is provided a method of inhibiting beta-lactamase enzymes, wherein said method comprises administering a pharmaceutically effective amount of a compound of Formula (I), or a stereoisomer or a pharmaceutically acceptable derivative thereof.

In another general aspect, there is provided a method of inhibiting beta-lactamase enzymes, wherein said method comprises administering a pharmaceutically effective amount of a pharmaceutical composition comprising a compound of Formula (I), or a stereoisomer or a pharmaceutically acceptable derivative thereof.

In yet another general aspect, there is provided a method for increasing antibacterial effectiveness of an antibacterial agent in a subject, said method comprising co-administering said antibacterial agent or a pharmaceutically acceptable derivative thereof with a compound of Formula (I), or a stereoisomer or a pharmaceutically acceptable derivative thereof.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the following description including claims.

DETAILED DESCRIPTION OF THE INVENTION

Reference will now be made to the exemplary embodiments, and specific language will be used herein to describe the same. It should nevertheless be understood that no limitation of the scope of the invention is thereby intended. Alterations and further modifications of the inventive features illustrated herein, which would occur to one skilled in the relevant art and having possession of this disclosure, are to be considered within the scope of the invention. It must be noted that, as used in this specification and the appended claims, the singular forms “a”, “an”, and “the” include plural referents unless the content clearly dictates otherwise. All references including patents, patent applications, and literature cited in the specification are expressly incorporated herein by reference in their entirety.

The inventors have surprisingly discovered novel bicyclic nitrogen containing compounds having antibacterial properties.

The term “C₁-C₆ alkyl” as used herein refers to branched or unbranched acyclic hydrocarbon radical with 1 to 6 carbon atoms. Typical non-limiting examples of “C₁-C₆ alkyl” include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *tert*-pentyl, neopentyl, *sec*-pentyl, 3-pentyl, *n*-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and the like. The “C₁-C₆ alkyl” may be unsubstituted, or substituted with one or more substituents. Typical, non-limiting examples of such substituents include halogen, alkoxy, CN, SH, COOH, COOC₁-C₆alkyl, CONH₂, OH, NH₂, NHCOCH₃, cycloalkyl, heterocycloalkyl, heteroaryl, aryl and the like.

The term “cycloalkyl” as used herein refers to three to seven member cyclic hydrocarbon radicals. The cycloalkyl group optionally incorporates one or more double or triple bonds, or a combination of double or triple bonds, but which is not aromatic. Typical, non-limiting examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. The cycloalkyl may be unsubstituted, or substituted with one or more substituents. Typical, non-limiting examples of such substituents include C₁-C₆ alkyl, halogen, alkoxy, CN, SH, COOH, COOC₁-C₆alkyl, CONH₂, OH, NH₂, NHCOCH₃, heterocycloalkyl, heteroaryl, aryl, SO₂-alkyl, SO₂-aryl, OSO₂-alkyl, OSO₂-aryl and the like.

The term “aryl” as used herein refers to a monocyclic or polycyclic aromatic hydrocarbon. Typical, non-limiting examples of aryl groups include phenyl, naphthyl, anthracenyl, flourenyl, phenanthrenyl, indenyl and the like. The aryl group may be unsubstituted, or substituted with one or more substituents. Typical, non-limiting examples of such substituents include C₁-C₆ alkyl, halogen, alkoxy, CN, COOH, CONH₂, OH, NH₂, NHCOCH₃, heterocycloalkyl, heteroaryl, aryl, SO₂-alkyl, SO₂-aryl, OSO₂-alkyl, OSO₂-aryl and the like. The term “aryl” includes six to fourteen membered monocyclic or polycyclic aromatic hydrocarbon.

The term “heteroaryl” as used herein refers to a monocyclic or polycyclic aromatic hydrocarbon group wherein one or more carbon atoms have been replaced with heteroatoms selected from nitrogen, oxygen, and sulfur. If the heteroaryl group contains more than one heteroatom, the heteroatoms may be the same or different. Typical, non-limiting example of heteroaryl groups include pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furanyl, pyrrolyl, thienyl, oxadiazolyl, thiadiazolyl, tetrazolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazonyl, isoxazolyl, oxadiazolyl, oxatriazolyl, isothiazolyl, thiatriazolyl, thiazinyl, oxazinyl, thiadiazinyl, oxadiazinyl, dithiazinyl, dioxazinyl, oxathiazinyl, tetrazinyl, thiatriazinyl, oxatriazinyl, dithiadiazinyl, imidazolinyl, dihydropyrimidyl, tetrahydropyrimidyl, tetrazolo-pyridazinyl, purinyl, benzofuranyl, isobenzofuranyl, benzothienyl, benzothiophenyl, carbazolyl, benzimidazolyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzotriazolyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, acridinyl, naphthothienyl, thianthrenyl, chromenyl, xanthenyl, phenoxathienyl, indoliziny, indazolyl, phthalazinyl, naphthyridinyl, qinoxaliny, quinazolinyl, cinnolinyl, pteridinyl, beta-carboliny, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl and the like. The heteroaryl group may be unsubstituted, or substituted with one or more substituents. Typical, non-limiting examples of such substituents include C₁-C₆ alkyl, halogen, alkoxy, CN, COOH, CONH₂, OH, SH, SCH₃, NH₂, NHCOCH₃, heterocycloalkyl, heteroaryl, aryl, SO₂-alkyl, SO₂-aryl, OSO₂-alkyl, OSO₂-aryl and the like. The term “heteroaryl” includes five to fourteen membered monocyclic or polycyclic aromatic hydrocarbon group containing at least one heteroatom selected from nitrogen, oxygen, and sulfur.

The term “heterocycloalkyl” as used herein refers to three to seven member cycloalkyl group containing one or more heteroatoms selected from nitrogen, oxygen or sulfur. The heterocycloalkyl group optionally incorporates one or more double or triple bonds, or a combination of double bonds and triple bonds, but which is not aromatic. Typical, non-limiting example of heterocycloalkyl groups include aziridinyl, azetidiny, pyrrolidinyl, 2-oxo-pyrrolidinyl, imidazolidin-2-one-yl, piperidinyl, oxazinyl, thiazinyl, piperazinyl, piperazin-2,3-dione-yl, morpholinyl, thiomorpholinyl, azepanyl, and

the like. The heterocycloalkyl may be unsubstituted, or substituted with one or more substituents. Typical, non-limiting examples of such substituents include C₁-C₆ alkyl, halogen, alkoxy, CN, COOH, CONH₂, OH, NH₂, NHCOCH₃, heteroaryl, aryl, SO₂-alkyl, SO₂-aryl, OSO₂-aryl and the like. The term "heterocycloalkyl" includes three to seven membered cycloalkyl containing at least one heteroatom selected from nitrogen, oxygen, and sulfur.

The term "halogen" or halo as used herein refers to chlorine, bromine, fluorine or iodine.

The term "Boc" as used herein refers to *tert*-butoxycarbonyl.

The term "stereoisomers" as used herein refers to compounds that have identical chemical constitution, but differ with regard to the arrangement of their atoms or groups in space. The compounds of Formula (I) may contain asymmetric or chiral centers and, therefore, exist in different stereoisomeric forms. It is intended, unless specified otherwise, that all stereoisomeric forms of the compounds of Formula (I) as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers (including *cis* and *trans*-forms), as well as mixtures thereof, are embraced within the scope of the invention. In general, a reference to a compound is intended to cover its stereoisomers and mixture of various stereoisomers.

The term "optionally substituted" as used herein means that substitution is optional and therefore includes both unsubstituted and substituted atoms and moieties. A "substituted" atom or moiety indicates that any hydrogen on the designated atom or moiety can be replaced with a selection from the indicated substituent group, provided that the normal valency of the designated atom or moiety is not exceeded, and that the substitution results in a stable compound.

The term "pharmaceutically acceptable derivative" as used herein refers to and includes any pharmaceutically acceptable salt, pro-drug, metabolite, ester, ether, hydrate, polymorph, solvate, complex, and adduct of a compound described herein which, upon administration to a subject, is capable of providing (directly or indirectly) the parent compound. For example, the term "antibacterial agent or a pharmaceutically acceptable derivative thereof" includes all derivatives of the antibacterial agent (such as salts, pro-drugs, metabolites, esters, ethers, hydrates, polymorphs, solvates, complexes, and adducts) which, upon administration to a subject, are capable of providing (directly or indirectly) the antibacterial agent.

The term "pharmaceutically acceptable salt" as used herein refers to one or more salts of a given compound which possesses the desired pharmacological activity of the free compound and which are neither biologically nor otherwise undesirable. In general, the "pharmaceutically acceptable salts" refer to salts that are suitable for use in contact with the tissues of human and animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. (*J. Pharmaceutical Sciences*, 66; 1-19, 1977), incorporated herein by reference in its entirety, describes various pharmaceutical acceptable salts in details.

In general, the compounds according to the invention contain basic (e.g. nitrogen atoms) as well as acid moieties (e.g. compounds of Formula (I) wherein M is hydrogen). A person of skills in the art would appreciate that such compounds, therefore, can form acidic salts (formed with inorganic and/or organic acids), as well as basic salts (formed with inorganic and/or organic bases). Such salts can be prepared using procedures described in the art. For example, the basic moiety can be converted to its salt by treating a compound with a suitable amount of acid. Typical, non-limiting examples of such suitable acids include hydrochloric acid, trifluoroacetic acid, methanesulphonic acid or the like. Alternatively, the acid moiety may be converted into its salt by treating with a suitable base. Typical

non-limiting examples of such bases include sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate or the like. In case of compounds containing more than one functional group capable of being converted into salt, each such functional group may be converted to salt independently. For example, in case of compounds containing two basic nitrogen atoms, one of the basic nitrogen can form salt with one acid while the other basic nitrogen can form salt with another acid. Some compounds according to the invention contain both acidic as well as basic moieties, and thus can form inner salts or corresponding zwitterions. In general, all pharmaceutically acceptable salt forms of compound of Formula (I) according to invention including acid addition salts, base addition salts, zwitterions or the like are contemplated to be within the scope of the present invention and are generically referred to as pharmaceutically acceptable salts.

The term “infection” or “bacterial infection” as used herein includes presence of bacteria, in or on a subject, which, if its growth were inhibited, would result in a benefit to the subject. As such, the term “infection” in addition to referring to the presence of bacteria also refers to presence of other floras, which are not desirable. The term “infection” includes infection caused by bacteria.

The term “treat”, “treating” or “treatment” as used herein refers to administration of a medicament, including a pharmaceutical composition, or one or more pharmaceutically active ingredients, for prophylactic and/or therapeutic purposes. The term “prophylactic treatment” refers to treating a subject who is not yet infected, but who is susceptible to, or otherwise at a risk of infection (preventing the bacterial infection). The term “therapeutic treatment” refers to administering treatment to a subject already suffering from infection. The terms “treat”, “treating” or “treatment” as used herein also refer to administering compositions, or one or more of pharmaceutically active ingredients discussed herein, with or without additional pharmaceutically active or inert ingredients, in order to: (i) reduce or eliminate either a bacterial infection, or one or more symptoms of a bacterial infection, or (ii) retard progression of a bacterial infection, or one or more symptoms of a bacterial infection, or (iii) reduce severity of a bacterial infection, or one or more symptoms of a bacterial infection, or (iv) suppress clinical manifestation of a bacterial infection, or (v) suppress manifestation of adverse symptoms of a bacterial infection.

The terms “pharmaceutically effective amount” or “therapeutically effective amount” or “effective amount” as used herein refer to an amount, which has a therapeutic effect or is the amount required to produce a therapeutic effect in a subject. For example, a “therapeutically effective amount” or “pharmaceutically effective amount” or “effective amount” of an antibacterial agent or a pharmaceutical composition is the amount of the antibacterial agent or the pharmaceutical composition required to produce a desired therapeutic effect as may be judged by clinical trial results, model animal infection studies, and/or in vitro studies (e.g. in agar or broth media). Such effective amount depends on several factors, including but not limited to, the microorganism (e.g. bacteria) involved, characteristics of the subject (for example height, weight, sex, age and medical history), severity of infection and particular type of the antibacterial agent used. For prophylactic treatments, a prophylactically effective amount is that amount which would be effective in preventing the bacterial infection.

The term “administration” or “administering” refers to and includes delivery of a composition, or one or more pharmaceutically active ingredients to a subject, including for example, by any appropriate method, which serves to deliver the composition or its active ingredients or other pharmaceutically active ingredients to the site of infection. The method of administration may vary depending on various factors, such as for example, the components of the pharmaceutical composition or type/nature of the pharmaceutically active or inert ingredients, site of the potential or actual infection, the microorganism involved, severity of the infection, age and physical condition of the subject and a like. Some non-limiting examples of ways to administer a composition or a pharmaceutically active ingredient to a subject according to this invention include oral, intravenous,

topical, intrarespiratory, intraperitoneal, intramuscular, parenteral, sublingual, transdermal, intranasal, aerosol, intraocular, intratracheal, intrarectal, vaginal, gene gun, dermal patch, eye drop and mouthwash. In case of a pharmaceutical composition comprising more than one ingredients (active or inert), one of the ways of administering such composition is by admixing the ingredients (e.g. in the form of a suitable unit dosage form such as tablet, capsule, solution, powder or a like) and then administering the dosage form. Alternatively, the ingredients may also be administered separately (simultaneously or one after the other) as long as these ingredients reach beneficial therapeutic levels such that the composition as a whole provides a synergistic and/or desired effect.

The term “growth” as used herein refers to a growth of one or more microorganisms and includes reproduction or population expansion of the microorganism (e.g. bacteria). The term “growth” also includes maintenance of on-going metabolic processes of the microorganism, including the processes that keep the microorganism alive.

The term, “effectiveness” as used herein refers to ability of a treatment, or a composition, or one or more pharmaceutically active ingredients to produce a desired biological effect in a subject. For example, the term “antibacterial effectiveness” of a composition or of an antibacterial agent refers to the ability of the composition or the antibacterial agent to prevent or treat bacterial infection in a subject.

The term “synergistic” or “synergy” as used herein refers to the interaction of two or more agents so that their combined effect is greater than their individual effects.

The term “antibacterial agent” as used herein refers to any substance, compound, a combination of substances, or a combination of compounds capable of: (i) inhibiting, reducing or preventing growth of bacteria; (ii) inhibiting or reducing ability of a bacteria to produce infection in a subject; or (iii) inhibiting or reducing ability of bacteria to multiply or remain infective in the environment. The term “antibacterial agent” also refers to compounds capable of decreasing infectivity or virulence of bacteria.

The term “beta-lactamase” or “beta-lactamase enzyme” as used herein refers to any enzyme or protein or any other substance that breaks down a beta-lactam ring. The term “beta-lactamase” includes enzymes that are produced by bacteria and have the ability to hydrolyze the beta-lactam ring in a beta-lactam compound, either partially or completely.

The term “extended spectrum beta-lactamase” (ESBL) as used herein includes those beta-lactamase enzymes, which are capable of conferring bacterial resistance to various beta-lactam antibacterial agents such as penicillins, cephalosporins, aztreonam and the like.

The term “beta-lactamase inhibitor” as used herein refers to a compound capable of inhibiting activity of one or more beta-lactamase enzymes, either partially or completely.

The term “colony forming units” or “CFU” as used herein refers to an estimate of number of viable bacterial cells per ml of the sample. Typically, a “colony of bacteria” refers to a mass of individual bacteria growing together.

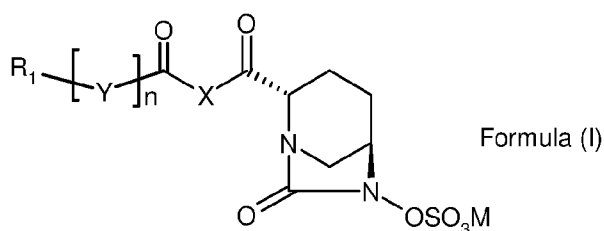
The term “pharmaceutically inert ingredient” or “carrier” or “excipient” refers to and includes compounds or materials used to facilitate administration of a compound, for example, to increase the solubility of the compound. Typical, non-limiting examples of solid carriers include starch, lactose, dicalcium phosphate, sucrose, and kaolin. Typical, non-limiting examples of liquid carriers include sterile water, saline, buffers, non-ionic surfactants, and edible oils. In addition, various adjuvants commonly used in the art may also be included. These and other such compounds are described in

literature, e.g., in the Merck Index (Merck & Company, Rahway, N.J.). Considerations for inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman et al. (Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press., 1990), which is incorporated herein by reference in its entirety.

The term "subject" as used herein refers to vertebrate or invertebrate, including a mammal. The term "subject" includes human, animal, a bird, a fish, or an amphibian. Typical, non-limiting examples of a "subject" include humans, cats, dogs, horses, sheep, bovine cows, pigs, lambs, rats, mice and guinea pigs.

The term "cation" as used herein refers to all organic and inorganic positively charged ions. The term "organic cation" refers to all positively charged organic ions. Typical, non-limiting examples of organic cations include unsubstituted ammonium cations, alkyl substituted ammonium cations, cycloalkyl substituted ammonium cations, primary, secondary and tertiary amines, alkyl amines, cycloalkyl amines, aryl amines, *N,N'*-dibenzylethylenediamine and the like. The term "inorganic cation" refers to a positively charged metal ion. Typical, non-limiting examples of inorganic cations include Group I and Group II metal cations such as, for example, lithium, sodium, potassium, rubidium, cesium, beryllium, magnesium, calcium and the like.

In one general aspect, there are provided compounds of Formula (I):



or a stereoisomer or a pharmaceutically acceptable derivative thereof;

wherein:

X is: -NH- or -NH-NH-;

Y is: -CR₂R₃-, -NH-, -NHNH-, -ONH- or -O-;

provided that when X is -NH-NH-; Y is -NH- or -O-;

R₁ is:

- (a) hydrogen;
- (b) C₁-C₆ alkyl optionally substituted with one or more substituents independently selected from OR₂, NR₂R₃, SR₂, halogen, CN, COOR₂, CONR₂R₃, (CH₂)_mOR₂, (CH₂)_mNR₂R₃, cycloalkyl, heterocycloalkyl, aryl or heteroaryl;
- (c) cycloalkyl optionally substituted with one or more substituents independently selected from OR₂, NR₂R₃, SR₂, halogen, CN, COOR₂, CONR₂R₃, (CH₂)_mOR₂ or CH₂NR₂R₃;
- (d) aryl optionally substituted with one or more substituents independently selected from OR₂, NR₂R₃, SR₂, halogen, CN, COOR₂, CONR₂R₃, (CH₂)_mOR₂ or (CH₂)_mNR₂R₃;
- (e) heteroaryl optionally substituted with one or more substituents independently selected from OR₂, NR₂R₃, SR₂, halogen, CN, COOR₂, CONR₂R₃, (CH₂)_mOR₂ or (CH₂)_mNR₂R₃ or;

- (f) heterocycloalkyl optionally substituted with one or more substituents independently selected from OR₂, NR₂R₃, SR₂, halogen, CN, COOR₂, CONR₂R₃, (CH₂)_mOR₂ or (CH₂)_mNR₂R₃;

R₂ and R₃ are each independently:

- (a) hydrogen,
- (b) C₁-C₆ alkyl,
- (c) cycloalkyl,
- (d) aryl,
- (e) heteroaryl, or
- (f) heterocycloalkyl;
- (g) R₂ and R₃ are joined together to form three to seven membered ring optionally containing one or more heteroatoms selected from nitrogen, sulfur and oxygen.

m is 1 to 5;

n is 0 or 1;

M is hydrogen or a cation.

