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(71) Applicant: WOCKHARDT LIMITED [IN/IN]; D-4, MIDC Area, Chikalthana, Aurangabad 431006 (IN).

(72) Inventors: PATIL, Vijaykumar Jagdishwar; Prem Nagar-2, Near Bharati Vidhyapeeth, Solapur-413004, Maharashtra, Solapur 413004 (IN). MAURYA, Sushilkumar; Wockhardt Research centre, D-4, MIDC Area, Chikalthana, Aurangabad - 431006, Maharashtra, Aurangabad 431006 (IN). PATEL, Piyush Ambalal; B/22, Jalaram Society, Nana Bazar, Vallabh Vidhyanager-388 120, Dist : Anand, Gujarat, Anand 388120 (IN). BHUNIYA, Rajib; Jagatberh, Jilipibagan, Sripally, Burdwan, West Bengal, 713103, India, Burdwan 713103 (IN). MUNSHI, Zaki Ahmed Burhanuddin; Room no 105, A-Wing, Hayat Complex, Govindwadi road, Koliwada, Kalyan (W) - 421301, Maharashtra Kalyan 421301 (IN). PATEL, Mahesh Vitthalbhai; Plot No. 157, Opp. Saint Meera School, N-3, CIDCO, Aurangabad - 431003, Maharashtra, Aurangabad 431003 (IN).

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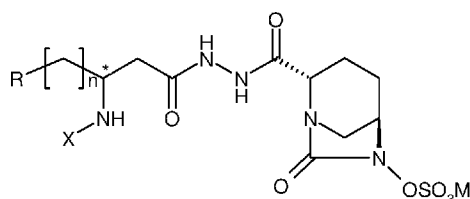
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(54) Title: N-(ALKANOYL)-7-OXO-6-SULFOXY-1,6-DIAZABICYCLO[3.2.1]OCTANE-2-CARBONYLHYDRAZIDE DERIVATIVES AND THEIR USE AS ANTIBACTERIAL AGENTS



Formula (I)

(57) Abstract: Compounds of Formula (I), or a stereoisomer or a pharmaceutically acceptable salt thereof, their preparation, pharmaceutical compositions comprising such compounds and their use in treating and/or preventing bacterial infections are disclosed.

N-(ALKANOYL)-7-OXO-6-SULFOOXY-1,6-DIAZABICYCLO[3.2.1]OCTANE-2-CARBONYLHYDRAZIDE DERIVATIVES AND THEIR USE AS ANTIBACTERIAL AGENTS

RELATED PATENT APPLICATIONS

This application claims the priority to and benefit of Indian Provisional Patent Application No. 201621020850 filed on June 17, 2016; 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 compounds, their preparation and their use in preventing or treating infections.

BACKGROUND OF THE INVENTION

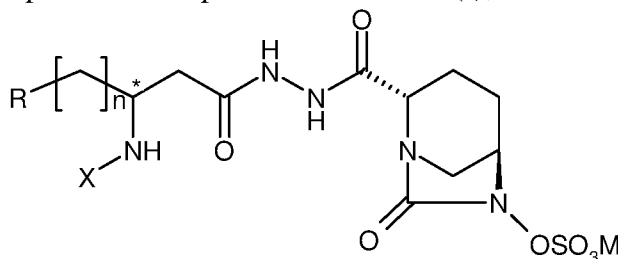
Emergence of bacterial resistance to known antibacterial agents is becoming a major challenge in treating bacterial infections. One way forward to treat bacterial infections, and especially those caused by resistant bacteria, is to develop newer antibacterial agents that can overcome the bacterial resistant. 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 compounds having antibacterial activity.

SUMMARY OF THE INVENTION

Accordingly, there are provided nitrogen containing 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 aspect, there are provided compounds of Formula (I),



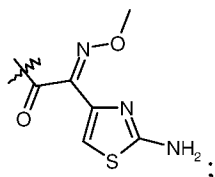
Formula (I)

or a stereoisomer or a pharmaceutically acceptable salt thereof.

wherein R is:

- (a) heterocycloalkyl, optionally substituted with one or more substituents independently selected from OH, NH₂, CN, halogen, or
- (b) aryl, optionally substituted with one or more substituents independently selected from OH, NH₂, CN, halogen;

X is hydrogen, or



n is 0, 1, 2, 3 or 4; and

M is hydrogen or a cation.