Typical, non-limiting examples of compounds according to the invention include:

(2*S*, 5*R*)-7-Oxo-*N*- (piperidin-4-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*- [(3*R*)-piperidin-3-yl-carbamoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*- (piperidin-3-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*- [(3*S*)-piperidin-3-yl-carbamoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-[(3*R*)-pyrrolidin-3-yl-carbamoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*- [(3*S*)-pyrrolidin-3-yl-carbamoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(pyrrolidin-3-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(pyrrolidin-3-yl-acetyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(pyrrolidin-2-yl-acetyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-[3-(pyrrolidin-2-yl)propanoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-[3-(pyrrolidin-3-yl)propanoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

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

(2*S*, 5*R*)-7-Oxo-*N*-[(3*R*)-piperidin-3-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-[(3*S*)-piperidin-3-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(piperidin-3-yl-carbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(piperidin-4-yl-carbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*- [(2*S*)-pyrrolidin-2-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-[(3*R*)-pyrrolidin-3-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-[(3*S*)-pyrrolidin-3-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(pyrrolidin-3-yl-carbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

2-{[(2*S*, 5*R*)-7-Oxo-6- (sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl}-*N*- [((2*R*, 5*S*)-5-aminopiperidine-2-carboxamide);

2-Aminoethyl {[(2*S*, 5*R*)-7-oxo-6- (sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} carbamate;

(2*S*)-Pyrrolidin-2-ylmethyl {[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl} carbamate;

(3*R*)-Pyrrolidin-3-yl- {[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2- yl]carbonyl} carbamate;

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

(2*S*, 5*R*)-7-Oxo-*N*- {[(2*S*)-pyrrolidin-2-ylmethoxy] carbamoyl}-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*- {[(3*R*)-pyrrolidin-3-yloxy] carbamoyl}-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide

(2*S*, 5*R*)-7-Oxo-*N*-(phenylcarbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(pyridin-3-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(pyridin-4-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(pyridin-2-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(ethoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(tert-butoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(propoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(isopropoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(acetyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-[2-(2,2-dimethylpropanoyl)] -6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

2- {[(2*S*, 5*R*)-7-Oxo-6- (sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl}-*N*- phenylhydrazinecarboxamide;

N- (2-methoxyphenyl)-2- {[(2*S*, 5*R*)-7-oxo-6- (sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} hydrazinecarboxamide;

2- {[(2*S*, 5*R*)-7-Oxo-6- (sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl}-*N*- (pyridin-3-yl) hydrazinecarboxamide;

N-Cyclohexyl-2- {[(2*S*,5*R*) -7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl} hydrazinecarboxamide;

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

N-Benzyl-2-[[[(2*S*,5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl]hydrazinecarboxamide;

2-[[[(2*S*,5*R*)-7-Oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl]-*N*-(pyridin-4-ylmethyl)hydrazinecarboxamide;

N-(2-Aminoethyl)-2- [[[(2*S*,5*R*)- 7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl]hydrazinecarboxamide;

2-[[[(2*S*,5*R*)-7-Oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl]-*N*-[(2*S*)-pyrrolidin-2-ylmethyl]hydrazinecarboxamide;

2-[4-(2-Aminoethoxy)phenyl]ethyl [[[(2*S*,5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl] carbamate;

3-Aminopropyl [[[(2*S*,5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl] carbamate;

Methyl 2-amino-3-[[[(2*S*,5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl] carbamoyl]oxy]propanoate;

2-(Phenyl amino) ethyl [[[(2*S*,5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl] carbamate;

2-(Benzyl amino) ethyl [[[(2*S*,5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl] carbamate;

2-(Pyridine-4-methylamino) ethyl [[[(2*S*,5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl] carbamate;

2-(Pyridin-2-ylamino) ethyl [[[(2*S*,5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1]oct-2-yl]carbonyl] carbamate;

2-(Pyridin-3-ylamino)ethyl [[[(2*S*,5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1]oct-2-yl]carbonyl] carbamate;

(2*S*)-2-Aminopropyl [[[(2*S*,5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1]oct-2-yl]carbonyl] carbamate;

(2*S*,5*R*)-7-Oxo-6-(sulfooxy)-*N*-[[2-(2*H*-1,2,3-triazol-2-yl)ethyl]carbamoyl]-1,6- diazabicyclo [3.2.1]octane-2-carboxamide;

(2*S*,5*R*)-7-Oxo-6-(sulfooxy)-*N*-[[2-(1*H*-1,2,3-triazol-1-yl)ethyl]carbamoyl]-1,6- diazabicyclo [3.2.1]octane-2-carboxamide;

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

(2*S*)-2-Amino-2-phenylethyl[[[(2*S*,5*R*)-7-oxo-6-(sulfooxy)-1,6- diazabicyclo [3.2.1] oct-2-yl]carbonyl] carbamate;

or a stereoisomer or a pharmaceutically acceptable derivative thereof.

In some embodiments, typical, non-limiting examples of compounds according to the invention include:

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*- (piperidin-4-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*- [(3*R*)-piperidin-3-yl-carbamoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*- (piperidin-3-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-[(3*S*)-piperidin-3-yl-carbamoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-[(3*R*)-pyrrolidin-3-yl-carbamoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-[(3*S*)-pyrrolidin-3-yl-carbamoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(pyrrolidin-3-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(pyrrolidin-3-yl-acetyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(pyrrolidin-2-yl-acetyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-[3-(pyrrolidin-2-yl)propanoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-[3-(pyrrolidin-3-yl)propanoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-*N*-(3-aminopropanoyl)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-[(3*R*)-piperidin-3-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-[(3*S*)-piperidin-3-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(piperidin-3-yl-carbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(piperidin-4-yl-carbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-[(2*S*)-pyrrolidin-2-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-[(3*R*)-pyrrolidin-3-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-[(3*S*)-pyrrolidin-3-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(pyrrolidin-3-yl-carbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of 2-{[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl}-*N*-[(2*R*, 5*S*)-5-aminopiperidine-2-carboxamide];

Sodium salt of 2-aminoethyl {[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} carbamate;

Sodium salt of (2*S*)-pyrrolidin-2-ylmethyl {[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} carbamate;

Sodium salt of (3*R*)-pyrrolidin-3-yl-[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} carbamate;

Sodium salt of (2*S*, 5*R*)-*N*-[(2-aminoethoxy) carbamoyl]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-{[(2*S*)-pyrrolidin-2-ylmethoxy] carbamoyl}-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-{[(3*R*)-pyrrolidin-3-yloxy] carbamoyl}-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(phenylcarbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(pyridin-3-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(pyridin-4-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(pyridin-2-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(ethoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(tert-butoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(propoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(isopropoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(acetyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-[2-(2,2-dimethylpropanoyl)] -6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of 2-{[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl}-*N*-phenylhydrazinecarboxamide;

Sodium salt of *N*-(2-methoxyphenyl)-2-{[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} hydrazinecarboxamide;

Sodium salt of 2-{[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl}-*N*-(pyridin-3-yl) hydrazinecarboxamide;

Sodium salt of *N*-cyclohexyl-2-{[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} hydrazinecarboxamide;

Sodium salt of (2*S*, 5*R*)-*N*-carbamoyl-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of *N*-benzyl-2-{[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} hydrazinecarboxamide;

Sodium salt of 2-{[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl}-*N*-(pyridin-4-ylmethyl) hydrazinecarboxamide;

Sodium salt of *N*-(2-aminoethyl)-2-{[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} hydrazinecarboxamide;

Sodium salt of 2-{[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl}-*N*-[(2*S*)-pyrrolidin-2-ylmethyl] hydrazinecarboxamide;

Sodium salt of 2-[4-(2-aminoethoxy)phenyl]ethyl {[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} carbamate;

Sodium salt of 3-aminopropyl {[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} carbamate;

Sodium salt of methyl 2-amino-3-[[[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl] carbamoyl]oxy]propanoate;

Sodium salt of 2-(phenyl amino)ethyl {[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} carbamate;

Sodium salt of 2-(benzyl amino)ethyl {[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} carbamate;

Sodium salt of 2-(pyridine-4-methylamino)ethyl {[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} carbamate;

Sodium salt of 2-(pyridin-2-ylamino)ethyl {[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} carbamate;

Sodium salt of 2-(pyridin-3-ylamino)ethyl {[*(2S,5R)*]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl}carbonyl} carbamate;

Sodium salt of (*2S*)-2-aminopropyl {[*(2S,5R)*]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl}carbonyl} carbamate;

Sodium salt of (*2S,5R*)-7-oxo-6-(sulfooxy)-*N*-{[2-(*2H*-1,2,3-triazol-2-yl)ethyl]carbonyl}-1,6-diazabicyclo [3.2.1]octane-2-carboxamide;

Sodium salt of (*2S,5R*)-7-oxo-6-(sulfooxy)-*N*-{[2-(*1H*-1,2,3-triazol-1-yl)ethyl]carbonyl}-1,6-diazabicyclo [3.2.1]octane-2-carboxamide;

Sodium salt of (*2S,5R*)-*N*-[(2-hydroxyethyl)carbonyl]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide;

Sodium salt of (*2S*)-2-amino-2-phenylethyl{[*(2S,5R)*]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl}carbonyl} carbamate;

or a stereoisomer thereof.

In general, the compounds of the invention can be prepared according to the general procedure given in Scheme 1, Scheme 2 or Scheme 3. A person of skills in the art would appreciate that the described method can be varied or optimized further to provide the desired and related compounds. In the following procedures all variables are as defined above.

In one general aspect, a compound of Formula (I) can be prepared by the general procedure as described in Scheme 1. A compound of Formula (1a) is treated with a suitable carboxyl group activating reagent to obtain a compound of Formula (1b). Typical, non-limiting examples of carboxyl group activating reagent include thionyl chloride, oxalyl chloride, phosphorous trichloride, phosphorous oxychloride, phosphorous pentachloride, α -bromoacetyl bromide, pivaloyl chloride, diphenylphosphonic azide dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl), 1,1'-carbonyldiimidazole, di-*tert*-butyldicarbonate, acetic anhydride, ethyl chloroformate, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EDDQ), 1-hydroxybenzotriazole (HOBt), *N*-hydroxysuccinimide, 1-hydroxy-7-aza-1*H*-benzotriazole, 4-(*N,N*-dimethylamino)pyridine, 2-propanephosphonic acid anhydride, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium salts, bis-trichloromethylcarbonate, triphosgene, *p*-nitrophenol (PNP), pentafluorophenol (PFP), 4-trifluoromethyl benzoic anhydride, 2-methyl-6-nitrobenzoic anhydride and the like or mixture thereof. A compound of Formula (1b) is also activated with a suitable reagent such as magnesium bromide, lithium bromide, or magnesium bromide diethyletherate in a suitable solvent such as dichloromethane, dimethylformamide, or 1,4-dioxane. The activated compound of Formula (1b) is then reacted with a compound of Formula (1c) in presence of suitable solvent such as tetrahydrofuran or dichloromethane at a temperature of about -15°C to about 10°C for about 1 hour to about 24 hour to obtain a coupled compound of Formula (1d).

The compound of Formula (1d) is debenzylated by subjecting it for hydrogenolysis by using hydrogen source in presence of transition metal catalyst in a suitable solvent such as methanol, ethanol, methanol dichloromethane mixture, *N,N* dimethyl formamide dichloromethane mixture, ethyl acetate, tetrahydrofuran, or ethyl acetate and tetrahydrofuran mixture at a temperature ranging from about 10 °C to about 60°C for about 1 hour to about 14 hour to provide a compound of Formula (1e). Typical, non-limiting examples of hydrogen source include hydrogen gas, ammonium formate, cyclohexene, lithium –liquid ammonia, ammonia – *tert*-butanol, sodium – liquid ammonia – *tert*-butanol, triethyl silyl hydride and the like. Typical, non-limiting examples of transition metal catalyst include 5% palladium on carbon, 10% palladium on carbon, 20% palladium hydroxide on carbon, Raney-Nickel and the like. In some embodiments, compound of Formula (1d) is treated with 10% palladium on carbon in presence of hydrogen gas at 2 atmospheric pressure and at temperature of about 25°C for about 2 hour to provide a compound of Formula (1e). In some embodiments, the

solvent used in conversion of a compound of Formula (1d) to a compound of Formula (1e) is mixture of dimethylformamide and dichloromethane.

The compound of Formula (1e) is sulfonated by reacting with suitable sulfonating reagent in a suitable solvent such as pyridine, dichloromethane or *N,N*-dimethylformamide, at a temperature ranging from about 0°C to about 80°C for about 1 hour to about 24 hour. Typical non-limiting examples of sulfonating reagent include sulfur trioxide pyridine complex, sulfur trioxide trimethylamine complex, sulfur trioxide triethylamine complex, sulfur trioxide *N,N*-dimethylaniline complex, sulfur trioxide 2-methylpyridine complex, sulfur trioxide dioxane complex, sulfur trioxide thioxane complex, sulfur trioxide dimethyl sulfide complex, sulfur trioxide dimethylsulfoxide complex, sulfur trioxide *N,N*-dimethylformamide complex and the like. In some embodiments, compound of Formula (1e) is treated with dimethylformamide sulfur trioxide complex or pyridine sulfur trioxide complex to obtain the sulfonated compound.

The obtained sulfonated compound is converted to corresponding tetrabutylammonium salt. In some embodiments, the obtained sulfonated compound is treated with tetrabutylammonium acetate (TBAA) to provide tetrabutylammonium salt of sulfonic acid compound of Formula (1f). The compound according to the invention is then isolated as zwitterions, by removing the protecting groups of compound of Formula (1f). The compound of Formula (1f) is reacted with suitable deprotecting agent such as trifluoroacetic acid in presence of a suitable solvent such as dichloromethane, chloroform or acetonitrile, at a temperature ranging from about -15°C to about 40°C for about 0.5 hours to about 14 hour to obtain a compound of Formula (I). In some embodiments, compound of Formula (1f) is treated with trifluoroacetic acid in presence of dichloromethane at temperature of about 0°C to about -10°C for about 1 hour to provide a compound of Formula (I), wherein M is H.

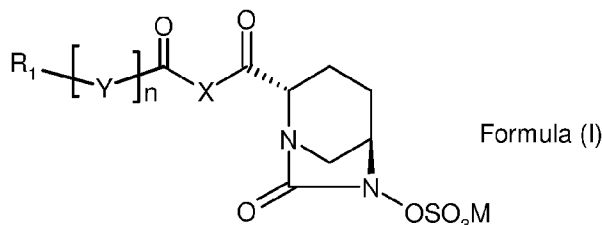
The compound of Formula (1f) may also be converted to compound of Formula (I), wherein M is a cation. In some embodiments, compound of Formula (1f) is dissolved in suitable solvent such as 10% tetrahydrofuran: water mixture and passed through the column packed with Dowex 50WX8 200 Na⁺ resin or passing through Indion 225 Na resin to provide sodium salt of a compound of Formula (I). In some embodiments, compound of Formula (1f) was dissolved in suitable solvent such as acetone, tetrahydrofuran, ethanol, isopropanol or acetonitrile and thereby treating with sodium ethylhexanoate or potassium ethylhexanoate to provide sodium or potassium salt of compound of Formula (I).

In another general aspects, compound of Formula (I), wherein X=Y= -NH, can be prepared by the general procedure as described in Scheme 2. The compound of Formula (1c) is activated by treating with suitable reagent such as magnesium bromide or lithium bromide, or magnesium bromide diethyletherate in presence of suitable solvent such as dichloromethane, dimethylformamide, or 1,4-dioxane. This activated compound is reacted with an isocyanate compound of Formula (2a) in presence of suitable solvent such as dichloromethane, dimethylformamide or 1,4-dioxane at a temperature of about -15°C to about 15°C to obtain a compound of Formula (2b). In some embodiments, compound of Formula (1c) is reacted with an isocyanate compound of Formula (2a) in presence of magnesium bromide or lithium bromide and in presence of dichloromethane at a temperature of about 0°C to about 5°C to obtain a compound of Formula (2b). The compound of Formula (2b) is subjected through same sequence of reactions as described in Scheme 1 to obtain a compound of Formula (I), wherein X=Y= NH.

In another general aspect, compound of Formula (I), wherein X= -NHNH- and Y= -NH-, can be prepared by the general procedure as described in Scheme 3. The compound of Formula (3e) (prepared according to the procedure disclosed in International Patent Application No. PCT/IB2013/059264) is reacted with a semicarbazide compound of Formula (3a) in presence of suitable coupling agent, suitable base and suitable solvent such as water, tetrahydrofuran, acetonitrile,

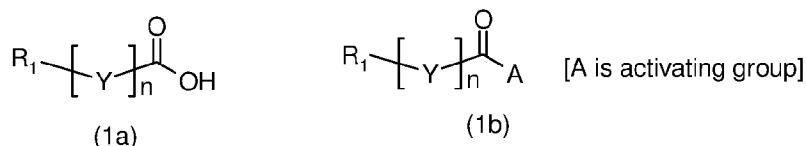
dimethylformamide, dichloromethane or mixtures thereof at a temperature of about 0°C to about 50°C to obtain a compound of Formula (3b). In some embodiments, compound of Formula (3e) is reacted with a semicarbazide compound of Formula (3a) in presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC.HCl) and 1-hydroxybenzotriazole (HOBt) at a temperature of about 25°C for about 16 hours to obtain a compound of Formula (3b). The compound of Formula (3b) is subjected through same sequence of reactions as described in Scheme 1 to obtain a compound of Formula (I), wherein X= -NHNH- and Y= -NH.

In some embodiments, there is provided a process for preparation of a compound of Formula (I), wherein X is NH,

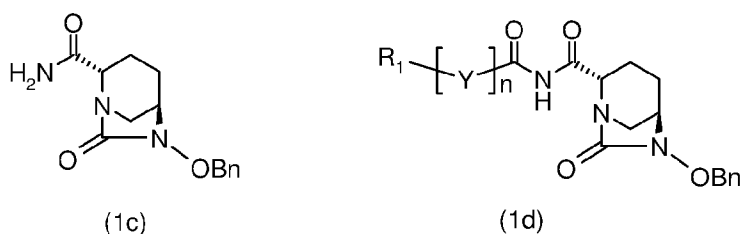


said process comprising:

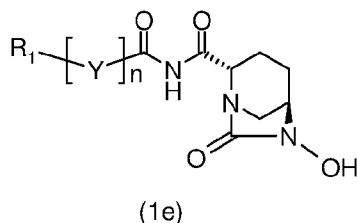
- (a) converting a compound of Formula (1a) to a compound of Formula (1b);



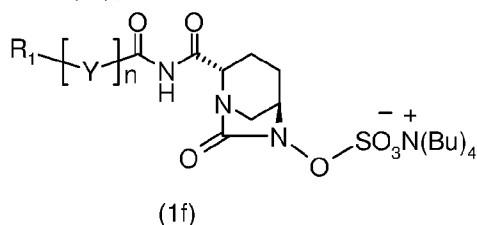
- (b) reacting a compound of Formula (1b) with a compound of Formula (1c) to obtain a compound of Formula (1d);



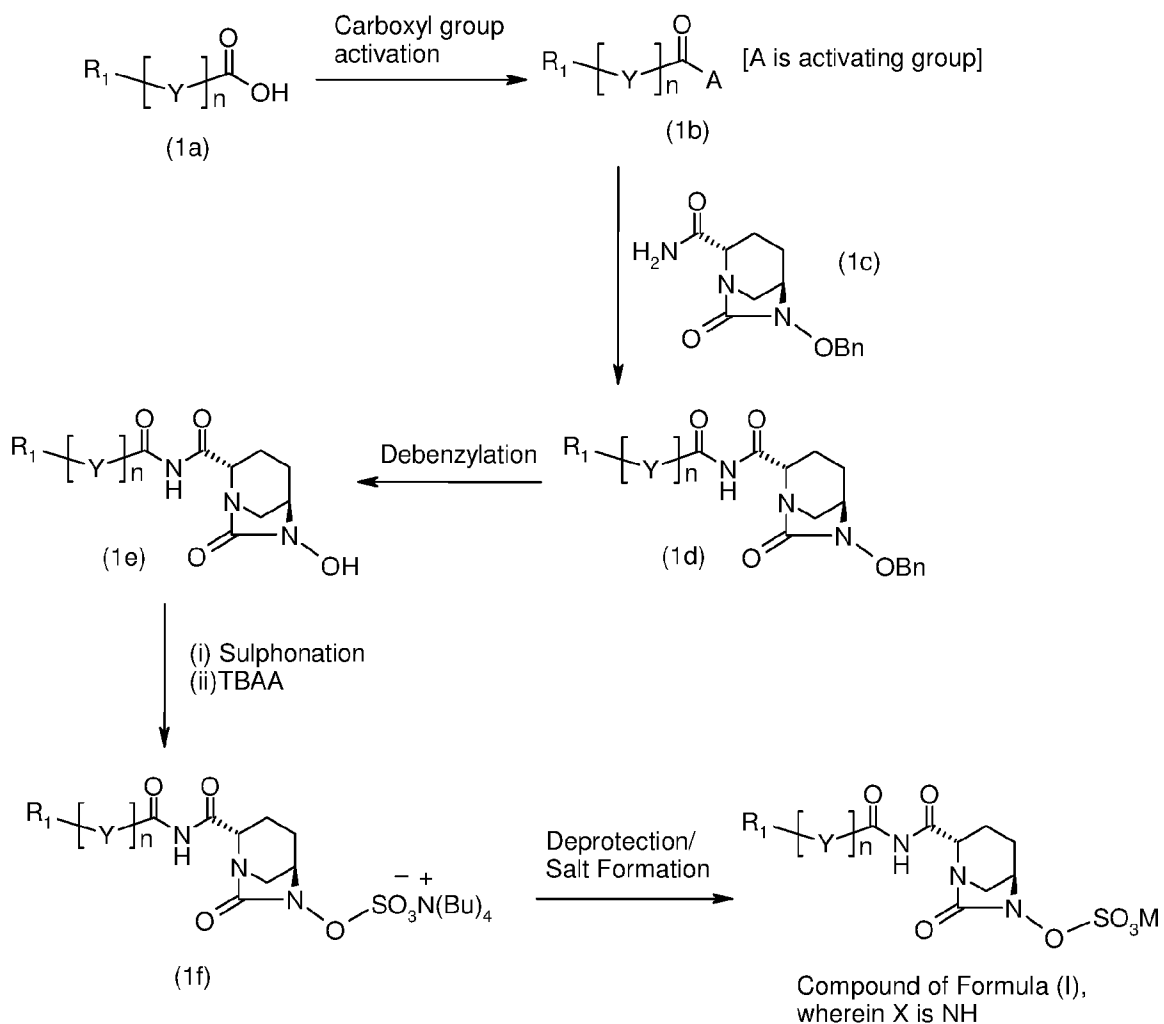
- (c) debenzylating a compound of Formula (1d) to obtain a compound of Formula (1e);



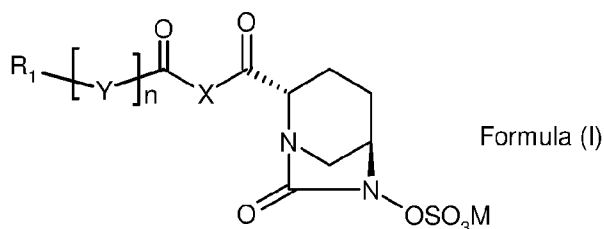
- (d) sulfonating a compound of Formula (1e), followed by tetrabutylammonium salt formation to obtain a compound of Formula (1f);



- (e) converting a compound of Formula (1f) to a compound of Formula (I).

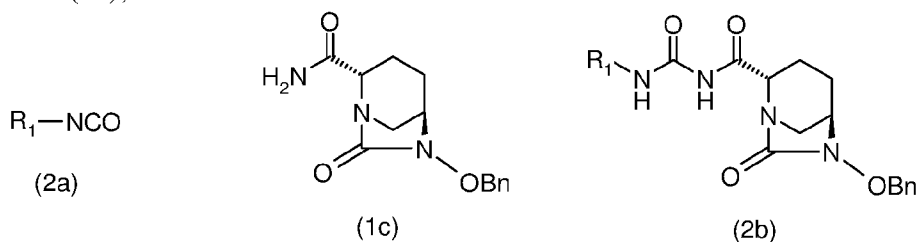
**Scheme 1**

In some embodiments, there is provided a process for preparation of a compound of Formula (I), wherein X=Y=NH,

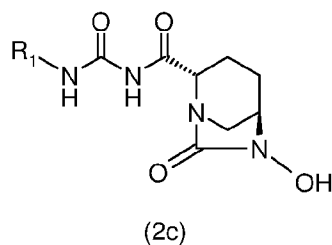


said process comprising:

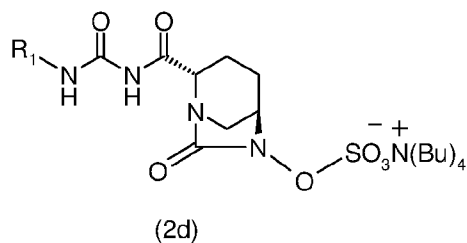
(a) reacting a compound of Formula (2a) with a compound of Formula (1c) to obtain a compound of Formula (2b);



- (b) debenzylating a compound of Formula (2b) to obtain a compound of Formula (2c);

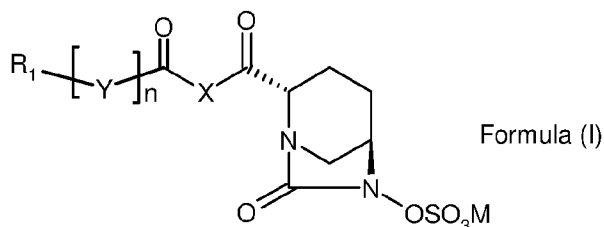


- (c) sulfonating a compound of Formula (2c), followed by tetrabutylammonium salt formation to obtain a compound of Formula (2d);



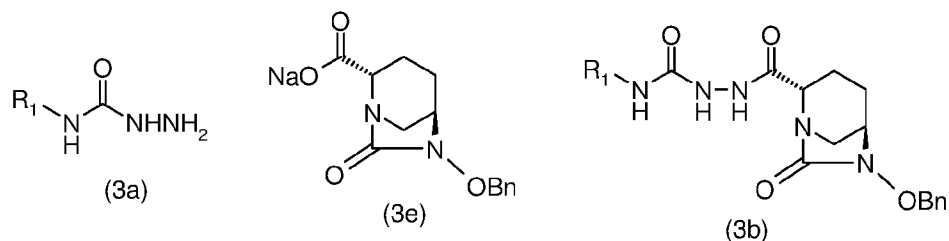
- (d) converting a compound of Formula (2d) to a compound of Formula (I).

In some embodiments, there is provided a process for preparation of a compound of Formula (I), wherein X= -NHNH- and Y= -NH-,

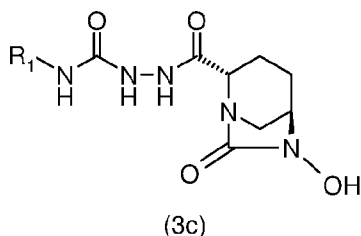


said process comprising:

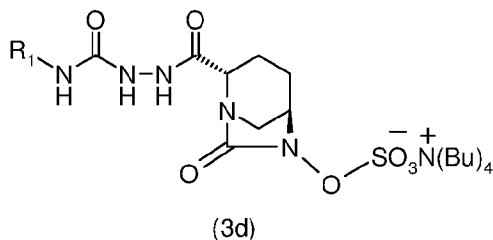
- (a) reacting a compound of Formula (3a) with a compound of Formula (1c) to obtain a compound of Formula (3b);



- (c) debenzylating a compound of Formula (3b) to obtain a compound of Formula (3c);



(c) sulfonating a compound of Formula (3c), followed by tetrabutylammonium salt formation to obtain a compound of Formula (3d);



(d) converting a compound of Formula (3d) to a compound of Formula (I).

In some embodiments, there are provided pharmaceutical compositions comprising a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof.

In some other embodiments, there are provided pharmaceutical compositions comprising: (a) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and (b) at least one beta-lactamase inhibitor or a pharmaceutically acceptable derivative thereof.

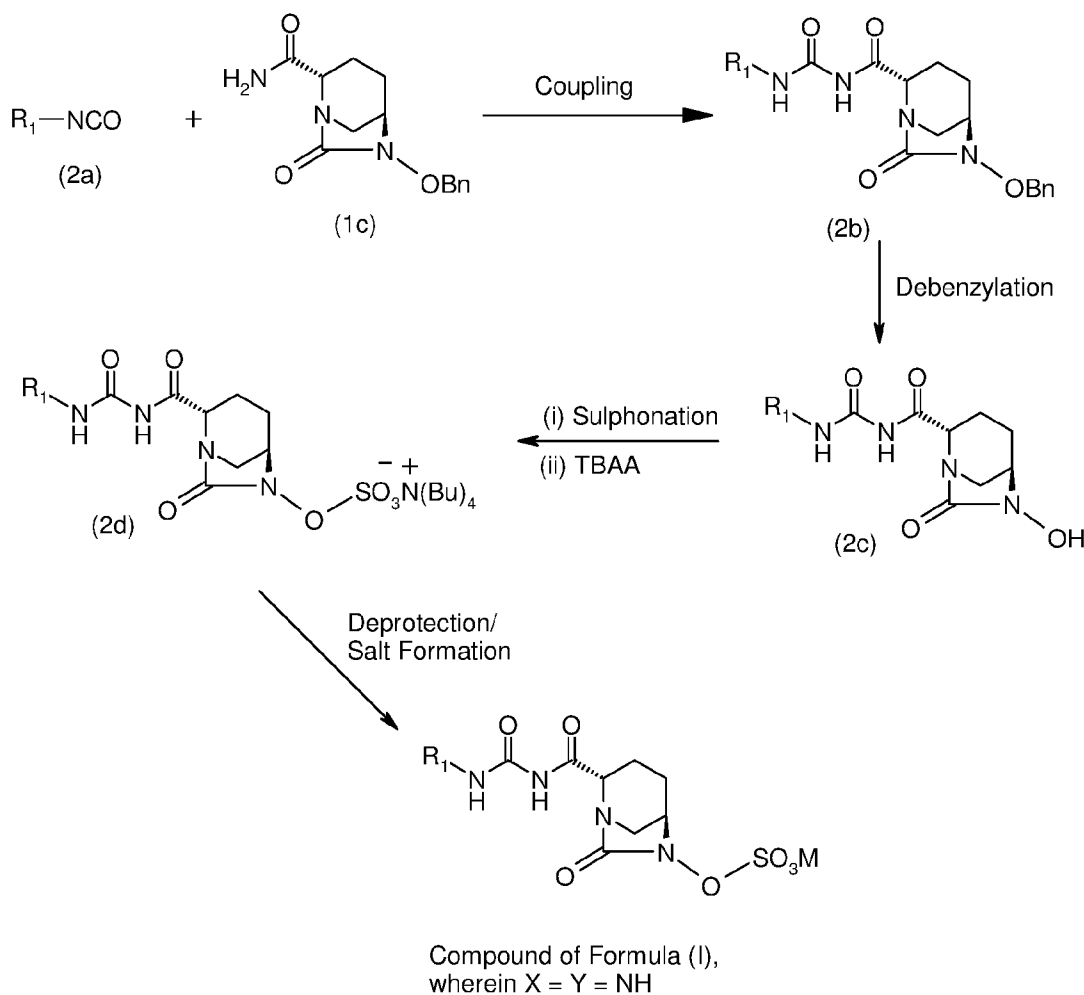
In some other embodiments, there are provided pharmaceutical compositions comprising: (a) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and (b) at least one beta-lactamase inhibitor selected from sulbactam, tazobactam, clavulanic acid, avibactam or a pharmaceutically acceptable derivative thereof.

In some other embodiments, there are provided pharmaceutical compositions comprising: (a) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and (b) at least one antibacterial agent or a pharmaceutically acceptable derivative thereof.

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In some other embodiments, there are provided pharmaceutical compositions comprising: (a) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, (b) at least one beta-lactamase inhibitor or a pharmaceutically acceptable derivative thereof, and (c) at least one antibacterial agent, or a pharmaceutically acceptable derivative thereof.

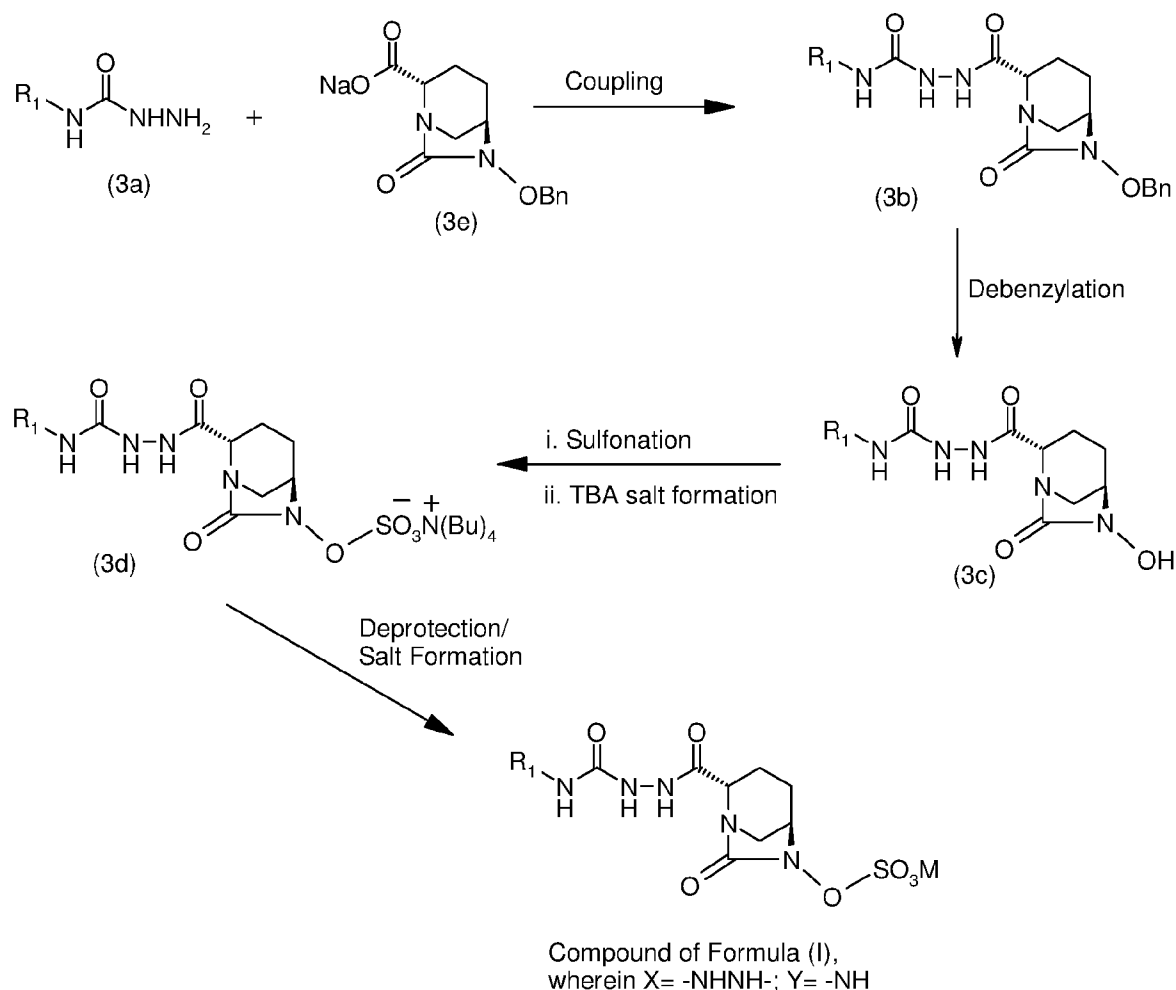
In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said methods comprising administering to said subject a pharmaceutical composition comprising a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof.

**Scheme 2**

In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said methods comprising administering to said subject a pharmaceutical composition comprising: (a) a compound of Formula (I), or a stereoisomer or a pharmaceutically acceptable derivative thereof and (b) at least one beta-lactamase inhibitor or pharmaceutically acceptable derivative thereof.

In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said methods comprising administering to said subject a pharmaceutical composition comprising: (a) a compound of Formula (I), or a stereoisomer or a pharmaceutically acceptable derivative thereof and (b) at least one beta-lactamase inhibitor selected from sulbactam, tazobactam, clavulanic acid, avibactam, or pharmaceutically acceptable derivative thereof.

In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said methods comprising administering to said subject a pharmaceutical composition comprising: (a) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and (b) at least one antibacterial agent or a pharmaceutically acceptable derivative thereof.

**Scheme 3**

In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said methods comprising administering to said subject a pharmaceutical composition comprising: (a) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and (b) at least one antibacterial agent selected from selected from cefepime, cefpirome, ceftaroline, ceftazidime, ceftalozane or a pharmaceutically acceptable derivative thereof.

In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said methods comprising administering to said subject a pharmaceutical composition comprising: (a) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, (b) at least one beta-lactamase inhibitor or pharmaceutically acceptable derivative thereof and (c) at least one antibacterial agent or a pharmaceutically acceptable derivative thereof.

In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said method comprising administering to said subject a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof.

In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said methods comprising administering to said subject: (a) a compound of

carboxamide or a stereoisomer thereof, (b) at least one beta-lactamase inhibitor or a pharmaceutically acceptable derivative thereof, and (c) at least one antibacterial agent, or a pharmaceutically acceptable derivative thereof.

In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said methods comprising administering to said subject a pharmaceutical composition comprising a sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(ethoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide or a stereoisomer thereof.

In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said methods comprising administering to said subject a pharmaceutical composition comprising: (a) a sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(ethoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide or a stereoisomer thereof, and (b) at least one beta-lactamase inhibitor or pharmaceutically acceptable derivative thereof.

In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said methods comprising administering to said subject a pharmaceutical composition comprising: (a) a sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(ethoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide or a stereoisomer thereof, and (b) at least one beta-lactamase inhibitor selected from sulbactam, tazobactam, clavulanic acid, avibactam, or pharmaceutically acceptable derivative thereof.

In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said methods comprising administering to said subject a pharmaceutical composition comprising: (a) a sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(ethoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide or a stereoisomer thereof, and (b) at least one antibacterial agent or a pharmaceutically acceptable derivative thereof.

In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said methods comprising administering to said subject a pharmaceutical composition comprising: (a) a sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(ethoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide or a stereoisomer thereof, and (b) at least one antibacterial agent selected from selected from cefepime, cefpirome, ceftaroline, ceftazidime, ceftalozane or a pharmaceutically acceptable derivative thereof.

In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said methods comprising administering to said subject a pharmaceutical composition comprising: (a) a sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(ethoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide or a stereoisomer thereof, (b) at least one beta-lactamase inhibitor or pharmaceutically acceptable derivative thereof and (c) at least one antibacterial agent or a pharmaceutically acceptable derivative thereof.

In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said method comprising administering to said subject a sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(ethoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide or a stereoisomer thereof.

In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said methods comprising administering to said subject: (a) a sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(ethoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide or a stereoisomer thereof, (b) at least one beta-lactamase inhibitor or pharmaceutically acceptable derivative thereof.

In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said methods comprising administering to said subject: (a) a sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(ethoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide or a stereoisomer thereof, (b) at least one beta-lactamase inhibitor selected from sulbactam, tazobactam, clavulanic acid, avibactam, or pharmaceutically acceptable derivative thereof.

In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said methods comprising administering to said subject: (a) a sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(ethoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide or a stereoisomer thereof, (b) at least one antibacterial agent or pharmaceutically acceptable derivative thereof.

In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said methods comprising administering to said subject: (a) a sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(ethoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide or a stereoisomer thereof, (b) at least one antibacterial agent selected from selected from cefepime, ceftiprome, ceftaroline, ceftazidime, ceftalozane or pharmaceutically acceptable derivative thereof.

In some other embodiments, there are provided methods for preventing or treating a bacterial infection in a subject, said methods comprising administering to said subject: (a) a sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(ethoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide or a stereoisomer thereof, (b) at least one beta-lactamase inhibitor or pharmaceutically acceptable derivative thereof, and (c) at least one antibacterial agent or pharmaceutically acceptable derivative thereof.

In some embodiments, the compositions and methods according to the invention use compounds of Formula (I), or a stereoisomer or a pharmaceutically acceptable derivative thereof in combination with at least one antibacterial agent or a pharmaceutically acceptable derivative thereof. A wide variety of antibacterial agents can be used. Typical, non-limiting examples of antibacterial agents include one or more of antibacterial compounds generally classified as aminoglycosides, Ansamycins, Carbacephems, Cephalosporins, Cephamycins, Lincosamides, Lipopeptides, Macrolides, Monobactams, Nitrofurans, Penicillins, Polypeptides, Quinolones, Sulfonamides, Tetracyclines, Oxazolidinone and the like. Typical, non-limiting examples of Aminoglycoside antibacterial agents include Amikacin, Gentamicin, Kanamycin, Neomycin, Netilmicin, Tobramycin, Paromomycin, Arbekacin, Streptomycin, Apramycin and the like. Typical, non-limiting examples of Ansamycin antibacterial agents include Geldanamycin, Herbimycin and the like. Typical, non-limiting examples of Carbacephem antibacterial agents include Loracarbef and the like. Typical, non-limiting examples of Carbapenem antibacterial agents include Ertapenem, Doripenem, Imipenem, Meropenem and the like.

Typical, non-limiting examples of Cephalosporin and Cephamycin antibacterial agents include Cefazolin, Cefacetrile, Cefadroxil, Cefalexin, Cefaloglycin, Cefalonium, Cefaloridine, Cefalotin, Cefapirin, Cefatrizine, Cefazedone, Cefazaflur, Cefradine, Cefroxadine, Ceftezole, Cefaclor, Cefamandole, Cefminox, Cefonicid, Ceforanide, Cefotiam, Cefprozil, Cefbuperazone, Cefuroxime, Cefuzonam, Cephamycin, Cefoxitin, Cefotetan, Cefmetazole, Carbacephem, Cefixime, Ceftazidime, Ceftriaxone, Cefcapene, Cefdaloxime, Cefdinir, Cefditoren, Cefetamet, Cefmenoxime, Cefodizime, Cefoperazone, Cefotaxime, Cefpimizole, Cefpiramide, Cefpodoxime, Cefsulodin, Cefteram, Ceftibuten, Ceftioleone, Ceftizoxime, Oxacephem, Cefepime, Cefozopran, Cefpirome, Cefquinome, Ceftobiprole, Ceftiofur, Cefquinome, Cefovecin, CXA-101, Ceftaroline, Ceftobiprole and the like.

Typical, non-limiting examples of Lincosamide antibacterial agents include Clindamycin, Lincomycin and the like. Typical, non-limiting examples of Macrolide antibacterial agents include Azithromycin, Clarithromycin, Dirithromycin, Erythromycin, Roxithromycin, Troleandomycin,

Telithromycin, Spectinomycin, Solithromycin and the like. Typical, non-limiting examples of Monobactam antibacterial agents include Aztreonam and the like. Typical, non-limiting examples of Nitrofuran antibacterial agents include Furazolidone, Nitrofurantoin and the like. Typical, non-limiting examples of Penicillin antibacterial agents include Amoxicillin, Ampicillin, Azlocillin, Carbenicillin, Cloxacillin, Dicloxacillin, Flucloxacillin, Mezlocillin, Methicillin, Nafcillin, Oxacillin, Penicillin G, Penicillin V, Piperacillin, Temocillin, Ticarcillin and the like. Typical, non-limiting examples of Polypeptide antibacterial agents include Bacitracin, Colistin, Polymyxin B and the like.

Typical, non-limiting examples of Quinolone antibacterial agents include Ciprofloxacin, Enoxacin, Gatifloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Nalidixic acid, Levonadifloxacin, Norfloxacin, Ofloxacin, Trovafloxacin, Grepafloxacin, Sparfloxacin, Temafloxacin and the like. Typical, non-limiting examples of Sulfonamide antibacterial agents include Mafenide, Sulfonamidochrysoidine, Sulfacetamide, Sulfadiazine, Sulfamethizole, Sulfamethoxazole, Sulfasalazine, Sulfisoxazole, Trimethoprim and the like. Typical, non-limiting examples of Tetracycline antibacterial agents include Demeclocycline, Doxycycline, Minocycline, Oxytetracycline, Tetracycline, Tigecycline and the like. Typical, non-limiting examples of Oxazolidinone antibacterial agents include Tedizolid, Linezolid, Ranbezolid, Torezolid, Radezolid and the like.

The pharmaceutical compositions according to the invention may include one or more pharmaceutically acceptable carriers or excipients or the like. Typical, non-limiting examples of such carriers or excipient include mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, sodium crosscarmellose, glucose, gelatin, sucrose, magnesium carbonate, wetting agents, emulsifying agents, solubilizing agents, pH buffering agents, lubricants, stabilizing agents, binding agents etc.

In some embodiments, pharmaceutical compositions according to the present invention are administered orally or parenterally.

The pharmaceutical compositions according to this invention can exist in various forms. In some embodiments, the pharmaceutical composition is in the form of a powder or a solution. In some other embodiments, the pharmaceutical compositions according to the invention are in the form of a powder that can be reconstituted by addition of a compatible reconstitution diluent prior to parenteral administration. Non-limiting example of such a compatible reconstitution diluent includes water.

In some other embodiments, the pharmaceutical compositions according to the invention are in the form of a frozen composition that can be diluted with a compatible diluent prior to parenteral administration.

In some other embodiments, the pharmaceutical compositions according to the invention are in the form ready to use for oral or parenteral administration.