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

In another aspect, there are provided methods for preventing or treating a bacterial infection in a subject, said methods 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 aspect, there are provided methods for preventing or treating a bacterial infection in a subject, said methods 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 aspect, there is provided 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 aspect, there are provided methods for preventing or treating a bacterial infection in a subject, said methods 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 aspect, there are provided methods for preventing or treating a bacterial infection in a subject, said methods 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 yet another aspect, there are provided methods for increasing antibacterial effectiveness of an antibacterial agent in a subject, said methods 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, and additional applications of the principles of the invention as illustrated herein, which would occur to one of ordinary skills 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 nitrogen containing compounds having antibacterial properties.

The term "stereoisomers" as used herein refers to and includes 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) contains asymmetric or chiral centres (including those marked with "**") 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, all geometric and positional isomers (including cis and trans-forms) as well as mixtures thereof, are also embraced within the scope of the invention. In general, a reference to a compound is intended to cover its stereoisomers and a mixture of various stereoisomers.

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 and include those 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 pharmaceutically 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. SO₃H group). 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 a 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. The 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 compounds 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 refers to and 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 normal flora, which is not desirable. The term “infection” includes infection caused by bacteria.

The term “treat”, “treating” or “treatment” as used herein refers to administering 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 the bacterial infection, or (ii) retard the progression of a bacterial infection or of one or more symptoms of the bacterial infection, or (iii) reduce the severity of a bacterial infection or of one or more symptoms of the bacterial infection, or (iv) suppress the clinical manifestation of a bacterial infection, or (v) suppress the manifestation of adverse symptoms of the bacterial infection.

The term “pharmaceutically effective amount” or “therapeutically effective amount” or “effective amount” as used herein refers 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 or pharmaceutically 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). The pharmaceutically 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 the particular type of the antibacterial agent used. For prophylactic treatments, a therapeutically or prophylactically effective amount is that amount which would be effective in preventing a microbial (e.g. bacterial) infection. The compounds and/or pharmaceutical compositions according to the invention are used in amounts that are effective in providing the desired therapeutic effect or result.

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 a microorganism (e.g. bacteria), including 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 an antibacterial agent refers to the ability of the composition or the antibacterial agent to treat or prevent the microbial (e.g. 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 or a combination of substances or a combination 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-lactam antibacterial agent” as used herein refers to compounds with antibacterial properties and containing a beta-lactam nucleus in their molecular structure.

The term “beta-lactamase” 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 hydrolyse the beta-lactam ring in a beta-lactam compound, either partially or completely.

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 “pharmaceutically inert ingredient” or “carrier” or “excipient” refers to a compound or material used to facilitate administration of a compound, including for example, to increase the solubility of the compound. Typical, non-limiting examples of solid carriers include, starch, lactose, dicalcium phosphate, sucrose, and kaolin and so on. Typical, non-limiting examples of liquid carriers include sterile water, saline, buffers, non-ionic surfactants, and edible oils such as oil, peanut and sesame oils and so on. In addition, various adjuvants commonly used in the art may be included. These and other such compounds are described in the literature, for example, in the Merck Index (Merck & Company, Rahway, N.J.). Considerations for inclusion of various components in pharmaceutical compositions are described, for example, in Gilman et al. (Eds.) (1990); Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press., which is incorporated herein by reference in its entirety.

The term “subject” as used herein refers to a 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” includes humans, cats, dogs, horses, sheep, bovine cows, pigs, lambs, rats, mice and guinea pigs.

The term “pharmaceutically acceptable derivative” as used herein refers to and includes any pharmaceutically acceptable salt, pro-drugs, metabolites, esters, ethers, hydrates, polymorphs, solvates, complexes, enantiomers or adducts 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 salt, pro-drugs, metabolites, esters, ethers,

hydrates, polymorphs, solvates, complexes, enantiomers or adducts) which, upon administration to a subject, is capable of providing (directly or indirectly) the antibacterial compound.