In the methods according to the invention, the pharmaceutical composition and/or other pharmaceutically active ingredients disclosed herein may be administered by any appropriate method, which serves to deliver the composition or its constituents or the active ingredients to the desired site. The method of administration can vary depending on various factors, such as for example, the components of the pharmaceutical composition and nature of the active ingredients, the site of the potential or actual infection, the microorganism (e.g. bacteria) involved, severity of infection, age and physical condition of the subject. Some non-limiting examples of administering the composition to a subject according to this invention include oral, intravenous, topical, intrapulmonary, intraperitoneal, intramuscular, parenteral, sublingual, transdermal, intranasal, aerosol, intraocular, intratracheal, intrarectal, vaginal, gene gun, dermal patch, eye drop, ear drop or mouthwash.

The compositions according to the invention can be formulated into various dosage forms wherein the active ingredients and/or excipients may be present either together (e.g. as an admixture) or as separate components. When the various ingredients in the composition are formulated as a mixture, such composition can be delivered by administering such a mixture to a subject using any suitable route of administration. Alternatively, pharmaceutical compositions according to the invention may also be formulated into a dosage form wherein one or more ingredients (active or inactive ingredients) are present as separate components. The composition or dosage form wherein the ingredients do not come as a mixture, but come as separate components, such composition/dosage form may be administered in several ways. In one possible way, the ingredients may be mixed in the desired proportions and the mixture is then administered as required. Alternatively, the components or the ingredients (active or inert) may be separately administered (simultaneously or one after the other) in appropriate proportion so as to achieve the same or equivalent therapeutic level or effect as would have been achieved by administration of the equivalent mixture.

In some embodiments, pharmaceutical compositions according to the invention are formulated into a dosage form such that the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and the antibacterial agent or a pharmaceutically acceptable derivative thereof, are present in the composition as admixture or as a separate components. In some other embodiments, pharmaceutical compositions according to the invention are formulated into a dosage form such that the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and the antibacterial agent or a pharmaceutically acceptable derivative thereof, are present in the composition as separate components.

Similarly, in the methods according to the invention, the active ingredients disclosed herein may be administered to a subject in several ways depending on the requirements. In some embodiments, the active ingredients are admixed in appropriate amounts and then the admixture is administered to a subject. In some other embodiments, the active ingredients are administered separately. Since the invention contemplates that the active ingredients agents may be administered separately, the invention further provides for combining separate pharmaceutical compositions in kit form. The kit may comprise one or more separate pharmaceutical compositions, each comprising one or more active ingredients. Each of such separate compositions may be present in a separate container such as a bottle, vial, syringes, boxes, bags, and the like. Typically, the kit comprises directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral) or are administered at different dosage intervals. When the active ingredients are administered separately, they may be administered simultaneously or sequentially.

The pharmaceutical composition or the active ingredients according to the present invention may be formulated into a variety of dosage forms. Typical, non-limiting examples of dosage forms include solid, semi-solid, liquid and aerosol dosage forms; such as tablets, capsules, powders, solutions, suspensions, suppositories, aerosols, granules, emulsions, syrups, elixirs and a like.

In general, the pharmaceutical compositions and method disclosed herein are useful in preventing or treating bacterial infections. Advantageously, the compositions and methods disclosed herein are also effective in preventing or treating infections caused by bacteria that are considered be less or not susceptible to one or more of known antibacterial agents or their known compositions. Some non-limiting examples of such bacteria known to have developed resistance to various antibacterial agents include *Acinetobacter*, *E. coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Enterobacter*, *Klebsiella*, *Citrobacter* and a like. Other non-limiting examples of infections that may be prevented or treated using the compositions and/or methods of the invention include: skin and soft tissue infections, febrile neutropenia, urinary tract infection, intraabdominal infections, respiratory tract infections, pneumonia (nosocomial), bacteremia meningitis, surgical, infections etc.

Surprisingly, the compounds, compositions and methods according to the invention are also effective in preventing or treating bacterial infections that are caused by bacteria producing one or more beta-lactamase enzymes. The ability of compositions and methods according to the present invention to treat such resistant bacteria with typical beta-lactam antibiotics represents a significant improvement in the art.

In some embodiments, there is provided a method of inhibiting beta-lactamase enzymes, wherein said method comprises administering a pharmaceutically effective amount of a compound of Formula (I), or a stereoisomer or a pharmaceutically acceptable derivative thereof.

In some embodiments, there is provided a method of inhibiting beta-lactamase enzymes, wherein said method comprises administering a pharmaceutically effective amount of a pharmaceutical composition comprising a compound of Formula (I), or a stereoisomer or a pharmaceutically acceptable derivative thereof.

In some embodiments, there is provided a method for preventing or treating a bacterial infection in a subject, said infection being caused by one or more beta-lactamase enzymes, wherein the method comprises administering to said subject a pharmaceutically effective amount of a compound of Formula (I), or a stereoisomer or a pharmaceutically acceptable derivative thereof.

In general, the compounds of Formula (I), or a stereoisomer or pharmaceutically acceptable salt thereof according to invention are also useful in increasing antibacterial effectiveness of antibacterial agent in a subject. The antibacterial effectiveness of one or more antibacterial agents may increased, for example, by co-administering said antibacterial agent or a pharmaceutically acceptable derivative thereof with a pharmaceutically effective amount of a compound of Formula (I), or a stereoisomer or a pharmaceutically acceptable salt thereof according to the invention. In some embodiments, there is provided a method for increasing antibacterial effectiveness of the antibacterial agent in a subject, said method comprising co-administering said antibacterial agent or a pharmaceutically acceptable derivative thereof with a of a compound of Formula (I), or a stereoisomer or a pharmaceutically acceptable derivative thereof.

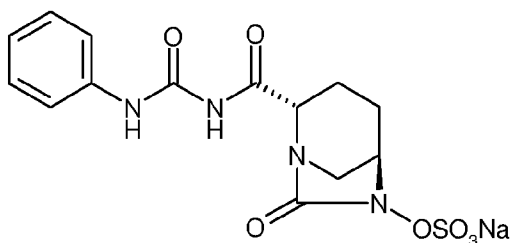
It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. For example, those skilled in the art will recognize that the invention may be practiced using a variety of different compounds within the described generic descriptions.

EXAMPLES

The following examples illustrate the embodiments of the invention that are presently best known. However, it is to be understood that the following are only exemplary or illustrative of the application of the principles of the present invention. Numerous modifications and alternative compositions, methods and systems may be devised by those skilled in the art without departing from the spirit and scope of the present invention. The appended claims are intended to cover such modifications and arrangements. Thus, while the present invention has been described above with particularity, the following examples provide further detail in connection with what are presently deemed to be the most practical and preferred embodiments of the invention.

Example 1

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(phenylcarbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide:



Step 1: Preparation of 3-{3-[(2S,5R)-(6-Benzyloxy-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carbonyl)]-ureido}-benzene: To a clear solution of (2S, 5R)-6-(benzyloxy)-7-oxo-1, 6-diazabicyclo[3.2.1] octane-2-carboxamide (1 g, 0.003 mol) in dichloromethane (10 ml) was added triethyl amine (1 ml, 0.007 mol) and lithium bromide (0.63 g, 0.0 07 mol) at about 0-5°C, under stirring. After 10 minutes, a solution of isocyanatobenzene (0.43 g, 0.003 mol) in dichloromethane (2 ml) was added drop wise, at about 0-5°C, under continuous stirring. Then the reaction mass temperature was allowed to warm to about 25°C and stirred for about 1 hour. The completion of the reaction was monitored by thin layer chromatography using mixture of acetone and hexane (35:65) as solvent system. After completion of the reaction, the resulting mixture was diluted with water (20 ml) and dichloromethane (20 ml). The organic layer was separated and the aqueous layer was re-extracted with dichloromethane (10 ml). The combined organic extracts were dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the resulting oily mass was triturated with ether (3×10 ml) to produce 0.9 g of the titled product as a white solid in 64% yield.

Analysis:

Mass: 395.4 (M+1); for Molecular Weight: 394.43 and Molecular Formula: C₂₁H₂₂N₄O₄.

Step 2: Preparation of 3-{3-[(2S,5R)-(6-hydroxy-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carbonyl)]-ureido}-benzene: A solution of 3-{3-[(2S,5R)-(6-benzyloxy-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carbonyl)]-ureido}-benzene (0.6 g, 0.001 mol) in a mixture of dimethylformamide and dichloromethane (1:1, 3 ml: 3 ml), containing 10% palladium over carbon (0.12 g, 50% wet) was hydrogenated, at 2 psi hydrogen pressure, for about 2 hours, at about 25°C. The reaction was monitored by thin layer chromatography (chloroform: methanol, 9:1). After completion of the reaction, the resulting mixture was filtered through a celite pad. The residue was washed with dichloromethane (5 ml). The solvent from the filtrate was evaporated under reduced pressure to obtain 0.46 g of the titled product as an oil, which was used as such for the next reaction without further purification.

Analysis:

Mass: 303.4 (M-1); for Molecular Weight: 304.4 and Molecular Formula: C₁₄H₁₆N₄O₄.

Step 3: Preparation of tetrabutylammonium salt of 3-{3-[(2S,5R)-6-(sulfooxy)-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carbonyl]-ureido}-benzene: To a stirred solution of 3-{3-[(2S,5R)-(6-hydroxy-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carbonyl)]-ureido}-benzene (0.46 g, 0.0015 mol) in dimethylformamide (4.5 ml) was added dimethylformamide-sulphur trioxide complex (0.256 g, 0.0016 mol) in one portion, at about 10°C under stirring. The reaction mass was stirred at the same temperature for about 30 minutes and allowed to warm to room temperature. After 1 hour, a solution of tetrabutylammonium acetate (0.501 g, 0.0016 mol) in water (2 ml) was added slowly to the resulting reaction mass under stirring. After 1 hour, the solvent from the reaction mixture was evaporated under reduced pressure to obtain an oily residue. The oily mass was co-evaporated with xylene (2 × 10 ml) to obtain thick mass. This mass was partitioned between dichloromethane (10 ml) and water (10 ml). The combined organic extracts were washed with water (3×10 ml) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the resulting oily mass was triturated with ether (3×10 ml) (each time the ether layer was decanted). Finally, the residue was concentrated under reduced pressure to obtain the 0.4 g of the titled product as white foam in 44% yield.

Analysis:

Mass: 383.54 (M-1) as free acid; for Molecular Weight: 625.82 and Molecular Formula: $C_{30}H_{51}N_5O_7$ S.

Step 4: Preparation of sodium salt of (2S, 5R)-7-oxo-N-(phenylcarbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide: A solution of tetrabutylammonium salt of 3-{3-[(2S,5R)-6-(sulfooxy)-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carbonyl]-ureido}-benzene (0.4 g) in tetrahydrofuran (5 ml) was passed through the Dowex 200 Na resin using mixture of tetrahydrofuran and water (10:90) as a mobile phase. The fractions containing the compound were collected and distilled out under reduced pressure to yield 0.180 g of the titled product as a white solid in 70% yield.

Analysis:

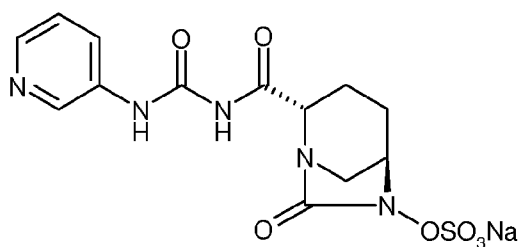
Melting Point: 202-204°C (decomposes)

Mass: 383.3 as free acid; for Molecular Weight: 406.34 and Molecular Formula: $C_{14}H_{15}N_4O_7SNa$

^1H NMR (400MHz, DMSO- D_6): δ 10.27 (s, 1H), 10.19 (s, 1H), 7.51-7.52 (d, 2H), 7.31-7.34 (t, 2H), 7.06-7.09 (t, 1H), 4.07-4.03 (m, 2H), 3.07 (s, 2H), 1.72-2.04 (m, 4H).

Example 2

Sodium salt of (2S, 5R)-7-oxo-N-(pyridin-3-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide:



Step 1: Preparation of 3-{3-[(2S,5R)-(6-benzyloxy-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carbonyl)]-ureido}-pyridine: To a clear solution of (2S, 5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo [3.2.1] octane-2-carboxamide (1c) (2 g, 0.0072 mol) in dichloromethane (20 ml) under stirring was added triethyl amine (2 ml, 0.014 mol) and lithium bromide (1.2 g, 0.014 mol) at about 0-5°C. After 10 minutes of stirring, a solution of 3-isocyanatopyridine (0.87 g, 0.0072 mol, prepared according to reference US20090105166) in dichloromethane (5 ml) was added drop wise, at about 0-5°C under continuous stirring. Then reaction mass temperature was allowed to warm to room temperature and stirring continued further for about 1 hour. The completion of the reaction was confirmed by performing thin layer chromatography using solvent system acetone: hexane (35:65). The resulting mixture was diluted with water (20 ml) and dichloromethane (20 ml). The organic layer was separated and the aqueous layer re-extracted with dichloromethane (10 ml). The combined organic extracts dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the resulting oily mass was triturated with ether (3×10 ml), to obtain the 0.6 g of the titled product as a white solid in 21% yield.

Analysis:

Mass: 396.4 (M+1); for Molecular Weight: 395.43 and Molecular Formula: $C_{20}H_{21}N_5O_4$.

Step 2: Preparation of 3-{3-[(2S,5R)-(6-hydroxy-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carbonyl)]-ureido}-pyridine: A solution of 3-{3-[(2S,5R)-(6-benzyloxy-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carbonyl)]-ureido}-pyridine (0.5 g, 0.0012 mol) in a mixture of dimethylformamide: dichloromethane (1:1, 2.5 ml: 2.5 ml), containing 10% palladium over carbon (0.100 g, 50% wet) was hydrogenated, at 2 psi pressure, for 2 hours at 25°C. The reaction was monitored by thin layer chromatography. After completion, the resulting mixture was filtered through a celite pad. The residue was washed with dichloromethane (5 ml). The solvent from the filtrate was

evaporated under reduced pressure to yield the 0.383 g of titled product as oil, which was used as such for the next reaction without further purification.

Analysis:

Mass: 304.2 (M-1); for Molecular Weight: 304.4 and Molecular Formula: $C_{13}H_{15}N_5O_4$.

Step 3: Preparation of tetrabutylammonium salt of 3-{3-[(2*S*,5*R*)-6-(sulfooxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carbonyl]-ureido}-pyridine: To a stirred solution of 3-{3-[(2*S*,5*R*)-6-(sulfooxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carbonyl]-ureido}-pyridine (0.385 g, 0.0012 mol) in dimethylformamide (4.5 ml) was added dimethylformamide sulphur trioxide complex (0.256 g, 0.0016 mol) in one portion, at about 10°C. The reaction mass was stirred at the same temperature for 30 minutes and allowed to warm to room temperature. After 1 hour, to the resulting reaction mass was added slowly a solution of tetra butyl ammonium acetate (0.501 g, 0.0016 mol) in water (2 ml) under stirring. After 1 hour the solvent from the reaction mixture was evaporated under reduced pressure to obtain an oily residue. The oily mass was co-evaporated with xylene (2×10 ml) to obtain thick mass. This mass was partitioned between dichloromethane (10 ml) and water (10 ml). The combined organic extracts were washed with water (3×10 ml) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the resulting oily mass was triturated with ether (3×10 ml), each time the ether layer was decanted and finally the residue was dried under reduced pressure to obtain 0.4 g of the titled product as white foam in 44% yield.

Analysis:

Mass: 384.3 (M-1) as free acid; for Molecular Weight: 626.8 and Molecular Formula: $C_{29}H_{50}N_6O_7S$.

Step 4: Preparation of sodium salt of (2*S*,5*R*)-7-oxo-*N*-(pyridin-3-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide: This compound was prepared by passing the solution of tetrabutylammonium salt of 3-{3-[(2*S*,5*R*)-6-(sulfooxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane -2-carbonyl]-ureido}-pyridine in tetrahydrofuran through the Dowex 200 Na resin using tetrahydrofuran: water (10:90) as an mobile phase. The collected fractions were confirmed for the product by performing thin layer chromatography. The combined fractions containing the product were distilled under reduced pressure to obtain 0.180 g of the titled product as a white solid, in 70% yield.

Analysis:

Melting Point: 188-190°C (decomposes);

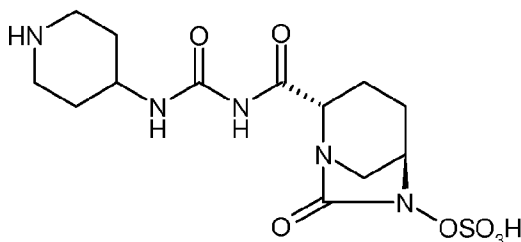
Mass: 384.3 as free acid; for Molecular Weight: 407.33 and Molecular Formula: $C_{13}H_{14}N_5O_7SNa$;

¹H NMR (400 MHz, DMSO-*D*₆): δ 10.29 (s, 1H), 8.69 (d, 1H), 8.29-8.28 (d, 1H), 8.01-7.99 (d, 1H), 7.35-7.38 (m, 1H), 4.03 (s, 1H), 3.97 (s, 2H), 3.07 (s, 1H), 1.63-1.97 (m, 4H);

Purity as determined by HPLC: 86.82%.

Example 3

(2*S*, 5*R*)-7-Oxo-*N*-(piperidin-4-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide:



Step 1: Preparation of 4-{3-[(2*S*,5*R*)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carbonyl] -ureido}-piperidine-1-carboxylic acid *tert*-butyl ester: To a stirred solution of (2*S*, 5*R*)-

6-benzyloxy-7-oxo-1, 6-diazabicyclo [3.2.1] octane-2-carboxamide (1c) (1 g, 0.003 mol) in dichloromethane (10 ml), at about 0-5°C, were added triethyl amine (1.04 ml, 0.007 mol) and lithium bromide (0.63 g, 0.007 mol) successively. After 10 minutes, a solution of *tert*-butyl-4-isocyanatopiperidine-1-carboxylate (1.23 g, 0.005 mol, synthesized as described in reference WO 2001068604) in tetrahydrofuran (10 ml) was added drop wise. The resulting mixture was allowed to warm to room temperature and stirred further for 1 hour. The completion of the reaction was determined by thin layer chromatography using acetone: hexane (35:65) solvent system. The resulting mixture was diluted with water (10 ml) and dichloromethane (10 ml). The organic layer was separated and the aqueous layer re-extracted with dichloromethane (10 ml). The combined organic extracts were dried over anhydrous sodium sulphate and the solvent evaporated under reduced pressure, and the resulting oily mass was purified by column chromatography using 20% acetone in hexane as a mobile phase. The solvent from the combined fractions was evaporated under reduced pressure to obtain 0.6 g of the titled product as white solid in 30% yield.

Analysis:

Mass: 502.5 (M+1); for Molecular Weight: 501.5 and Molecular Formula: C₂₅H₃₅N₅O₆.

Step 2: Preparation of 4-{3-[(2*S*,5*R*)-(6-hydroxy-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carbonyl)]-ureido}-piperidine-1-carboxylic acid *tert*-butyl ester: A solution of 4-{3-[(2*S*,5*R*)-(6-benzyloxy-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carbonyl)]-ureido}-piperidine-1-carboxylic acid *tert*-butyl ester (0.5 g, 0.0009 mol) in a mixture of dimethylformamide and dichloromethane (1:1, 2.5 ml: 2.5 ml), containing 10% palladium over carbon (0.1 g, 50% wet) was hydrogenated, at 2 psi pressure, for 2 hours, at 25°C. The completion of the reaction was monitored by thin layer chromatography using acetone: hexane (35:65) solvent system. The resulting mixture was filtered through celite bed and the residue was washed with dichloromethane (5 ml). The solvent from the combined filtrate was evaporated under reduced pressure to obtain 0.4 g of the titled product as oil, which was used as such for the next reaction without further purification.

Analysis:

Mass: 410.04 (M-1); for Molecular Weight: 411.04 and Molecular Formula: C₁₈H₂₉N₅O₆.

Step 3: Preparation of tetrabutylammonium salt of 4-{3-[(2*S*,5*R*)-6-(sulfooxy)-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carbonyl]-ureido}-piperidine-1-carboxylic acid *tert*-butyl ester: To a stirred solution of 4-{3-[(2*S*,5*R*)-(6-hydroxy-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carbonyl)-ureido]}-piperidine-1-carboxylic acid *tert*-butyl ester (0.41 g, 0.0009 mol) in dimethylformamide (4.1 ml), at 10°C, was added dimethylformamide sulfur trioxide complex (0.183 g, 0.0019 mol) in one portion. The reaction mass was stirred at the same temperature for about 30 minutes and then allowed to warm to room temperature. After 1 hour, to the resulting reaction mixture was added slowly a solution of tetrabutylammonium acetate (0.359 g, 0.0019 mol) in dichloromethane (2 ml) under stirring. After 1 hour, the solvent from the reaction mixture was evaporated under reduced pressure to yield an oily residue. The oily mass was co-evaporated with xylene (2×10ml) to obtain a thick mass. This mass was partitioned between dichloromethane (10 ml) and water (10 ml). The combined organic extracts were washed with water (3×10ml) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the resulting oily mass was triturated with ether (3×10 ml), each time the ether layer was decanted and finally the residue was concentrated under reduced pressure to obtain 0.260 g of the titled product as white foam in 35% yield.

Analysis:

Mass: 490.4 (M-1) as free acid; for Molecular Weight: 732.9, Molecular Formula: C₃₄H₆₄N₆O₉S.

Step 4: Preparation of (2*S*,5*R*)-7-oxo-*N*-(piperidin-4-ylcarbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide: To a stirred solution of tetrabutylammonium salt of 4-{3-[(2*S*,5*R*)-6-(sulfooxy)-7-oxo-1,6-diaza-bicyclo[3.2.1]octane-2-carbonyl]-ureido}-piperidine-1-carboxylic acid *tert*-butyl ester (0.260 g) in dichloromethane (1.5 ml) at -10 °C, was added trifluoroacetic acid (1.5

ml) drop wise. The reaction mixture was stirred further at same temperature for 1 hour. The resulting mixture was poured into cyclohexane (15 ml), stirred well for 10 minutes and the separated oily layer collected. This procedure was repeated one more time and finally the separated oily layer was added to diethyl ether (50 ml) under vigorous stirring, at room temperature. The ether layer was removed by decantation from the precipitated solid. This procedure was repeated twice again with diethyl ether (2×10 ml). The solid thus obtained was stirred with fresh dichloromethane (10 ml) for 30 minutes and filtered. The residual solid was dried at 45°C under reduced pressure to obtain 0.120 g of the titled product as a white solid in 85% yield.

Analysis:

Melting Point: 178-183°C (decomposes);

Mass: 390.3 (M-1), Molecular Weight: 391.4 and Molecular Formula: C₁₃H₂₁N₅O₇S;

¹H NMR (400MHz, DMSO-D₆): 10.04 (s, 1H), 8.45 (br, 1H), 8.12-8.13 (d, 2H), 4.00 (br, 1H), 3.93-3.94 (d, 1H), 3.81-3.82 (m, 1H), 3.23-3.25 (d, 1H), 3.12-3.16 (t, 1H), 2.95-3.05 (m, 4H), 1.56-2.00 (8H);

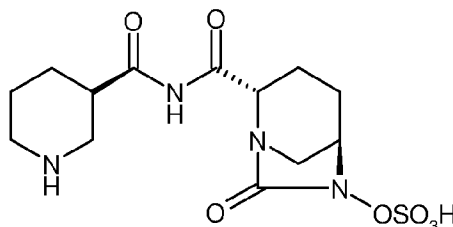
Purity as determined by HPLC: 98.73%.

The compounds of Examples 4 and 5 (Table 1) were prepared using the procedure described in Example 3 and corresponding starting reagents in place of *tert*-butyl-4-isocyanatopiperidine-1-carboxylate.

Table 1				
Example No.	Structure	Starting Reagent	¹ H NMR (DMSO-d ₆)	Mass as free acid (Molecular Formula)
4			10.15 (s, 1H), 8.55 (br, 2H), 8.19-8.20 (d, 1H), 4.02 (br, 1H), 3.91-3.96 (dd, 2H), 3.27 (s, 1H), 3.14-3.17 (d, 1H), 3.05-3.07 (d, 1H), 2.97-3.00 (d, 1H), 2.89-2.93 (t, 1H), 2.78-2.82 (t, 1H), 1.58-1.95 (m, 8H).	390.3 (M-1) (C ₁₃ H ₂₁ N ₅ O ₇ S)
5			10.22 (s, 1H), 8.70 (s, 1H), 8.36-8.35 (d, 1H), 4.40-4.37 (m, 1H), 4.03 (s, 1H), 3.97-3.95 (d, 1H), 3.28-3.13 (m, 2H), 3.13-2.98 (dd, 2H), 2.24-2.19 (m, 1H), 1.93-1.72 (m, 6H).	376.3 (M-1) (C ₁₂ H ₁₉ N ₅ O ₇ S)

Example 6

(2S,5R)-N-[(3R)-Piperidine-3-carbonyl]-6-(sulfoxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxamide:



Step 1: Preparation of *tert*-butyl-(3*R*)-1-(*tert*-butoxycarbonyl) piperidine-3-carboxylate: To a stirred solution of (3*R*)-1-(*tert*-butoxycarbonyl) piperidine-3-carboxylic acid (5 g, 0.021 mol) in tetrahydrofuran (50 ml), at 0-5°C, was added triethyl amine (3.78 ml, 0.026 mol) in one portion. After 10 minutes of stirring, pivaloyl chloride (3.21 ml, 0.024 mol) was added drop wise to the above solution. The reaction mixture was allowed to warm to room temperature and stirring continued further for 1 hour. The completion of the reaction was monitored by thin layer chromatography using acetone and hexane (35:65) as solvent system. The resulting mixture was filtered through celite bed and filtrate was used in next step without any workup.

Step 2: Preparation of (2*S*,5*R*)-N-[(3*R*)-1-(*tert*-butoxycarbonyl)piperidine-3-carbonyl]-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxamide: To a stirred solution of (2*S*,5*R*)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxamide (3 g, 0.007 mol) in dichloromethane (20 ml), at about 0-5°C, were added successively triethylamine (4.7 ml, 0.032 mol) and lithium bromide (1.8 g, 0.0218 mol). After 10 minutes, a solution of (3*R*)-1-(*t*-butoxycarbonyl) piperidine-3-carboxylic-2,2-dimethylpropanoic anhydride (2) (6.8g, 0.0218 mol) in tetrahydrofuran (35 ml) was added drop wise. The reaction mass was allowed to warm to room temperature and stirring continued further for an hour. The completion of the reaction was monitored by thin layer chromatography using mixture acetone and hexane (35: 65) as solvent system. The resulting mixture was diluted with water (20 ml) and dichloromethane (20 ml). The organic layer was separated and the aqueous layer re-extracted with dichloromethane (10 ml). The combined organic extracts were dried (over anhydrous sodium sulphate) and the solvent evaporated under reduced pressure. The residual oily mass was purified by column chromatography using 20% acetone in hexane as an eluent. The solvent from the combined fractions was evaporated to obtain 0.8 g of the titled product as a white solid in 15% yield.

Analysis:

Mass: 487.4 (M+1); for Molecular Weight: 486.5 and Molecular Formula: C₂₅H₃₄N₄O₆.

Step 3: Preparation of (2*S*,5*R*)-N-[(3*R*)-1-(*tert*-butoxycarbonyl)piperidine-3-carbonyl]-6-hydroxy-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxamide: A solution of (2*S*,5*R*)-N-[(3*R*)-1-(*tert*-butoxycarbonyl)piperidine-3-carbonyl]-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxamide (0.6g, 0.001 moles) in a mixture of dimethylformamide and dichloromethane (1:1, 3 ml: 3 ml), containing 10% palladium over carbon (0.12 g, 50% wet) was hydrogenated, at 2 psi pressure, for 2 hours, at 25°C. The completion of the reaction was monitored by thin layer chromatography using mixture acetone and hexane (35: 65) as solvent system. The resulting mixture was filtered through celite bed and the residue was washed with fresh dichloromethane (5 ml). The solvent from the combined filtrate was evaporated under reduced pressure to obtain 0.48 g of the titled product as oil, which was used as such for the next reaction without further purification.

Analysis:

Mass: 395.3 (M-1); for Molecular Weight: 396.4 and Molecular Formula: C₁₈H₂₈N₄O₆.

Step 4: Preparation of tetrabutylammonium salt of (2*S*,5*R*)-N-[(3*R*)-1-(*tert*-butoxycarbonyl) piperidine-3-carbonyl]-6-(sulfooxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxamide: To a stirred solution of (2*S*,5*R*)-N-[(3*R*)-1-(*tert*-butoxycarbonyl)piperidine-3-carbonyl]-6-hydroxy-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxamide (0.480 g, 0.0012 mol) in dimethylformamide (4.8 ml), at about 10°C, was added dimethylformamide sulphur trioxide complex (0.207 g, 0.0013 mol) in one

portion. The reaction mass was stirred at the same temperature for 30 minutes and allowed to warm to room temperature. After 1 hour of stirring, to the reaction mixture was added, slowly, a solution of tetrabutylammonium acetate (0.408 g, 0.0013 mol) in dichloromethane (2 ml) and the stirring continued further. After 1 hour, the solvent from the reaction mixture was evaporated under reduced pressure to obtain an oily residue. The oily mass was co-evaporated with xylene (2×10 ml) resulting in a thick mass. This mass was partitioned between dichloromethane (10 ml) and water (10 ml) for three times. The combined organic extracts were washed with water (3×10 ml), dried (over anhydrous sodium sulphate) and the solvent was evaporated under reduced pressure. The resulting oily mass was triturated with ether (3×10 ml), each time the ether layer was decanted and finally the residue was concentrated under reduced pressure to obtain 0.7 g of the titled product as white foam in 80% yield.

Analysis:

Mass: 475.4 (M-1) as free acid; for Molecular Weight: 717.95 and Molecular Formula: C₃₄H₆₃N₅O₉S.

Step 5: Preparation of (2S,5R)-N-[(3R)-piperidine-3-carbonyl]-6-(sulfooxy)-7-oxo-1,6-diazabicyclo [3.2.1]octane- 2-carboxamide: To a stirred solution of tetrabutylammonium salt of (2S,5R)-N-[(3R)-1-(*tert*-butoxycarbonyl)piperidine-3-carbonyl]-6-(sulfooxy)-7-oxo-1,6-diazabicyclo [3.2.1]octane -2-carboxamide (0.710 g) in dichloromethane (3.5 ml), at about -10°C, was added trifluoroacetic acid (3.5 ml) drop wise. The resulting mixture was further stirred at same temperature for about 1 hour. The completion of the reaction was monitored by thin layer chromatography using mixture of chloroform and methanol (90:10) as solvent system. The resulting mixture was poured into cyclohexane (25 ml), stirred well for 10 minutes and the separated oily layer collected. This procedure was repeated one more time and finally the separated oily layer was poured into diethyl ether (50 ml) under vigorous stirring at room temperature. The ether layer was removed by decantation from the precipitated solid. This procedure was repeated twice again with diethyl ether (2×50 ml). The solid thus obtained was stirred with fresh dichloromethane (50 ml) for 30 minutes and filtered. The residual solid was dried at 45°C under reduced pressure to 0.30 g of the titled product. The solid obtained was further purified by dissolving in water (1 ml) under stirring and followed by slow addition of isopropanol (3 ml) to the solution at about 25°C. The solution was further stirred for about 1 hour. The separated solid was filtered and washed with additional isopropanol (2 ml) and dried under reduced pressure to obtain about 0.11 g of the titled product as a white solid in 37% yield.

Analysis:

Melting Point: 197-199°C (decomposes);

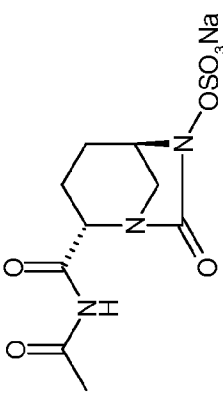
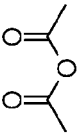
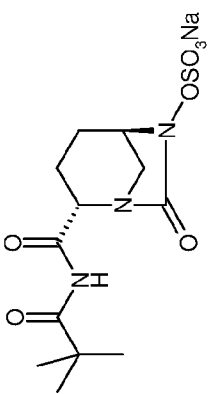
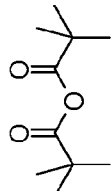
Mass: 375.3 (M-1); Molecular Weight: 376.3 and Molecular Formula: C₁₃H₂₀N₄O₇S;

¹H NMR (400MHz, DMSO-D₆): δ 10.82 (s, 1H), 8.42 (s, 2H), 4.00 (s, 2H), 3.26 (s, 1H), 3.13-3.15 (d, 2H), 2.88-3.05 (m, 4H), 1.88-1.95 (m, 3H), 1.50-1.75 (m, 5H).

The compounds 7 to 12 (Table 2) were prepared using the procedure described in Example 6 starting from steps 2 to 4 using corresponding suitably activated acids, anhydrides, or acid chlorides in step 2. In Examples 9 to 12 the tetrabutylammonium salt is converted to the sodium salt by using the procedure described in step 4 of Example 1.

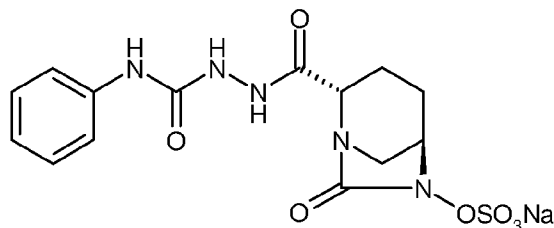
Table 2

Example No.	Structure	Starting Reagent	¹ H NMR (DMSO-d ₆)	Mass as free acid (Molecular Formula)
7			11.30 (s, 1H), 9.08 (s, 1H), 8.65 (s, 1H), 4.68 (m, 1H), 4.02-4.04 (d, 1H), 3.19-4.68 (m, 4H), 3.63-2.93 (dd, 1H), 2.31-2.64 (m, 3H), 1.67-2.05 (m, 5H).	363.2 (M+1) C ₁₂ H ₁₈ N ₄ O ₇ S
8			10.84 (s, 1H), 7.87 (br, 1H), 7.66 (br, 2H), 4.00-4.02 (d, 2H), 3.14-3.17 (t, 1H), 2.99-3.04 (m, 3H), 2.93-2.95 (m, 2H), 1.66-1.96 (m, 4H).	337.3 (M+1) C ₁₀ H ₁₆ N ₄ O ₇ S
9			10.20 (s, 1H), 4.08-4.13 (q, 2H), 3.99 (s, 2H), 2.96-3.03 (m, 2H), 1.85-1.91 (m, 2H), 1.69-1.76 (m, 2H), 1.20-1.22 (t, 3H).	336 (C ₁₀ H ₁₄ N ₃ O ₈ SNa)
10			10.01 (s, 1H), 4.16-4.17 (d, 1H), 3.97-3.98 (d, 1H), 2.95-3.06 (dd, 2H), 1.83-1.90 (m, 2H), 1.67-1.75 (m, 2H), 1.14 (s, 9H).	364.3 (C ₁₂ H ₁₈ N ₃ O ₈ SNa)

11			10.20 (s, 1H), 4.08-4.13 (q, 2H), 3.99 (s, 2H), 2.96-3.03 (m, 2H), 1.85-1.91 (m, 2H), 1.69-1.76 (m, 2H), 1.20-1.22 (t, 3H).	336 (C₁₀H₁₄N₃O₈SNa)
12			10.01 (s, 1H), 4.16-4.17 (d, 1H), 3.97-3.98 (d, 1H), 2.95-3.06 (dd, 2H), 1.83-1.90 (m, 2H), 1.67-1.75 (m, 2H), 1.14 (s, 9H).	348.3 (C₁₂H₁₈N₃O₇SNa)

Example 13

Sodium salt of 2-[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl]-*N*-phenylhydrazinecarboxamide:



Step 1: Preparation of 2-[(2*S*, 5*R*)-6-(benzyloxy)-7-oxo-1, 6-diazabicyclo [3.2.1] oct-2-yl] carbonyl]-*N*-Phenylhydrazinecarboxamide: To a clear solution of sodium (2*S*, 5*R*)-6-(benzyloxy)-7-oxo-1, 6-diazabicyclo [3.2.1] octane-2-carboxylate (2.0 g, 0.006 mol) in water (35 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.92 g, 0.01 mol) at about 25°C under stirring. After 10 minutes of the stirring a solution of phenyl hydrazine carboximide (1.01 g, 0.006 mol, prepared as per the literature) in dimethylformamide (5 ml) was added drop wise under continuous stirring at about 25°C. To this resulted reaction mass was added 1-hydroxybenzotriazole (0.905 g, 0.006 mol) in one portion. After about 16 hours the completion of the reaction was confirmed by performing thin layer chromatography using mixture of acetone and hexane (1:1) as solvent system. The reaction mass was filtered and washed with water (100 ml). The white solid thus obtained was taken in water (200 ml) and heated at about 50°C under stirring. After three hours, the resulted suspension was filtered to obtain 2.3 g of the titled compound as off white solid in 84% yield.

Analysis:

Mass: 410.3 (M+1); for Molecular Weight: 409.45 and Molecular Formula: C₂₁H₂₃N₅O₄.

Step 2: Preparation of 2-[(2*S*, 5*R*)-6-hydroxy-7-oxo-1, 6-diazabicyclo [3.2.1] oct-2-yl] carbonyl]-*N*-phenylhydrazinecarboxamide: To a solution of 2-[(2*S*, 5*R*)-6-(benzyloxy)-7-oxo-1, 6-diazabicyclo [3.2.1] oct-2-yl] carbonyl]-*N*-phenylhydrazinecarboxamide (2.3 g, 0.005 mol) in methanol (50 ml) was added 10% palladium over carbon (1.0 g, 50% wet) and exposed to hydrogen balloon at 25°C under stirring. After 2 hours of the stirring the completion of the reaction was confirmed by performing the thin layer chromatography (chloroform: methanol). The reaction mass was filtered through celite and washed with dichloromethane (30 ml). The filtrate was evaporated under reduced pressure to obtain 1.5 g of the titled compound as white solid, in 83.7% yield.

Analysis:

Mass: 318.2 (M-1) for Molecular Weight: 319.32 and Molecular Formula: C₁₄H₁₇N₅O₄.

Step 3: Preparation of tetra butyl ammonium salt of 2-[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl]-*N*-phenylhydrazinecarboxamide: To a solution of 2-[(2*S*, 5*R*)-6-hydroxy-7-oxo-1, 6-diazabicyclo [3.2.1] oct-2-yl] carbonyl]-*N*-phenylhydrazinecarboxamide (1.0 g, 0.003 mol) in dichloromethane (15 ml) was added pyridine sulphur trioxide complex (0.829 g, 0.005 mol) in one portion at about 25°C under stirring. The resulting reaction mixture was stirred at same temperature for 2 hours. The completion of the reaction was confirmed by performing thin layer chromatography using mixture of chloroform and methanol. Then to a reaction mass was added a solution of 0.5 M aqueous solution of potassium dihydrogen phosphate (30 ml) and ethyl acetate (30 ml). The organic layer was separated and to the separated aqueous layer (30 ml) was added tetra butyl ammonium hydrogen sulphate (0.794 g) at room temperature under stirring. After 1 hour of stirring, dichloromethane (30 ml) was added and layers were separated. The aqueous layer was extracted with dichloromethane (3 × 30 ml). The combined organic layer was dried over anhydrous sodium sulphate

and the solvent was evaporated under reduced pressure to obtain an oily residue. The residue was purified by silica gel column chromatography using 4% methanol in chloroform as an eluent. The solvent from the combined fractions was evaporated under reduced pressure to obtain 1.90 g of the titled compound as white solid, in 95% yield.

Analysis:

Mass: 398.3 (M-1) for Molecular Weight: 640.85 and Molecular Formula: C₃₀H₅₂N₆O₇S.

Step 4: Preparation of sodium salt of 2-[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl]-*N*-phenylhydrazinecarboxamide: A solution of tetra butyl ammonium salt of 2-[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl]-*N*-phenylhydrazinecarboxamide (1.9 g) in tetrahydrofuran (5 ml) was passed through Amberlite 200 C Na cation exchange resin by eluting with 10% tetrahydrofuran water mixture. The compound containing fractions were combined, and tetrahydrofuran from the mixture was evaporated under reduced pressure. The obtained aqueous layer was washed with dichloromethane (2×20 ml). Finally the aqueous layer was evaporated under reduced pressure to obtain 0.980 mg of sodium salt of 2-[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl]-*N*-phenylhydrazinecarboxamide as white solid, in 78 % yield.

Analysis:

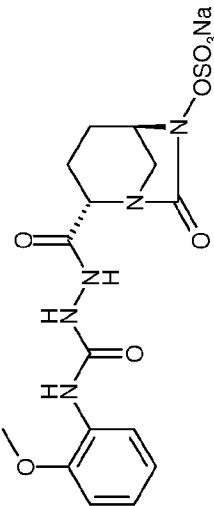
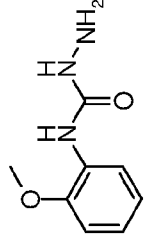
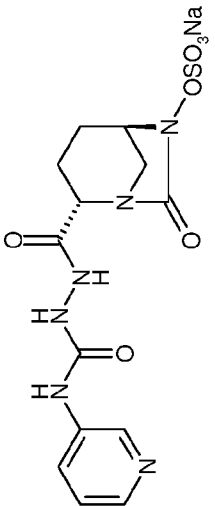
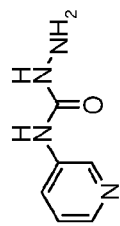
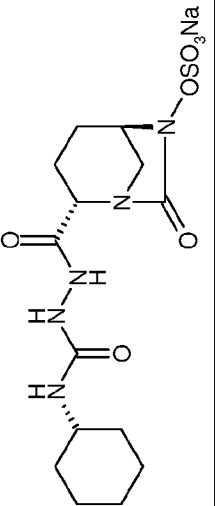
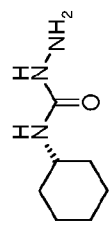
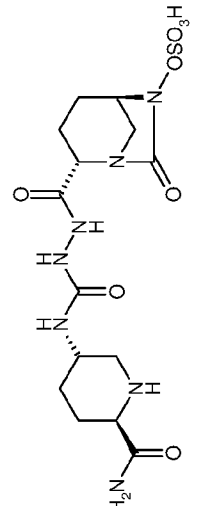
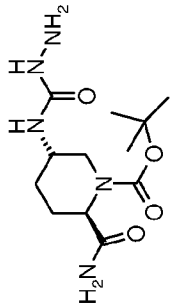
Mass: 398.3 (M-1); for Molecular Weight: 421.3 and Molecular Formula: C₁₄H₁₆N₅O₇SNa;

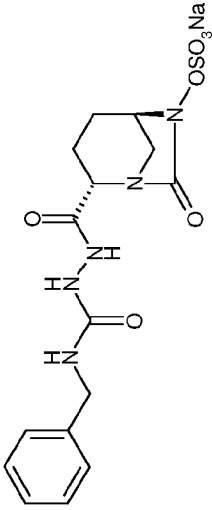
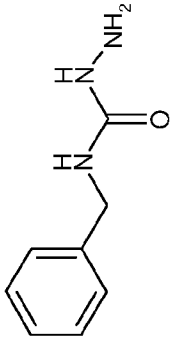
¹H NMR (400MHz, DMSO-D₆): δ 9.76 (s, 1H), 8.69 (s, 1H), 7.99 (s, 1H), 7.43-7.41 (d, 2H) 7.25-7.21 (t, 2H) 6.94-6.91 (t, 1H), 4.00 (s, 1H), 3.88-3.87 (d, 1H), 3.19-3.16 (d, 1H), 3.02-2.99 (d, 1H), 2.01-1.60-1.73 (m, 4H);

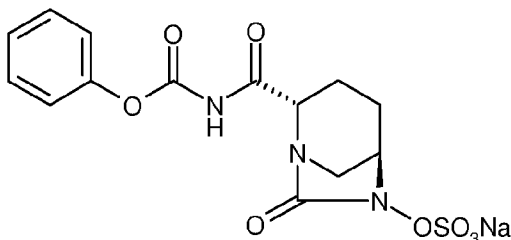
Purity as determined by HPLC: 99.03%.