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, indolizinyl, indazolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, beta-carbolinyl, 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,

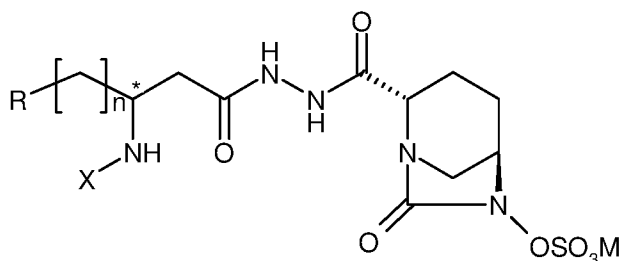
imidazolidin-2-one-yl, piperidinyl, oxazinyl, thiazinyl, piperazinyl, piperazin-2,3-dione-yl, morpholinyl, thiomorpholinyl, azepanyl, and the like. The heterocycloalkyl may be unsubstituted, or substituted with one or more substituents. Typical, non-limiting examples of such substituents include C₁-C₆ 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 "TFA" as used herein refers to trifluoroacetate. The term "Boc anhydride" as used herein refers to di-*tert*-butyl dicarbonate.

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 "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),



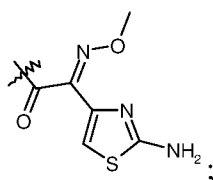
Formula (I)

or a stereoisomer or a pharmaceutically acceptable salt thereof.

wherein R is:

- (a) heterocycloalkyl optionally substituted, with one or more substituents independently selected from OH, NH₂, CN, halogen, or
- (b) aryl optionally substituted, with one or more substituents independently selected from OH, NH₂, CN, halogen;

X is hydrogen or



n is 0, 1, 2, 3 or 4; and
M is hydrogen or a cation.

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

(2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(4-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(4-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(4-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-[(2*S*)-pyrrolidin-2-yl]propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-[(2*S*)-pyrrolidin-2-yl]propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-[(2*S*)-pyrrolidin-2-yl]propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*RS*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*S*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(2-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(2-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(2-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(3-hydroxyphenyl)propanoyl]-7-oxo-6-hydroxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(3-hydroxyphenyl)propanoyl]-7-oxo-6-hydroxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(3-hydroxyphenyl)propanoyl]-7-oxo-6-hydroxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(3-aminophenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(3-aminophenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(3-aminophenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(2,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(2,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(2,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

(2*S*,5*R*)-*N*-[(3*R**S*)-3-amino-3-(2-chloro-3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(2-chloro-3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(2-chloro-3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
or a stereoisomer or a pharmaceutically acceptable derivative thereof.

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

Sodium salt of (2*S*,5*R*)-*N*-[(3*R**S*)-3-amino-3-(4-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(4-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(4-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

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

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

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

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R**S*)-3-amino-3-(3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*R**S*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R**S*)-3-amino-3-(2-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(2-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(2-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R**S*)-3-amino-3-(3-hydroxyphenyl)propanoyl]-7-oxo-6-hydroxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(3-hydroxyphenyl)propanoyl]-7-oxo-6-hydroxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(3-hydroxyphenyl)propanoyl]-7-oxo-6-hydroxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and di-trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R**S*)-3-amino-3-(3-aminophenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and di-trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(3-aminophenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and di-trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(3-aminophenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R**S*)-3-amino-3-(2,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;
 Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(2,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;
 Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(2,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;
 Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R**S*)-3-amino-3-(2-chloro-3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;
 Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(2-chloro-3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;
 Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(2-chloro-3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;
 or a stereoisomer thereof.