The compounds of Examples 14 to 18 (Table 3) were prepared using the procedure described in Example 13 and by using corresponding starting reagents in place of phenylhydrazine carboximide. For compound of Example 17 Step 5 of Example 6 was followed to obtain the zwitterion.

Table-3

Example No.	Structure	Starting Reagent	¹ H NMR (DMISO-d ₆)	Mass as free acid (Molecular Formula)
14			-	428.4 (C ₁₅ H ₁₈ N ₅ O ₈ SNa)
15			-	399.3 (C ₁₃ H ₁₅ N ₆ O ₇ SNa)
16			9.52 (s, 1H), 7.55 (s, 1H), 6.08 (s, 1H), 3.98 (s, 1H), 3.84-3.78 (m, 1H), 3.21-3.14 (m, 1H), 2.98-2.92 (m, 1H), 2.04-1.96 (m, 1H), 1.89-1.82 (m, 1H), 1.78-1.48 (m, 8H), 1.76-1.02 (m, 6H)	404.2 (C ₁₄ H ₂₂ N ₅ O ₇ SNa)
17			9.63 (s, 1H), 8.93-8.85 (m, 2H), 7.87-7.82 (d, 2H), 7.62 (s, 1H), 6.40-6.38 (d, 1H), 4.00 (s, 1H), 3.86-3.85 (d, 1H), 3.18-3.11 (m, 3H), 3.00-2.97 (d, 1H), 2.76-2.72 (m, 2H), 2.20-2.17 (m, 1H), 2.07 (m, 1H), 1.88 (bs, 2H), 1.64-1.58 (m, 4H)	448.2 (C ₁₄ H ₂₃ N ₇ O ₈ S)

18			9.63 (s, 1H), 7.80 (s, 1H), 7.17-7.30 (m, 5H), 6.87 (s, 1H), 4.14-4.27 (m, 2H), 3.97 (s, 1H), 3.85-3.86 (d, 1H), 3.10-3.13 (d, 1H), 2.94-2.97 (d, 1H), 1.61-1.84 (m, 4H).	412.3 (C₁₅H₁₈N₅O₇SNa)
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Example 19**Synthesis of sodium salt of phenyl {[(2S, 5R)-7-oxo-6-(sulfooxy)-1, 6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} carbamate**

Step 1: Synthesis of phenyl {[(2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate: To a clear solution of (2S, 5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxamide (25 g, 0.090 mol) in dichloromethane (100 ml) was added mixture of magnesium bromide (33.46 g, 0.1818 mol) in dichloromethane (100 ml) containing diisopropylethylamine (50 ml, 0.272 mol) under stirring at 0-5°C. After 10 minutes of stirring, phenyl chloroformate (22.15 ml, 0.1818 mol) was added drop wise, at 0-5°C, under continuous stirring. Then the reaction mass temperature was allowed to warm to room temperature for 1 hour. The completion of the reaction was confirmed by performing thin layer chromatography using mixture of acetone and hexane (35:65) as solvent system. After completion of reaction, the resulting mixture was diluted with water (20 ml) and dichloromethane (20 ml). The organic layer was separated and the aqueous layer re-extracted with dichloromethane (10 ml). The combined organic extracts were dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to yield an oily mass, which was purified by silicagel column chromatography using mixture of acetone and hexane as an eluent. The product containing fractions were collected and evaporated under reduced pressure to provide 16 g of the titled product as a white solid in 44.5% yield.

Step 2: Synthesis of phenyl {[(2S,5R)-6-hydroxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate: To a solution of phenyl {[(2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate (2 g, 0.005 mol, obtained from step 1) in a mixture of dimethylformamide and dichloromethane (1:1, 10 ml: 10 ml) was added 10% palladium over carbon (0.4 g, 50% wet) and was hydrogenated at 2 psi hydrogen pressure for 2 hours at 25°C. The reaction was monitored by performing thin layer chromatography using mixture of acetone and hexane (35:65) as solvent system. After completion of reaction, the resulting mixture was filtered through celite bed. The residue was washed with dichloromethane (5 ml). The solvent from the filtrate was evaporated under reduced pressure to obtain 1.5 g of the product as oil in 100% yield, which was used as such for the next reaction without further purification.

Step 3: Synthesis of tetrabutyl ammonium of salt of phenyl {[(2S, 5R)-7-oxo-6-(sulfooxy)-1, 6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} carbamate: To a solution of phenyl {[(2S,5R)-6-hydroxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate (1.5 g, 0.004 mol) in dimethylformamide (15 ml) was added dimethylformamide sulfur trioxide complex (0.978 g, 0.006 mol) in one portion under stirring at 10°C. The reaction mass was stirred at the same temperature for 30 minutes and then allowed to warm to room temperature. After 1 hour of stirring, to the resulting reaction mass was slowly added a solution of tetra butyl ammonium acetate (1.8 g, 0.0063 mol) in dichloromethane (2 ml) under stirring. After 1 hour, the solvent from the reaction mixture was evaporated under reduced pressure to obtain an oily residue. The oily mass was co-evaporated with xylene (2 × 10 ml) to obtain thick mass. This mass was partitioned between dichloromethane (10 ml) and water (10 ml). The combined organic extracts were washed with water (3 × 10 ml) and dried over anhydrous sodium

sulfate. The solvent was evaporated under reduced pressure and the resulting oily mass was triturated with ether (3 × 10 ml), each time the ether layer was decanted and finally the residue was concentrated under reduced pressure to obtain 2.3 g of the titled product as white foam in 80% yield.

Step 4: Synthesis of sodium salt of phenyl {[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1, 6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} carbamate: This compound was prepared by passing the solution of tetrabutyl ammonium salt of phenyl {[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1, 6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} carbamate (2.03 mol, 1.3 g) in tetrahydrofuran (7 ml) through the Dowex 200 Na resin using mixture of tetrahydrofuran and water (10:90) as an eluent. The obtained fractions containing the compound were mixed and distilled out to provide 0.8 g of the product as a white solid.

Analysis:

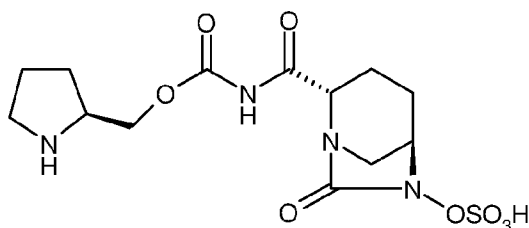
Mass: 384.1 (M-1); for Molecular weight 407.33 and Molecular formula C₁₄H₁₄N₃O₈SNa.

¹H NMR (400MHz, DMSO-D₆): 11.14 (s, 1H), 7.41-7.45(t, 2H), 7.26-7.30(t, 2H), 7.20-7.22(d, 2H), 4.06-4.08 (d, 1H), 4.02 (s, 1H), 3.02 (m, 2H), 1.72-1.97 (m, 4H).

Purity as determined by HPLC: 95.59%.

Example 20

Synthesis of (2*S*)-pyrrolidin-2-yl-methyl {[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate



Step 1: Synthesis of (2*S*)-pyrrolidin-2-yl-methyl {[(2*S*, 5*R*)-7-oxo-6-(benzyloxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate: A solution of phenyl {[(2*S*, 5*R*)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate (3 g, 0.007 mol, prepared according to the procedure described in Step 1 of Example 19) and Boc-prolinol (1.67 g, 0.008 mol) in 1,4-dioxane was stirred at 110°C for about 8 hours. The completion of the reaction was further confirmed by performing the thin layer chromatography using mixture of ethyl acetate and hexane (50:50) as solvent system. The resulting mixture was evaporated under reduced pressure and obtained oily mass was purified by normal column chromatography using mixture of acetone and hexane as an eluent. The product containing fractions were collected and concentrated to provide 2.1 g of the titled product as white solid in 55% yield.

Step 2: Synthesis of (2*S*)-pyrrolidin-2-yl-methyl {[(2*S*, 5*R*)-7-oxo-6-(hydroxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate: To a solution (2*S*)-pyrrolidin-2-yl-methyl {[(2*S*, 5*R*)-7-oxo-6-(benzyloxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate (1 g, 0.0019 mol, obtained in the Step 1) in a mixture of dimethylformamide and dichloromethane (1:1, 5 ml: 5 ml), was added 10% palladium over carbon (0.2g, 50% wet) and hydrogenated at 2 psi hydrogen pressure for 2 hours at 25°C. The reaction was monitored by performing thin layer chromatography using mixture of acetone and hexane as solvent system (35:65). After completion of the reaction, the resulting mixture was filtered through celite bed and residue was washed with dichloromethane (5 ml). The solvent from the filtrate was evaporated under reduced pressure to obtain 0.9 g of the titled product as oil in about 100% yield, which was used as such for the next reaction without further purification.

Step 3: Synthesis of tetrabutyl ammonium salt of (2S)-pyrrolidin-2-yl-methyl {[(2S, 5R)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate: To a stirred solution of (2S)-pyrrolidin-2-yl-methyl {[(2S, 5R)-7-oxo-6-(hydroxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl} carbamate (0.984 g, 0.002 mol) in dimethylformamide (10 ml) was added dimethylformamide sulfur trioxide complex (0.548 g, 0.0035 mol) in one portion under stirring at 10°C. The reaction mass was stirred at the same temperature for 30 minutes and allowed to warm to room temperature. After 1 hour, a solution of tetrabutylammonium acetate (1.05 g, 0.0035 mol) in dichloromethane (2 ml) was added to the reaction mixture under continuous stirring. After 1 hour of stirring the solvent from the reaction mixture was evaporated under reduced pressure to obtain an oily residue. The oily mass was co-evaporated with xylene (2×10 ml) to obtain thick mass. This mass was partitioned between dichloromethane (10 ml) and water (10 ml). The combined organic extracts were washed with water (3×10 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the resulting oily mass was triturated with ether (3×10 ml), each time the ether layer was decanted and finally the residue was concentrated under reduced pressure to obtain 1.2 g of the titled product as white foam in 80% yield.

Step 4: Synthesis of (2S)-pyrrolidin-2-yl-methyl {[(2S, 5R)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate: To a stirred solution of tetrabutyl ammonium salt of (2S)-pyrrolidin-2-yl-methyl {[(2S, 5R)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate (0.5 g) in dichloromethane (2.5 ml) was added trifluoroacetic acid (2.5 ml) drop wise at -10°C. After stirring at same temperature for 1 hour, the resulting mixture was poured into cyclohexane (25 ml). After stirring for 30 minutes, the separated oily layer was collected. This procedure was repeated one more time and finally the separated oily layer was added to diethyl ether (50 ml) under vigorous stirring at 25°C. The ether layer was removed by decantation from the precipitated solid. This procedure was repeated twice with diethyl ether (2×50 ml). The solid thus obtained was stirred with fresh dichloromethane (50 ml) for 30 minutes and filtered. The residual solid was dried at 45 °C under reduced pressure to provide 0.28 g of (2S)-pyrrolidin-2-yl-methyl {[(2S, 5R)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate as a white solid in 85% yield.

Analysis:

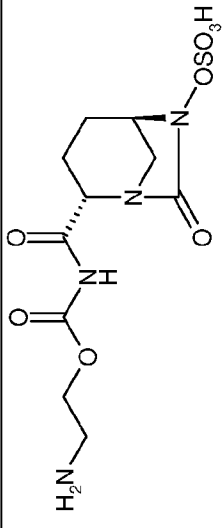
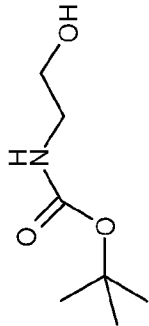
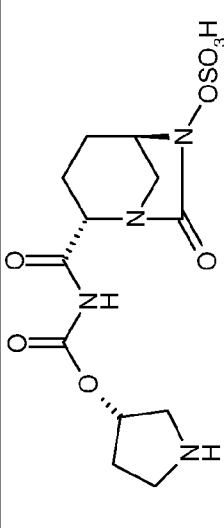
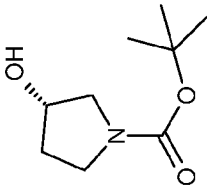
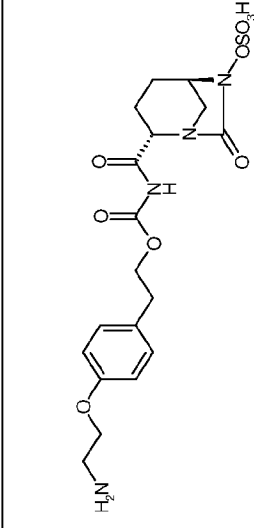
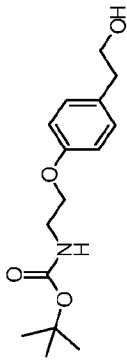
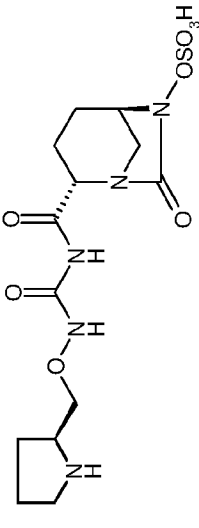
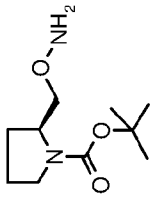
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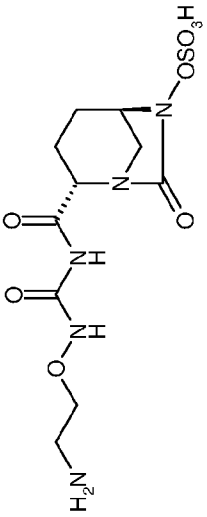
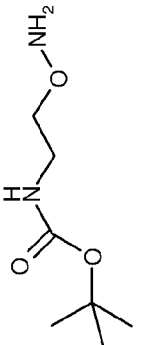
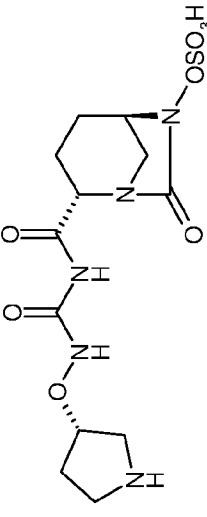
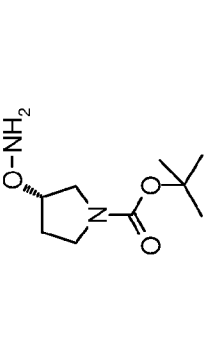
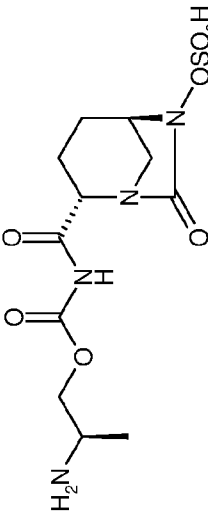
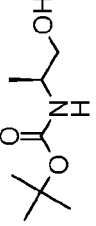
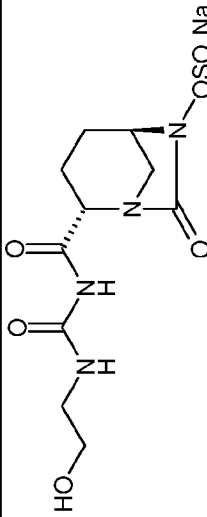
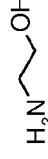
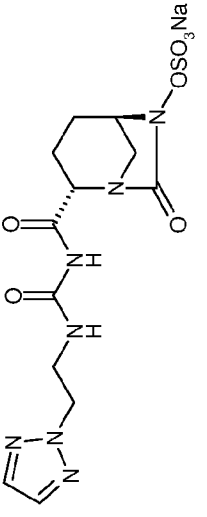
¹H NMR (400MHz, DMSO-D₆): 10.72 (s, 1H), 8.82 (s, 2H), 4.27-4.31 (dd, 1H), 4.14-4.19(m, 1H), 4.01 (s, 2H), 3.79-3.81 (m, 1H), 3.18-3.24 (m, 2H), 3.01-3.04(d,1H), 2.89-2.92(d,1H), 1.68-2.03 (m, 7H).

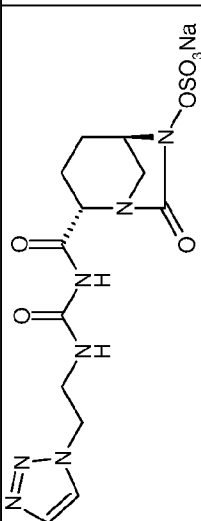
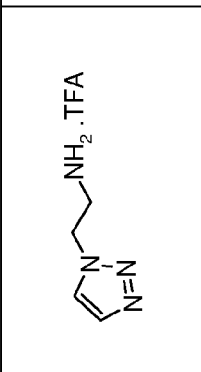
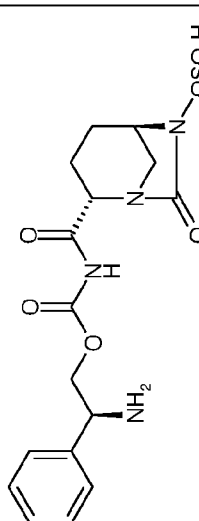
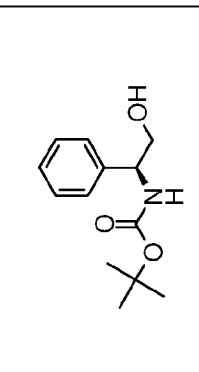
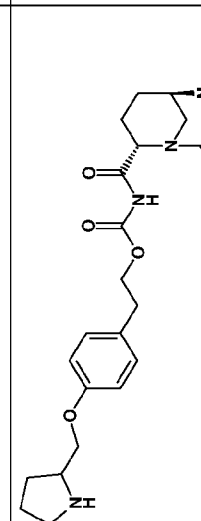
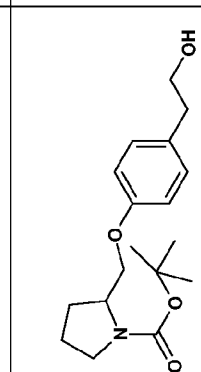
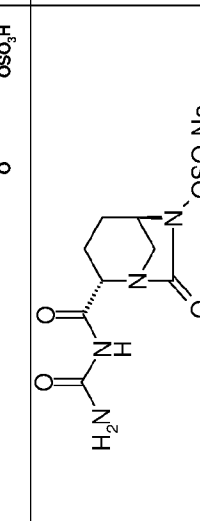
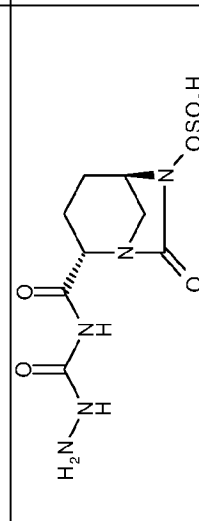
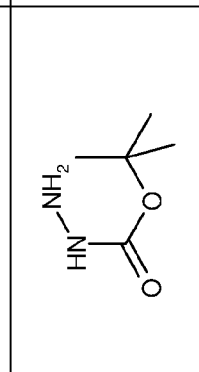
Purity as determined by HPLC: 87.68%.

The compounds of Examples 21 to 34 (Table 4) were prepared using the procedure described in Example 20 and by using corresponding starting reagents in place of Boc-prolinol.

Table-4

Example No.	Structure	Starting Reagent	¹ H NMR (DMISO-d ₆)	Mass as free acid (Molecular Formula)
21			10.31 (s, 1H), 7.81 (s, 2H), 4.32 (s, 2H), 4.02 (s, 2H), 3.04-3.13 (m, 4H), 1.66-2.00 (m, 4H).	351.2 (C ₁₀ H ₁₆ N ₄ O ₈ S)
22			10.56 (s, 1H), 8.87 (s, 2H), 5.28 (s, 1H), 4.02 (s, 2H), 3.41-3.46 (m, 2H), 3.22-3.27 (m, 2H), 3.02-3.06 (d, 1H), 2.90-2.93 (d, 1H), 1.67-2.18 (m, 7H).	377.2 (C ₁₂ H ₁₈ N ₄ O ₈ S)
23			10.51 (s, 1H), 7.89 (s, 3H), 7.22-7.24 (d, 2H), 6.90-6.92 (d, 2H), 4.32-4.33 (d, 1H), 4.21-4.26 (m, 2H), 4.11-4.13 (t, 3H), 3.39 (s, 1H), 2.95-3.02 (m, 2H), 2.86-2.88 (t, 2H), 1.87-1.90 (m, 2H), 1.68-1.72 (m, 2H).	471.2 (C ₁₈ H ₂₄ N ₄ O ₉ S)
24			10.95 (s, 1H), 10.39 (s, 1H), 8.89 (s, 1H), 8.57 (s, 1H), 3.79-4.09 (m, 4H), 2.95-3.32 (m, 5H), 1.54-2.67 (m, 8H).	408.2 (C ₁₃ H ₂₁ N ₅ O ₈ S)

25			3.95-4.00 (m, 3H), 3.57-3.59 (t, 1H), 2.94-3.03 (m, 3H), 1.68-1.95 (m, 4H).	366.2 (C ₁₀ H ₁₇ N ₅ O ₈ S)
26			10.81 (s, 1H), 10.32 (s, 1H), 8.79 (s, 2H), 4.69 (s, 1H), 4.02 (s, 1H), 3.96-3.98 (d, 1H), 3.28-3.44 (m, 5H), 2.96-3.07 (m, 2H), 2.14-2.17 (s, 1H), 1.68-2.04 (m, 4H).	392.2 (C ₁₂ H ₁₉ N ₅ O ₈ S)
27			10.30 (s, 1H), 7.83 (s, 2H), 4.15-4.19 (dd, 2H), 4.01-4.07 (m, 3H), 3.49-3.53 (m, 1H), 3.02-3.05 (d, 1H), 2.48-2.88 (d, 1H), 1.64-2.00 (m, 4H), 1.17-1.19 (d, 3H).	367.3 (C ₁₁ H ₁₈ N ₄ O ₈ S)
28			9.93 (s, 1H), 8.23 (t, 1H), 3.97 (s, 1H), 3.92-3.93 (d, 1H), 3.74-3.77 (t, 2H), 3.01 (s, 2H), 1.69-1.97 (m, 4H).	351.3 (C ₁₀ H ₁₅ N ₄ O ₈ SNa)
29			10.01 (s, 1H), 8.28-8.32 (t, 1H), 7.78 (s, 2H), 4.53-4.56 (t, 2H), 4.00 (d, 1H), 3.92 (d, 1H), 3.58-3.66 (m, 2H), 2.96-3.06 (m, 2H), 1.68-1.94 (m, 4H).	402.3 (C ₁₂ H ₁₆ N ₇ O ₇ SNa)

30			10.04(s, 1H), 8.28(t, 1H), 8.10(s, 1H), 7.72(s, 1H), 4.50-4.54(t, 2H), 4.00(d, 1H), 3.92(d, 1H), 3.58-3.66(m, 2H), 2.96-3.06(m, 2H), 1.68-1.94(m, 4H).	402.3 (C ₁₂ H ₁₆ N ₇ O ₇ SNa)
31			10.32(s, 1H), 8.46(s, 3H), 7.42-7.52(m, 5H), 4.65-4.71(m, 1H), 4.30-4.44(m, 2H), 4.04(s, 1H), 3.06-3.09(d, 1H), 2.50-2.90(dd, 1H) 1.66-2.02(m, 4H).	429.4 (C ₁₆ H ₂₀ N ₄ O ₈ S)
32			10.48 (s, 1H), 9.11 (br s, 1H), 8.63 (br s, 1H), 7.22(d, 2H, J=8.4Hz), 6.90(d, 2H, J=8.4Hz), 4.19-4.23 (m, 2H), 3.88-4.04 (m, 4H), 3.12-3.20 (m, 3H), 2.83-3.00 (m, 4H), 2.08-2.12 (m, 1H), 1.54-1.97 (m, 7H).	511.3 (C ₂₁ H ₂₈ N ₄ O ₉ S)
33		Aqueous Ammonia	9.75(s, 1H), 7.58(s, 1H), 7.32(s, 1H), 4.01(d, 1H), 3.94-4.06 (dd, 1H), 2.98-3.07 (m, 2H), 1.65-1.98 (m, 4H).	307 (C ₈ H ₁₁ N ₄ O ₇ SNa)
34			10.82 (s, 1H), 10.15 (s, 1H), 4.22 (d, 1H), 3.05-3.08 (d, 2H), 2.92-2.95 (d, 1H), 1.72-1.98 (m, 4H).	322.2 (C ₈ H ₁₂ N ₅ O ₇ S)

BIOLOGICAL ACTIVITY DATA

The biological activity of representative compounds according to the invention against various bacterial strains was investigated. In a typical study, overnight grown bacterial cultures were diluted appropriately and inoculated on the agar media containing doubling dilutions of the test compounds. Observations for growth or no growth was performed after 16-20 hours of incubation at $35\pm 2^\circ\text{C}$ in the ambient air. The overall procedure was performed as per Clinical and Laboratory Standards Institute (CLSI) recommendations, (Clinical and Laboratory Standards Institute (CLSI), Performance Standards for Antimicrobial Susceptibility Testing, 20th Informational Supplement, M 100-S20, Volume 30, No. 1, 2010).

Beta-Lactamase inhibition assay for the determination of IC₅₀: The degree of inactivation of beta-lactamase activity was determined with Nitrocefin as a substrate employing a spectrophotometric assay. The concentration of compounds which caused 50% reduction in hydrolysis of Nitrocefin (100 μM) i.e. IC₅₀, was measured after 10 minutes of pre incubation (37°C) of the crude enzymes and inhibitors. The change in colour of Nitrocefin from yellow to red was considered as an endpoint of the reaction, which was measured at 485nm by UV-spectrophotometer. The IC₅₀ was calculated by plotting Sigmoidal dose response curve using GraphPad-v5 software.

The results of Table 5 provide beta-lactamase inhibition details for representative compounds of Formula (I). The data suggest the compounds according to invention exhibited good beta-lactamase inhibition of SHV18, CMY/DHA, OXA 23, KPC 2 enzymes.

Table 5. Beta-lactamase enzyme inhibition (IC₅₀) of the representative compounds of Formula (I)					
Sr.	Compound of Example No.	Beta-lactamase enzymes inhibition MIC ($\mu\text{g/ml}$)			
		SHV 18	CMY/DHA	OXA 23	KPC 2
1.	1	0.002	0.001	0.026	0.009
2.	2	0.0066	0.0152	0.0149	0.0031
3.	3	0.01	0.0057	0.1454	0.0828
4.	4	0.0125	0.0068	0.1498	0.1129
5.	5	0.01314	0.01986	0.8952	0.03077
6.	6	0.0951	0.0354	2.286	0.1054
7.	7	0.013	0.021	1.412	0.094
8.	8	0.012	0.029	3.069	0.057
9.	9	0.0017	0.0015	0.2526	0.0089
10.	10	0.0061	0.0223	0.4726	0.0025
11.	11	0.0182	0.0025	0.172	0.0360
12.	12	0.0192	0.1472	3.772	0.0316
13.	13	0.0162	0.0392	1.615	0.0168
14.	17	0.109	0.082	1.533	-
15.	25	0.5359	0.0271	0.3193	0.6157
16.	33	0.0491	0.129	0.875	0.026
17.	Tazobactam	0.308	0.431	> 10	0.175

Method for the determination of MIC: The Minimum Inhibitory Concentration (MIC) determination for the combinations was carried out in Muller Hinton Agar (MHA) (BD, USA) according to Clinical and Laboratory Standards Institute (CLSI) recommendations, (Clinical and Laboratory Standards Institute (CLSI), Performance Standards for Antimicrobial Susceptibility Testing, 20th Informational Supplement, M 100-S20, Volume 30, No. 1, 2010). In short, the test strains were adjusted to deliver about 10^4 CFU per spot with a multipoint inoculator (Applied Quality

Services, UK). The plates were poured with MHA containing doubling concentration range of representative compounds according to present invention. The plates were inoculated and were incubated at 35°C for 18 hour. MICs were read as the lowest concentration of drug that completely inhibited bacterial growth. The Table 6 depicts the antibacterial activity profile of compounds according to present invention. These compounds when tested alone exhibited higher MIC values in comparison to standard.

The combinations of compounds according to present invention were also tested for their antibacterial activity in combination with Ceftazidime. The plates were poured with MHA containing doubling concentration range of Ceftazidime in combination with constant concentration (4 µg/ml) of representative compounds of Formula (I). The Table 7 shows the MIC values of Ceftazidime in presence of compounds according to the invention (at 4 µg/ml). As shown in Table 7, the MIC value of Ceftazidime was significantly lowered in presence of compounds according to the invention.

Table 6. Antibacterial activity of representative compounds according to the invention (MIC expressed in mcg/ml)

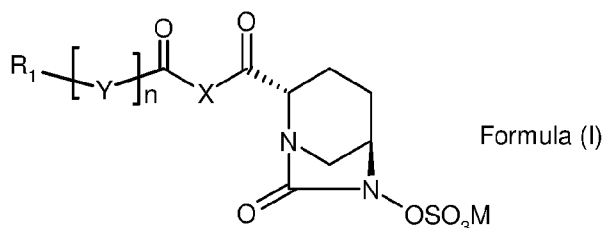
Sr.	Compounds	Bacterial Strains						
		<i>K. pneumoniae</i> ATCC 700603	<i>E. coli</i> NCTC 13352	<i>E. coli</i> NCTC 13353	<i>E. coli</i> M50	<i>E. coli</i> 7MP	<i>K. pneumoniae</i> H521	<i>K. pneumoniae</i> H525
1.	Example 1	> 32	> 32	> 32	> 32	> 32	> 32	> 32
2.	Example 2	> 32	> 32	> 32	> 32	> 32	> 32	> 32
3.	Example 3	> 32	> 32	> 32	> 32	> 32	> 32	> 32
4.	Example 4	> 32	> 32	> 32	> 32	> 32	> 32	> 32
5.	Example 5	> 32	> 32	> 32	> 32	> 32	> 32	> 32
6.	Example 6	> 32	> 32	> 32	> 32	> 32	> 32	> 32
7.	Example 7	> 32	> 32	> 32	> 32	> 32	> 32	> 32
8.	Example 8	> 32	> 32	> 32	> 32	> 32	> 32	> 32
9.	Example 9	> 32	> 32	> 32	> 32	> 32	> 32	> 32
10.	Example 10	> 32	> 32	> 32	> 32	> 32	> 32	> 32
11.	Example 11	> 32	> 32	> 32	> 32	> 32	> 32	> 32
12.	Example 12	> 32	> 32	> 32	> 32	> 32	> 32	> 32
13.	Example 13	> 32	32	8	32	16	16	16
14.	Example 15	> 32	4	2	2	8	16	16
15.	Example 17	> 32	32	8	32	16	16	16
16.	Example 18	>32	4	4	16	16	>32	>32
17.	Example 19	> 32	> 32	> 32	> 32	> 32	> 32	> 32
18.	Example 20	> 32	> 32	> 32	> 32	> 32	> 32	> 32
19.	Example 21	> 32	> 32	> 32	> 32	> 32	> 32	> 32
20.	Example 22	> 32	> 32	> 32	> 32	> 32	> 32	> 32
21.	Example 23	> 32	> 32	> 32	> 32	> 32	> 32	> 32
22.	Example 24	> 32	> 32	> 32	> 32	> 32	> 32	> 32
23.	Example 25	> 32	> 32	> 32	> 32	> 32	> 32	> 32
24.	Example 26	> 32	> 32	> 32	> 32	> 32	> 32	> 32
25.	Example 27	> 32	> 32	> 32	> 32	> 32	> 32	> 32
26.	Example 28	> 32	> 32	> 32	> 32	> 32	> 32	> 32
27.	Example 29	> 32	> 32	> 32	> 32	> 32	> 32	> 32
28.	Example 30	> 32	> 32	> 32	> 32	> 32	> 32	> 32
29.	Example 31	> 32	> 32	> 32	> 32	> 32	> 32	> 32
30.	Example 32	> 32	> 32	> 32	> 32	> 32	> 32	> 32
31.	Example 33	> 32	> 32	> 32	> 32	> 32	> 32	> 32
32.	Cefepime	0.5	4	32	> 32	16	32	32

Table 7. Antibacterial activity of representative compounds according to the invention in combination with Ceftazidime

Table 7. Antibacterial activity of representative compounds according to the invention in combination with Ceftazidime									
Sr.	Compounds	Ceftazidime MIC (expressed in mcg/ml)							
		<i>K. pneumoniae</i> ATCC 700603	<i>E. coli</i> NCTC 13352	<i>E. coli</i> NCTC 13353	<i>E. coli</i> M50	<i>E. coli</i> 7MP	<i>K. pneumoniae</i> H521	<i>K. pneumoniae</i> H525	
1.	Ceftazidime alone	32	> 32	32	> 32	> 32	> 32	> 32	
2.	Ceftazime +Example 1 (4mcg/ml)	2	16	0.5	2	32	> 32	> 32	
3.	Ceftazidime +Example 2 (4mcg/ml)	0.5	4	0.5	0.5	4	16	16	
4.	Ceftazidime +Example 3 (4mcg/ml)	0.5	2	0.5	1	2	8	8	
5.	Ceftazidime +Example 4 (4mcg/ml)	0.5	2	0.5	1	2	8	8	
6.	Ceftazidime +Example 5 (4mcg/ml)	0.5	4	0.5	1	2	8	8	
7.	Ceftazidime +Example 6 (4mcg/ml)	1	1	0.25	1	8	8	8	
8.	Ceftazidime +Example 7 (4mcg/ml)	1	2	0.25	1	16	16	16	
9.	Ceftazidime +Example 8 (4mcg/ml)	1	2	0.25	1	4	4	4	
10.	Ceftazidime +Example 9 (4mcg/ml)	1	2	0.25	0.5	4	16	8	
11.	Ceftazidime +Example 10 (4mcg/ml)	2	4	0.5	2	8	8	8	
12.	Ceftazidime +Example 11 (4mcg/ml)	2	1	0.25	2	4	8	4	
13.	Ceftazidime +Example 12 (4mcg/ml)	4	4	0.5	2	16	16	16	
14.	Ceftazidime +Example 13 (4mcg/ml)	2	4	0.25	2	16	8	8	
15.	Ceftazidime +Example 19 (4mcg/ml)	0.5	1	0.5	1	8	8	4	
16.	Ceftazidime +Example 20 (4mcg/ml)	1	2	0.5	1	8	8	8	
17.	Ceftazidime +Example 21 (4mcg/ml)	0.5	2	0.5	1	4	8	4	
18.	Ceftazidime +Example 23 (4mcg/ml)	4	32	1	4	> 32	> 32	> 32	
19.	Ceftazidime +Example 24 (4mcg/ml)	0.5	2	0.5	1	2	8	4	
20.	Ceftazidime +Example 25 (4mcg/ml)	0.25	2	0.25	0.5	2	4	4	
21.	Ceftazidime +Example 26 (4mcg/ml)	0.5	8	0.25	0.5	2	4	4	
22.	Ceftazidime +Example 27 (4mcg/ml)	1	2	0.5	1	4	8	8	
23.	Ceftazidime +Example 28 (4mcg/ml)	0.12	4	0.25	1	8	> 32	> 32	
24.	Ceftazidime +Example 29 (4mcg/ml)	4	> 32	1	8	> 32	> 32	> 32	
25.	Ceftazidime +Example 30 (4mcg/ml)	0.25	8	0.25	2	8	> 32	> 32	
26.	Ceftazidime +Example 31 (4mcg/ml)	1	8	0.5	4	4	16	32	
27.	Ceftazidime +Example 32 (4mcg/ml)	4	32	0.5	1	>32	>32	>32	
28.	Ceftazidime +Example 33 (4mcg/ml)	0.5	1	0.25	0.5	2	4	2	

CLAIMS

1. A compound of Formula (I):



or a stereoisomer or a pharmaceutically acceptable derivative thereof;

wherein:

X is: -NH- or -NH-NH-;

Y is: -CR₂R₃-, -NH-, -NHNH-, -ONH- or -O-;

provided that when X is -NH-NH-; Y is -NH- or -O-;

R₁ is:

- (a) hydrogen;
- (b) C₁-C₆ alkyl optionally substituted with one or more substituents independently selected from OR₂, NR₂R₃, SR₂, halogen, CN, COOR₂, CONR₂R₃, (CH₂)_mOR₂, (CH₂)_mNR₂R₃, cycloalkyl, heterocycloalkyl, aryl or heteroaryl;
- (c) cycloalkyl optionally substituted with one or more substituents independently selected from OR₂, NR₂R₃, SR₂, halogen, CN, COOR₂, CONR₂R₃, (CH₂)_mOR₂ or CH₂NR₂R₃;
- (d) aryl optionally substituted with one or more substituents independently selected from OR₂, NR₂R₃, SR₂, halogen, CN, COOR₂, CONR₂R₃, (CH₂)_mOR₂ or (CH₂)_mNR₂R₃;
- (e) heteroaryl optionally substituted with one or more substituents independently selected from OR₂, NR₂R₃, SR₂, halogen, CN, COOR₂, CONR₂R₃, (CH₂)_mOR₂ or (CH₂)_mNR₂R₃ or;
- (f) heterocycloalkyl optionally substituted with one or more substituents independently selected from OR₂, NR₂R₃, SR₂, halogen, CN, COOR₂, CONR₂R₃, (CH₂)_mOR₂ or (CH₂)_mNR₂R₃;

R₂ and R₃ are each independently:

- (a) hydrogen,
- (b) C₁-C₆ alkyl,
- (c) cycloalkyl,
- (d) aryl,
- (e) heteroaryl, or
- (f) heterocycloalkyl;
- (g) R₂ and R₃ are joined together to form three to seven membered ring optionally containing one or more heteroatoms selected from nitrogen, sulfur and oxygen.

m is 1 to 5;

n is 0 or 1;

M is hydrogen or a cation.

2. A compound according to Claim 1, selected from:
 - (2*S*, 5*R*)-7-Oxo-*N*-(piperidin-4-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;
 - (2*S*, 5*R*)-7-Oxo-*N*-[(3*R*)-piperidin-3-yl-carbamoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;
 - (2*S*, 5*R*)-7-Oxo-*N*-(piperidin-3-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;
 - (2*S*, 5*R*)-7-Oxo-*N*-[(3*S*)-piperidin-3-yl-carbamoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;
 - (2*S*, 5*R*)-7-Oxo-*N*-[(3*R*)-pyrrolidin-3-yl-carbamoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;
 - (2*S*, 5*R*)-7-Oxo-*N*-[(3*S*)-pyrrolidin-3-yl-carbamoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;
 - (2*S*, 5*R*)-7-Oxo-*N*-(pyrrolidin-3-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;
 - (2*S*, 5*R*)-7-Oxo-*N*-(pyrrolidin-3-yl-acetyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;
 - (2*S*, 5*R*)-7-Oxo-*N*-(pyrrolidin-2-yl-acetyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;
 - (2*S*, 5*R*)-7-Oxo-*N*-[3-(pyrrolidin-2-yl)propanoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;
 - (2*S*, 5*R*)-7-Oxo-*N*-[3-(pyrrolidin-3-yl)propanoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;
 - (2*S*, 5*R*)-*N*-(3-aminopropanoyl)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;
 - (2*S*, 5*R*)-7-Oxo-*N*-[(3*R*)-piperidin-3-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide;
 - (2*S*, 5*R*)-7-Oxo-*N*-[(3*S*)-piperidin-3-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;
 - (2*S*, 5*R*)-7-Oxo-*N*-(piperidin-3-yl-carbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;
 - (2*S*, 5*R*)-7-Oxo-*N*-(piperidin-4-yl-carbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;
 - (2*S*, 5*R*)-7-Oxo-*N*-[(2*S*)-pyrrolidin-2-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;
 - (2*S*, 5*R*)-7-Oxo-*N*-[(3*R*)-pyrrolidin-3-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;
 - (2*S*, 5*R*)-7-Oxo-*N*-[(3*S*)-pyrrolidin-3-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide;
 - (2*S*, 5*R*)-7-Oxo-*N*-(pyrrolidin-3-yl-carbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;
 - 2-[[[(2*S*, 5*R*)-7-Oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl]-*N*-[(2*R*, 5*S*)-5-aminopiperidine-2-carboxamide];
 - 2-Aminoethyl {[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} carbamate;
 - (2*S*)-Pyrrolidin-2-ylmethyl {[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl} carbamate;
 - (3*R*)-Pyrrolidin-3-yl-[[[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl} carbamate;
 - (2*S*, 5*R*)-*N*-[(2-aminoethoxy) carbamoyl]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*- {[(2*S*)-pyrrolidin-2-ylmethoxy] carbamoyl}-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*- {[(3*R*)-pyrrolidin-3-yloxy] carbamoyl}-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide

(2*S*, 5*R*)-7-Oxo-*N*-(phenylcarbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(pyridin-3-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(pyridin-4-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(pyridin-2-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(ethoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(tert-butoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(propoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(isopropoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-(acetyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

(2*S*, 5*R*)-7-Oxo-*N*-[2-(2,2-dimethylpropanoyl)] -6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

2- {[(2*S*, 5*R*)-7-Oxo-6- (sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl}-*N*-phenylhydrazinecarboxamide;

N- (2-methoxyphenyl)-2- {[(2*S*, 5*R*)-7-oxo-6- (sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} hydrazinecarboxamide;

2- {[(2*S*, 5*R*)-7-Oxo-6- (sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl}-*N*- (pyridin-3-yl) hydrazinecarboxamide;

N-Cyclohexyl-2- {[(2*S*,5*R*)- 7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl} hydrazinecarboxamide;

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

N-Benzyl-2- {[(2*S*,5*R*)- 7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl} hydrazinecarboxamide;

2- {[(2*S*,5*R*)-7-Oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl}-*N*-(pyridin-4-ylmethyl)hydrazinecarboxamide;

N-(2-Aminoethyl)-2- {[(2*S*,5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl} hydrazinecarboxamide;

2- {[(2*S*,5*R*)-7-Oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl}-*N*-[(2*S*)-pyrrolidin-2-ylmethyl]hydrazinecarboxamide;

2-[4-(2-Aminoethoxy)phenyl]ethyl {[(2*S*,5*R*) -7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl} carbamate;

3-Aminopropyl {[(2*S*,5*R*) -7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl} carbamate;

Methyl 2-amino-3-[[[(2*S*,5*R*) -7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl] carbamoyl]oxy]propanoate;

2-(Phenylamino)ethyl {[(2*S*,5*R*) -7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl} carbamate;

2-(Benzylamino)ethyl {[(2*S*,5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl} carbamate;

2-(Pyridine-4-methylamino)ethyl {[(2*S*,5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl} carbamate;

2-(Pyridin-2-ylamino) ethyl {[(2*S*,5*R*) -7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl} carbamate;

2-(Pyridin-3-ylamino) ethyl {[(2*S*,5*R*) -7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl]carbonyl} carbamate;

(2*S*)-2-Aminopropyl {[(2*S*,5*R*) -7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl} carbamate;

(2*S*,5*R*)-7-Oxo-6-(sulfooxy)-*N*-{[2-(2*H*-1,2,3-triazol-2-yl)ethyl]carbamoyl}-1,6- diazabicyclo [3.2.1]octane-2-carboxamide;

(2*S*,5*R*)-7-Oxo-6-(sulfooxy)-*N*-{[2-(1*H*-1,2,3-triazol-1-yl)ethyl]carbamoyl}-1,6- diazabicyclo [3.2.1]octane-2-carboxamide;

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

(2*S*)-2-Amino-2-phenylethyl{[(2*S*,5*R*)-7-oxo-6-(sulfooxy)-1,6- diazabicyclo[3.2.1]oct-2-yl]carbonyl} carbamate;

or a stereoisomer or a pharmaceutically acceptable derivative thereof.