In general, the compounds of the invention can be prepared according to the general procedures given in Scheme 1. 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 aspect, the compounds according to invention are prepared according to general procedure given in Scheme 1. In general, an aldehyde compound of Formula (II) is reacted with ammonium acetate and malonic acid in presence of a suitable solvent to obtain a compound of Formula (III). The free amino group of compound of Formula (III) is protected with Boc anhydride to obtain a compound of Formula (IV). The compound of Formula (IV) is reacted with a compound of Formula (V) in presence of coupling agent and diisopropylethylamine to obtain a compound of Formula (VI). Typical, non-limiting examples of suitable coupling agents include 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC.HCl), 1-hydroxybenzotriazole (HOBt), *N*-hydroxysuccinimide (HOSu), 1-hydroxy-7-azabenzotriazole (HOAt), (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxid hexafluorophosphate) (HATU), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), bromotris-pyrrolidino phosphoniumhexafluorophosphate (PyBrop), *O*-(7-azabenzotriazol-1-yl)-1,3-dimethyl-1,3-trimethylene uranium hexafluorophosphate (HAMTU), 2-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU), 2-(2-Pyridon-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU), and the like, or a mixture thereof.

The compound of Formula (VI) is converted to corresponding sodium salt of Formula (VII). The compound of Formula (VI) is dissolved in suitable solvent and passed through cation exchange resin. In some other embodiments, compound of Formula (VI) is dissolved in 10% tetrahydrofuran: water mixture and then passed through the column packed with cation exchange resin such as Dowex 50WX8 200 Sodium resin, Indion 225 Sodium resin and the like. In some embodiments, compound of Formula (VI) is dissolved in suitable solvent such as acetone, tetrahydrofuran, ethanol, isopropanol, acetonitrile, and the like, and treated with sodium ethylhexanoate or potassium ethylhexanoate to provide corresponding sodium or potassium salt of compound of Formula (VII).

The protecting groups of a compound of Formula (VII) are then removed to obtain a compound of Formula (I). The compound of Formula (VII) is treated with a suitable deprotecting agent 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 hours to obtain a compound of Formula (I). In some embodiments, compound of Formula (VII) is treated with trifluoroacetic acid in presence of dichloromethane at temperature of about -10°C to about 5°C for about 4 hours to provide a compound of Formula (I).

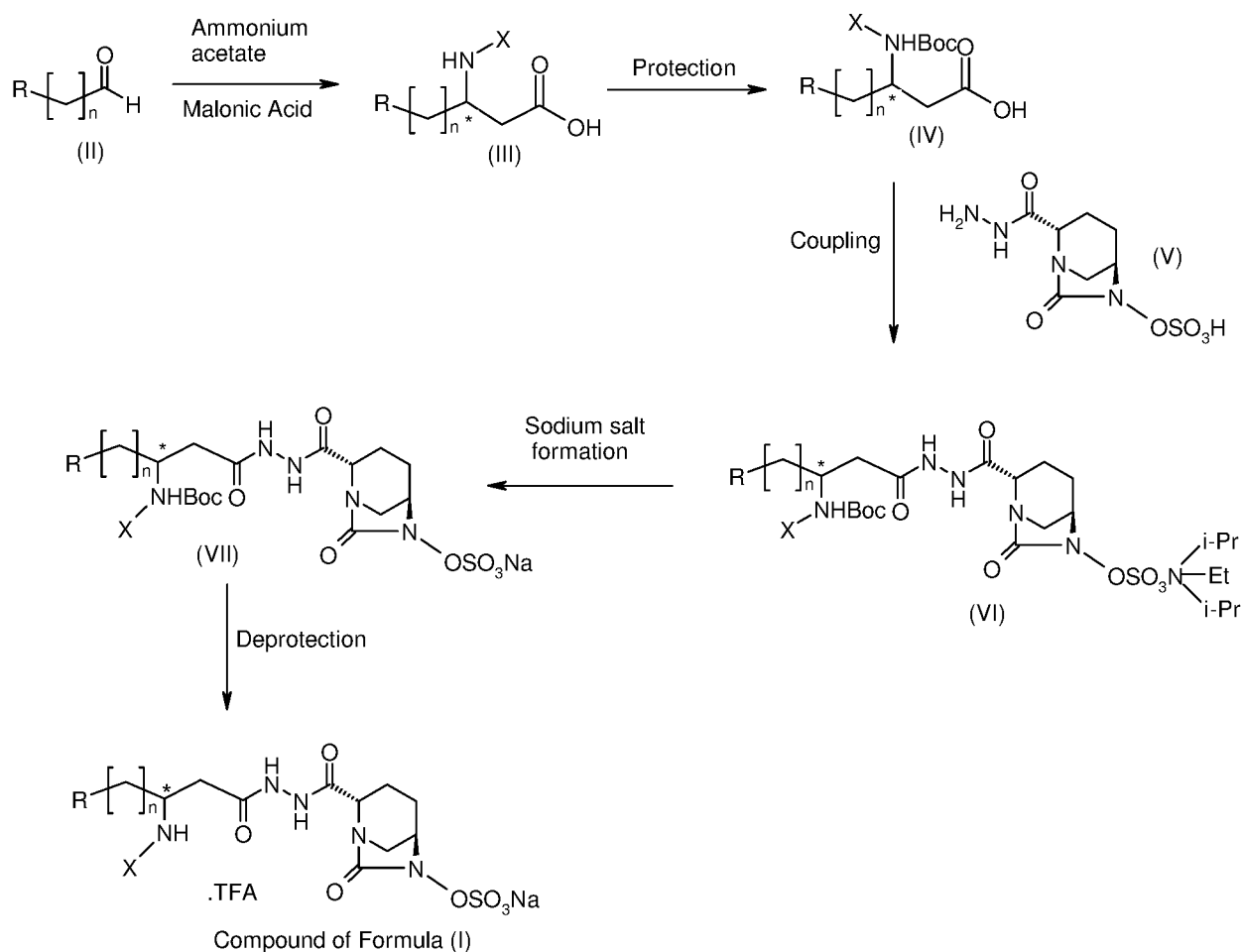
In some embodiments, there are provided pharmaceutical compositions comprising a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof.