3. A compound according to Claim 1, selected from:

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*- (piperidin-4-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*- [(3*R*)-piperidin-3-yl-carbamoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*- (piperidin-3-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*- [(3*S*)-piperidin-3-yl-carbamoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-[(3*R*)-pyrrolidin-3-yl-carbamoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*- [(3*S*)-pyrrolidin-3-yl-carbamoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(pyrrolidin-3-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(pyrrolidin-3-yl-acetyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(pyrrolidin-2-yl-acetyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-[3-(pyrrolidin-2-yl)propanoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-[3-(pyrrolidin-3-yl)propanoyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-*N*-(3-aminopropanoyl)-7-oxo-6- (sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-[(3*R*)-piperidin-3-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-[(3*S*)-piperidin-3-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(piperidin-3-yl-carbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(piperidin-4-yl-carbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*- [(2*S*)-pyrrolidin-2-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-[(3*R*)-pyrrolidin-3-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-[(3*S*)-pyrrolidin-3-yl-carbonyl]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(pyrrolidin-3-yl-carbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of 2-{[(2*S*, 5*R*)-7-oxo-6- (sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl}-*N*- [(2*R*, 5*S*)-5-aminopiperidine-2-carboxamide];

Sodium salt of 2-aminoethyl {[(2*S*, 5*R*)-7-oxo-6- (sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} carbamate;

Sodium salt of (2*S*)-pyrrolidin-2-ylmethyl {[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} carbamate;

Sodium salt of (3*R*)-pyrrolidin-3-yl- {[(2*S*, 5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} carbamate;

Sodium salt of (2*S*, 5*R*)-*N*- [(2-aminoethoxy) carbamoyl]-7-oxo-6- (sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*- {[(2*S*)-pyrrolidin-2-ylmethoxy] carbamoyl}-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*- {[(3*R*)-pyrrolidin-3-yloxy] carbamoyl}-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(phenylcarbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(pyridin-3-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(pyridin-4-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(pyridin-2-yl-carbamoyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(ethoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(tert-butoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(propoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(isopropoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(acetyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of (2*S*, 5*R*)-7-oxo-*N*-[2-(2,2-dimethylpropanoyl)] -6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of 2- {[(2*S*, 5*R*)-7-oxo-6- (sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl}-*N*-phenylhydrazinecarboxamide;

Sodium salt of *N*- (2-methoxyphenyl)-2- {[(2*S*, 5*R*)-7-oxo-6- (sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl} hydrazinecarboxamide;

Sodium salt of 2- {[(2*S*, 5*R*)-7-oxo-6- (sulfooxy)-1,6-diazabicyclo [3.2.1] oct-2-yl] carbonyl}-*N*- (pyridin-3-yl) hydrazinecarboxamide;

Sodium salt of *N*-cyclohexyl-2-[[*(2S,5R)*-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl]hydrazinecarboxamide;

Sodium salt of *(2S, 5R)*-*N*-carbamoyl-7-oxo-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide;

Sodium salt of *N*-benzyl-2-[[*(2S,5R)*-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl]hydrazinecarboxamide;

Sodium salt of 2-[[*(2S,5R)*-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl]-*N*-(pyridin-4-ylmethyl)hydrazinecarboxamide;

Sodium salt of *N*-(2-aminoethyl)-2-[[*(2S,5R)*-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl]hydrazinecarboxamide;

Sodium salt of 2-[[*(2S,5R)*-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl]-*N*-[(*2S*)-pyrrolidin-2-ylmethyl]hydrazinecarboxamide;

Sodium salt of 2-[4-(2-aminoethoxy)phenyl]ethyl {[*(2S,5R)*-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate;

Sodium salt of 3-aminopropyl {[*(2S,5R)*-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate;

Sodium salt of methyl 2-amino-3-[[[*(2S,5R)*-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl]carbamoyl]oxy]propanoate;

Sodium salt of 2-(phenyl amino)ethyl {[*(2S,5R)*-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate;

Sodium salt of 2-(benzyl amino)ethyl {[*(2S,5R)*-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate;

Sodium salt of 2-(pyridine-4-methylamino)ethyl {[*(2S,5R)*-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate;

Sodium salt of 2-(pyridin-2-ylamino)ethyl {[*(2S,5R)*-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate;

Sodium salt of 2-(pyridin-3-ylamino)ethyl {[*(2S,5R)*-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate;

Sodium salt of (*2S*)-2-aminopropyl {[*(2S,5R)*-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}carbamate;

Sodium salt of *(2S,5R)*-7-oxo-6-(sulfooxy)-*N*-[[2-(*2H*-1,2,3-triazol-2-yl)ethyl]carbamoyl]-1,6-diazabicyclo [3.2.1]octane-2-carboxamide;

Sodium salt of *(2S,5R)*-7-oxo-6-(sulfooxy)-*N*-[[2-(*1H*-1,2,3-triazol-1-yl)ethyl]carbamoyl]-1,6-diazabicyclo [3.2.1]octane-2-carboxamide;

Sodium salt of *(2S,5R)*-*N*-[(2-hydroxyethyl)carbamoyl]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide;

Sodium salt of (*2S*)-2-amino-2-phenylethyl{[*(2S,5R)*-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl} carbamate;

or a stereoisomer thereof.

4. A pharmaceutical composition comprising a compound according to any of the Claims 1 to 3.

5. A pharmaceutical composition comprising a sodium salt of *(2S, 5R)*-7-oxo-*N*-(ethoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide or a stereoisomer thereof.

6. A pharmaceutical composition according to any one of the Claims 4 or 5, further comprising at least one beta-lactamase inhibitor, or a pharmaceutically acceptable derivative thereof.

7. A pharmaceutical composition according to Claim 6, wherein the beta-lactamase inhibitor is selected from the group consisting of sulbactam, tazobactam, clavulanic acid, avibactam, or a pharmaceutically acceptable derivative thereof.

8. A pharmaceutical composition according to any one of the Claims 4 to 7, further comprising at least one antibacterial agent, or a pharmaceutically acceptable derivative thereof.

9. A pharmaceutical composition according to Claim 8, wherein the antibacterial agent is selected from a group consisting of aminoglycosides, ansamycins, carbapenems, carbacephems, cephalosporins, cephamycins, lincosamides, lipopeptides, macrolides, monobactams, nitrofurans, penicillins, polypeptides, penems, quinolones, sulfonamides, tetracyclines, or oxazolidinone antibacterial agents.

10. A pharmaceutical composition according to Claim 8, wherein the antibacterial agent is a beta-lactam antibacterial agent.

11. A pharmaceutical composition according to Claim 8, wherein the antibacterial agent is selected from the group consisting of cephalotin, cephaloridine, cefaclor, cefadroxil, cefamandole, cefazolin, cefalexin, cefradine, ceftizoxime, cefoxitin, cephacetrile, cefotiam, cefotaxime, cefsulodin, cefoperazone, cefmenoxime, cefmetazole, cefpaloglycin, cefonicid, cefodizime, cefpirome, ceftazidime, ceftriaxone, cefpiramide, cefbuperazone, cefozopran, cefepime, cefoselis, ceftuprenam, cefuzonam, cefpimizole, cefclidin, cefixime, ceftibuten, cefdinir, cefpodoxime auxetil, cefpodoxime proxetil, cefteram pivoxil, cefetamet pivoxil, cefcapene pivoxil, cefditoren pivoxel, cefuroxime, cefuroxime auxetil, loracarbacef, ceftaroline, ceftolozane, latamoxef, imipenem, doripenem, and meropenem.

12. A pharmaceutical composition according to any one of the Claims 4 to 11 for use in treatment or prevention of a bacterial infection.

13. A method of preventing or treating a bacterial infection in a subject, said method comprising administering to said subject a compound according to any one of the Claims 1 to 3.

14. A method of preventing or treating a bacterial infection in a subject, said method comprising administering to said subject sodium salt of (2*S*, 5*R*)-7-oxo-*N*-(ethoxycarbonyl)-6-(sulfooxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide or a stereoisomer thereof.

15. A method for preventing or treating a bacterial infection in a subject, said method comprising administering to said subject a pharmaceutical composition according to any one of the Claims 4 to 11.

16. A method for preventing or treating a bacterial infection in a subject, said method comprising administering to said subject a pharmaceutical composition comprising: (a) compounds according to any one of the Claims 1 to 3; and (b) at least one beta-lactamase inhibitor or a pharmaceutically acceptable derivative thereof.

17. A method for preventing or treating a bacterial infection in a subject, said method comprising administering to said subject a pharmaceutical composition comprising: (a) compounds according to any one of the Claims 1 to 3; and (b) at least one beta-lactamase inhibitor selected from

the group consisting of sulbactam, tazobactam, clavulanic acid, avibactam, or a pharmaceutically acceptable derivative thereof.

18. A method for preventing or treating a bacterial infection in a subject, said method comprising administering to said subject a pharmaceutical composition comprising: (a) compounds according to any one of the Claims 1 to 3; and (b) at least one antibacterial agent or a pharmaceutically acceptable derivative thereof.

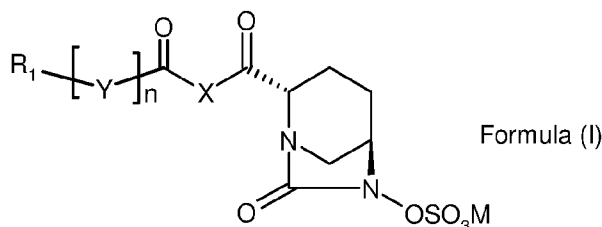
19. A method for preventing or treating a bacterial infection in a subject, said method comprising administering to said subject a pharmaceutical composition comprising: (a) compounds according to any one of the Claims 1 to 3; and (b) at least one antibacterial agent selected from cefepime, cefpirome, ceftaroline, ceftazidime, ceftalozane or a pharmaceutically acceptable derivative thereof.

20. A method for preventing or treating a bacterial infection in a subject, said method comprising administering to said subject: (a) a compound according to any one of the Claims 1 to 3, and (b) at least one beta-lactamase inhibitor, or a pharmaceutically acceptable derivative thereof.

21. A method for preventing or treating a bacterial infection in a subject, said method comprising administering to said subject: (a) a compound according to any one of the Claims 1 to 3, and (b) at least one antibacterial agent, or a pharmaceutically acceptable derivative thereof.

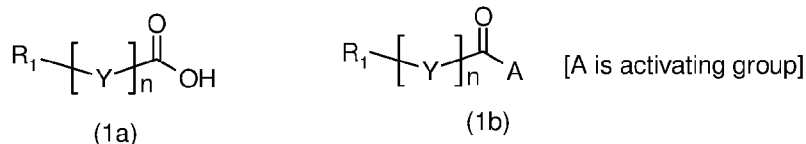
22. A method for increasing antibacterial effectiveness of an antibacterial agent in a subject, said method comprising co-administering said antibacterial agent, or a pharmaceutically acceptable derivative thereof, with a compound according to any one of the Claims 1 to 3.

23. A process for preparation of a compound of Formula (I), wherein X is NH,

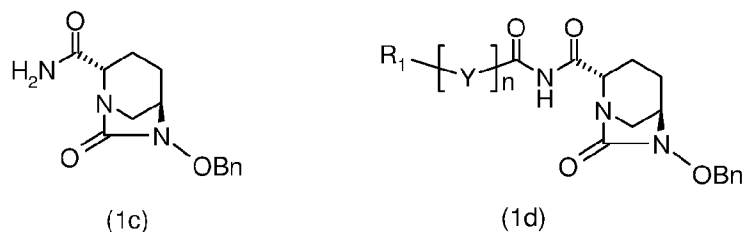


said process comprising:

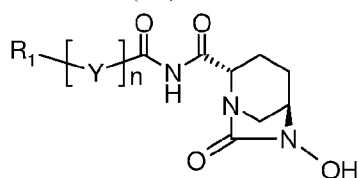
(a) converting a compound of Formula (1a) to a compound of Formula (1b);



(b) reacting a compound of Formula (1b) with a compound of Formula (1c) to obtain a compound of Formula (1d);

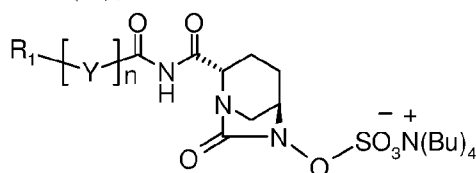


- (c) debenzylating a compound of Formula (1d) to obtain a compound of Formula (1e);



(1e)

- (d) sulfonating a compound of Formula (1e), followed by tetrabutylammonium salt formation to obtain a compound of Formula (1f);



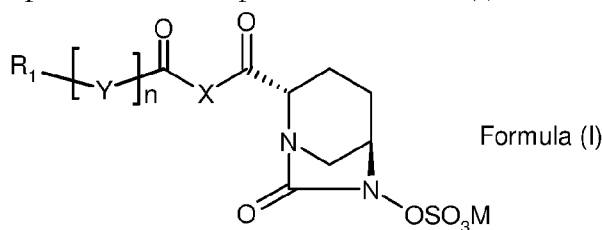
(1f)

- (e) converting a compound of Formula (1f) to a compound of Formula (I).

24. A process according to Claim 23, wherein a compound of Formula (1b) is obtained by treating a compound of Formula (1a) with a carboxyl activating reagent.

25. A process according to Claim 24, wherein carboxyl activating reagent is selected from thionyl chloride, oxalyl chloride, phosphorous trichloride, phosphorous oxychloride, phosphorous pentachloride, α -bromoacetyl bromide, pivaloyl chloride, diphenylphosphonic azide dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1,1'-carbonyldiimidazole, di-*tert*-butyldicarbonate, acetic anhydride, ethyl chloroformate, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, 1-hydroxybenzotriazole, N-hydroxysuccinimide, 1-hydroxy-7-aza-1H-benzotriazole, 4-(N,N-dimethylamino)pyridine, 2-propanephosphonic acid anhydride, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium salts, bis-trichloromethylcarbonate, triphosgene, p-nitrophenol, pentafluorophenol, 4-trifluoromethyl benzoic anhydride, 2-methyl-6-nitrobenzoic anhydride, magnesium bromide, lithium bromide, magnesium bromide diethyletherate or mixture thereof.

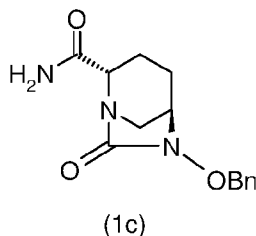
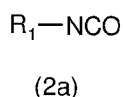
26. A process for preparation of a compound of Formula (I), wherein $X=Y=NH$,



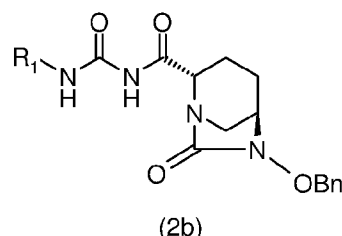
Formula (I)

said process comprising:

- (a) reacting a compound of Formula (2a) with a compound of Formula (1c) to obtain a compound of Formula (2b);

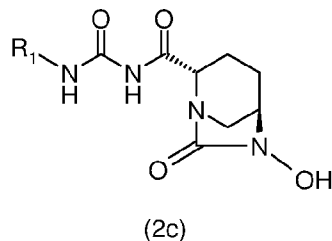


(1c)

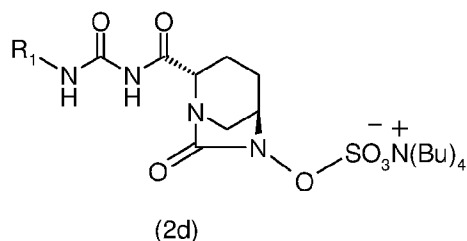


(2b)

- (b) debenzylating a compound of Formula (2b) to obtain a compound of Formula (2c);



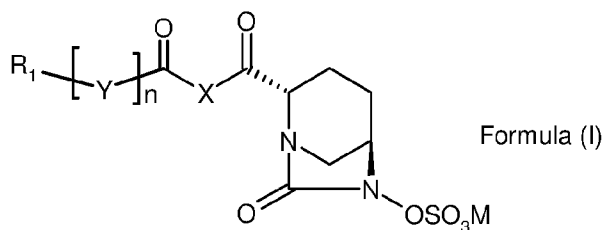
- (c) sulfonating a compound of Formula (2c), followed by tetrabutylammonium salt formation to obtain a compound of Formula (2d);



- (d) converting a compound of Formula (2d) to a compound of Formula (I).

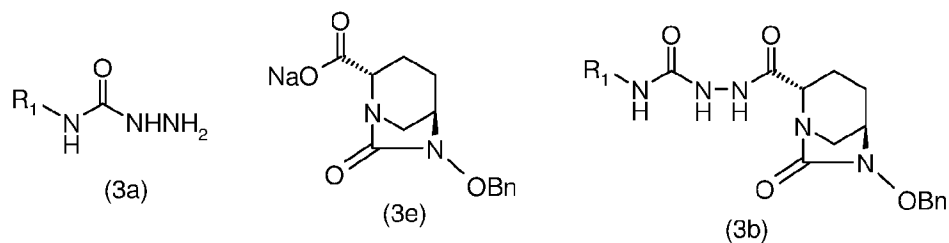
27. A process according to Claim 26, wherein a compound of Formula (2a) is reacted with a compound of Formula (1c) in presence of an activating reagent selected from magnesium bromide, lithium bromide or magnesium bromide diethyletherate to obtain a compound of Formula (2b).

28. A process for preparation of a compound of Formula (I), wherein X= -NHNH- and Y= -NH-,

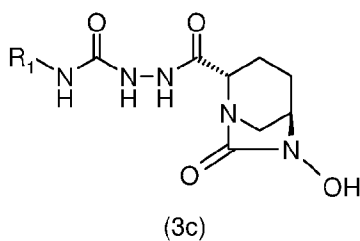


said process comprising:

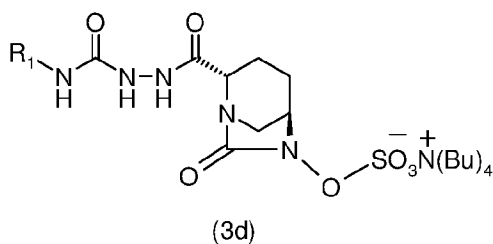
- (a) reacting a compound of Formula (3a) with a compound of Formula (3e) to obtain a compound of Formula (3b);



- (d) debenzylating a compound of Formula (3b) to obtain a compound of Formula (3c);



(c) sulfonating a compound of Formula (3c), followed by tetrabutylammonium salt formation to obtain a compound of Formula (3d);



(d) converting a compound of Formula (3d) to a compound of Formula (I).

29. A process according to Claim 28, wherein a compound of Formula (3b) is obtained by reacting a compound of Formula (3a) with a compound of Formula (3e) in presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and 1-hydroxybenzotriazole.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/059342

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/08 A61K31/439 A61P31/04
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/030733 A1 (WOCKHARDT LTD [IN]; PATEL MAHESH VITHALBHAI [IN]; DESHPANDE PRASAD KES) 7 March 2013 (2013-03-07) page 32 - page 36; examples 1-3 page 41 - page 55; examples 7-35, 37-39, 41-46, 48-49, 51 claims 5-31 -----	1-27
A	WO 2014/141132 A1 (NAEJA PHARMACEUTICAL INC [CA]) 18 September 2014 (2014-09-18) claim 1 -----	1-27



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

15 February 2016

Date of mailing of the international search report

06/05/2016

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Lewis, Sara

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2015/059342

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

5, 23-27(completely); 1-4, 6-22(partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 5, 23-27(completely); 1-4, 6-22(partially)

Compounds of formula (I) wherein X is NH, pharmaceutical compositions thereof, their use and process for preparing the same

2. claims: 28, 29(completely); 1-4, 6-22(partially)

Compounds of formula (I) wherein X is NH-NH, pharmaceutical compositions thereof, their use and process for preparing the same

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2015/059342

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013030733	A1	07-03-2013	
		AU 2012303691 A1	31-10-2013
		CA 2833241 A1	07-03-2013
		CN 103619843 A	05-03-2014
		EP 2748165 A1	02-07-2014
		JP 5666743 B2	12-02-2015
		JP 2014515041 A	26-06-2014
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		NZ 616542 A	30-01-2015
		RU 2013155902 A	10-10-2015
		US 2014148431 A1	29-05-2014
		US 2014275018 A1	18-09-2014
		US 2015005285 A1	01-01-2015
		US 2015174133 A1	25-06-2015
		US 2015328201 A1	19-11-2015
		WO 2013030733 A1	07-03-2013

WO 2014141132	A1	18-09-2014	NONE