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.

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 selected from cefepime, cefpirome, ceftaroline, ceftazidime, ceftalozane or a pharmaceutically acceptable derivative thereof.



Scheme 1

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.

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.

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 Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative 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 compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative 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 compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative 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 compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, (b) at least one antibacterial agent selected from selected from cefepime, cefpirome, 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 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 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, ceftiolene, ceftizoxime, cefacephem, cefepime, ceftazopran, cefpirome, ceftquinome, ceftobiprole, ceftiofur, ceftquinome, ceftovecin, ceftolozane, 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 nitrofurantoin 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, intraspiratory, 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 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. In some embodiments, there are provided methods of inhibiting beta-lactamase enzymes, wherein said methods comprise administering a pharmaceutically effective amount of a compound of Formula (I), or a stereoisomer or a pharmaceutically acceptable

derivative thereof. In some other embodiments, there are provided methods of inhibiting beta-lactamase enzymes, wherein said methods comprise 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 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.

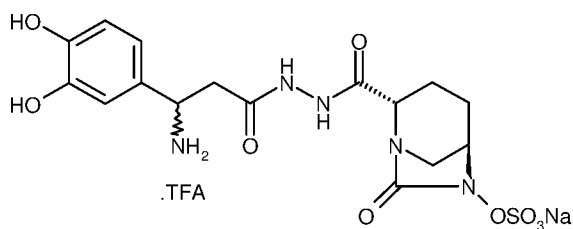
It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. For example, those skilled in the art will recognize that the invention may be practiced using 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*)-*N'*-{3-[(*tert* butoxycarbonyl)amino]-3-(3,4-dihydroxyphenyl)propanoyl}-6-(sulfooxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2 carbohydrazide



Step 1: Preparation of 3,4-bis-benzyloxy-benzaldehyde: To a solution of 3,4-dihydroxy-benzaldehyde (10 g, 0.07 mole) in acetone (100 ml) was added K₂CO₃ (30 g, 0.21739 M) and the mixture stirred for 30 min. Benzyl bromide 30.97 g, (0.181mole) was added drop wise at RT in 15 min. and the resulting mixture stirred further, at RT, for 17 hours. TLC showed absence of starting material (Ethyl acetate-Hexane, 10:90). The reaction mass was filtered and solid cake was washed with (2 X 25 ml) acetone. The filtrate was concentrated under reduced pressure at 40°C. To the residual solid mass 30 ml hexane was added and stirred for 30 minutes and the separated solid filtered under suction. The solid was dried under reduced pressure to obtain the product as a white solid, 21.5 gm, in 94% yield.

Step 2: Preparation of 3-amino-3-(3,4-bis-benzyloxy-phenyl)-propionic acid: To a stirred solution of 3,4-Bis-benzyloxy-benzaldehyde (21.78 g, 0.0685 mole) in ethanol (550 ml) were added ammonium acetate (10.54 g, 0.137 mole) and malonic acid (7.195 g, 0.069 mole) and the resulting mixture was heated to 70°C and the stirring continued further for 38 hours. Reaction mass was allowed to cool to room temperature and the separated solid was filtered under suction. The solid was washed with fresh ethanol (2 × 25 ml). The solid was dried under reduced pressure (4 mm Hg) at 40°C, for 1 hour to obtain 12 g of the titled product as a buff colored solid in 46% yield.

Analysis: Mass: 376 (M-1); for Molecular weight of 377.44 and Molecular Formula of $C_{23}H_{23}NO_4$;

¹H-NMR: (400MHz, DMSO- d_6): δ 7.49-7.24 (m, 13H), 7.15-7.01 (m, 4H), 5.19-5.14 (m, 2H), 5.10-5.07 (m, 1H).

Step 3: Preparation of 3-[(*tert*-butoxycarbonyl)amino]-3-(3,4-bis-benzyloxy-phenyl)-propionic acid: To a stirred solution of 3-amino-3-(3,4-bis-benzyloxy-phenyl)-propionic acid (5 g, 0.01326 M) in 1,4-dioxane (50 ml), at 0°C, was added dropwise sodium hydroxide solution (1.06 g, 26.52 mmol, NaOH was dissolved in 10 ml water). Reaction mass was stirred for 30 minutes and then Boc anhydride was added drop wise at 0°C in 30 minutes. Stirring was further continued for 2 hours and the reaction mixture was allowed to warm to room temperature and stirring continued at room temperature for 16 hours. Solvent was evaporated under reduced pressure at 40°C. The residue was diluted with water (25 ml) and the pH was adjusted between 3.5 to 4 with the 5% aqueous solution of potassium hydrogen sulfate. The mixture was then extracted with dichloromethane (3 × 25 ml). The dichloromethane layer was washed with (3 × 25 ml) water, dried over anhydrous sodium sulfate, filtered and the solvent evaporated under reduced pressure at 35°C to obtain 5.68 g the product as a white solid in 89% yield.

Analysis: Mass: 476 (M-1), for Molecular weight of 477.56 and Molecular Formula of $C_{28}H_{31}NO_6$;

¹H-NMR: (400MHz, DMSO- d_6): δ 7.47-7.03 (m, 9H), 7.28-6.79(m, 3H), 5.08-5.04(m, 6H), 1.35 (s, 9H).

Step 4: Preparation diisopropylethyl amine salt of (2*S*,5*R*)-*N'*-{3-[(*tert*-butoxycarbonyl)amino]-3-(3,4-bis-benzyloxy-phenyl)propanoyl}-6-(sulfooxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carbohydrazide: To a stirred solution of 3-[(*tert*-butoxycarbonyl)amino]-3-(3,4-bis-benzyloxy-phenyl)-propionic acid (0.850 g, 1.78 mmol) in dimethylformamide (2.5 ml) at 0°C were added successively *N,N'*-dicyclohexylcarbodiimide (0.588 g, 2.85 mmol) and hydroxybenzotriazole 0.276 g, 2.05 mmol). Reaction mass was stirred at 0°C for 30 minutes. To this solution was added *N,N*-diisopropyl ethylamine (1.38 g, 10.69 mol) and (2*S*,5*R*)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carbohydrazide (V) (0.500 g, 1.78 mmol, prepared according procedure described in PCT International Patent Application No. PCT/IB2016/053965) at 0°C. Stirring was continued for 1 hour and then the reaction mixture was allowed to warm to room temperature and stirring continued further for 16 hours. The solvent was evaporated under reduced pressure at 40°C and the residue diluted with 5 ml of xylene and stirred at room temperature for 5 minute. The solvent was re-evaporated under reduced pressure at 40°C and the residue dissolved in chloroform (40 ml). The chloroform layer was washed with water (2 × 2 ml), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the residue chromatographed over a column of silica-gel and elution was carried with mixture of chloroform and methanol, (1 to 10% methanol in chloroform). The combined solvent fraction was evaporated to provide 400 mg of product as fluffy solid in 25% yield.

Analysis: Mass: 738 (M-1) (as free acid); for Molecular weight of 739 and Molecular Formula of $C_{35}H_{41}N_5O_{11}S$. $C_8H_{19}N$.

Step 5: Preparation of diisopropylethylamine salt of (2*S*,5*R*)-*N'*-{3-[(*tert* butoxycarbonyl) amino] -3-(3,4-dihydroxyphenyl)propanoyl}-6-(sulfooxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carbohydrazide: A solution of diisopropylethylamine salt of (2*S*,5*R*)-*N'*-{3-[(*tert* butoxycarbonyl)amino]-3-(3,4-bis-benzyloxy-phenyl)propanoyl}-6-(sulfooxy)-7-oxo-1,6-

diazabicyclo[3.2.1]octane-2-carbo hydrazide (400 mg, 0.460 mmol) in dichloromethane (2 ml) and dimethylformamide (2 ml) containing 20% palladium hydroxide (50 mg, 50% wet)), at room temperature, was hydrogenated by balloon containing hydrogen gas for 4 hours under hydrogen atmosphere. The completion of reaction was monitored by thin layer chromatography using mixture of dichloromethane and methanol (8:2). The reaction mixture was filtered through celite bed and cake was washed with 25 ml of mixture of dichloromethane and dimethylformamide (50:50). The filtrate was evaporated under reduced pressure (4 mm Hg) at 40°C. The residue was diluted with 5 ml of xylene, stirred at room temperature for 5 minute and xylene was evaporated under reduced pressure at 40°C to obtain 400 mg of product as a semisolid.

Analysis: Mass 558 (M-1) (as free acid), for Molecular weight of 559 and Molecular Formula of $C_{21}H_{29}N_5O_{11}S$. $C_8H_{19}N$; **Purity as determined by HPLC:** 74.37%.

Step 6: Preparation Sodium salt of (2S,5R)-N'-{3-[(tert butoxycarbonyl)amino]-3-(3,4-dihydroxyphenyl)propanoyl}-6-(sulfooxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2

carbohydrazide: A glass column was charged with Na Resin (INDION 225 Na^+ resin) and eluted with HPLC grade water (200 ml). Then diisopropylethylamine salt of (2S,5R)-N'-{3-[(tert butoxycarbonyl)amino]-3-(3,4-dihydroxyphenyl)propanoyl}-6-(sulfooxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carbohydrazide (318 mg, 0.460 mmol) was dissolved in minimum tetrahydrofuran solvent (1 ml) and was loaded on column. Then column was eluted with 10% tetrahydrofuran in water and fractions were collected. The combined fractions containing sodium salt were concentrated under reduced pressure (4 mm Hg) at 40°C to obtain 165 mg of the product as off-white solid in 61% yield.

Analysis: Mass: 558 (M-1) (as free acid), for Molecular weight of 559 and Molecular Formula of $C_{21}H_{29}N_5O_{11}S$. Na; **Purity as determined by HPLC:** 77.45%.

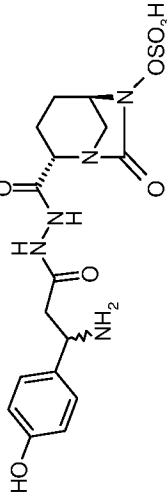
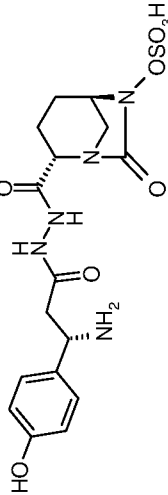
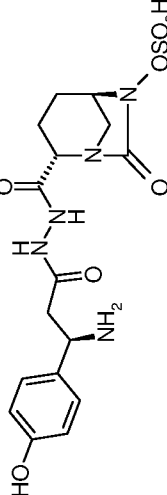
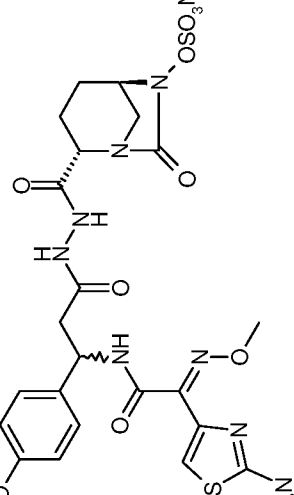
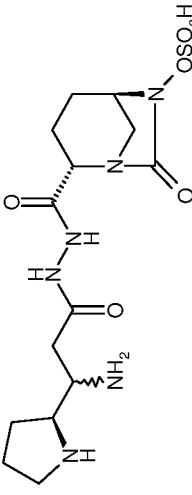
Step 7: Preparation sodium and trifluoroacetate salt of (2S,5R)-N'-[3-amino-3-(3,4-dihydroxyphenyl)propanoyl]-6-(sulfooxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carbohydrazide:

To a stirred solution of sodium salt of (2S,5R)-N'-{3-[(tert butoxycarbonyl)amino]-3-(3,4-dihydroxyphenyl)propanoyl}-6-(sulfooxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carbohydrazide (169 mg, 0.273 mmol) in dichloromethane was added trifluoroacetic acid (0.5 ml) drop wise at -15°C. The reaction mass was stirred at -7°C for 1 hour. The reaction was monitored by mass spectroscopy. The reaction mixture was diluted n-hexane (20 ml) and stirred for 10 minute at -7°C and then allowed to settle for 10 minute. The supernatant hexane was discarded and the oily layer was again washed with hexane (20ml). This process was repeated twice. Then Diethyl ether (20 ml) was added to the reaction mass and stirred for 10 minute at -7°C. The separated solid was allowed to settle and the ether layer discarded. This process was repeated twice. Then acetonitrile (5 ml) was added to the reaction mass and stirred for 30 minute at room temperature and then allowed to settle for 10 minute. The acetonitrile layer was discarded. This process was repeated twice. Then diethyl ether (10 ml) was added to the reaction mass and stirred for 10 minute at room temperature and then allowed to settle. The ether layer was discarded. The residual solid was dried under reduced pressure to obtain 110mg of the product as white solid in 67% yield.

Analysis: Mass: 458 (M-1) (as free acid); for Molecular weight of 459 and Molecular Formula of $C_{16}H_{20}N_5O_9S.C_2HO_2F_3.Na$;

1H -NMR: (400MHz, DMSO- d_6): δ 9.95 (2H, d, J=8Hz), 9.15 (s,1H), 9.03 (s,1H), 8.12 (m,2H), 6.82 (s, 1H), 6.73 (m,2H), 4.41 (m,1H), 4.01 (m,1H), 3.81 (m, 1H), 3.15 (m, 1H), 3.01 (m, 2H), 2.74 (m, 1H), 0.62-2.01 (m, 5H); **Purity as determined by HPLC:** 89.11%.

Examples 2 to 11 were prepared using the procedure described as in Example 1, wherein appropriately substituted compound of Formula (IV) (as shown in Schemes 1) were coupled with the compound of Formula (V).

Example No.	Structure	¹ H-NMR	Mass as free acid (Molecular Formula)
2		(400MHz, D ₂ O): δ 7.26 (d, 2H, J = 8.8Hz), 7.78 (d, 2H, J = 8.8Hz), 4.51 (t, 1H, J = 7.2Hz), 4.00 (s, 1H), 3.81 (d, 2H, J = 7.2Hz), 3.36-3.35 (m, 1H), 3.17-3.13 (m, 1H), 3.01-2.99 (m, 1H), 2.80-2.76 (m, 2H), 2.00-1.59 (m, 4H)	444.2 (M+1) (C ₁₆ H ₂₁ N ₅ O ₈ S)
3		(400MHz, DMSO-d ₆): δ 9.28 (s, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 4.20 (t, J = 6.8 Hz, 1H), 4.00 (s, 1H), 3.80 (d, J = 6.8 Hz, 1H), 3.19 - 3.15 (m, 2H), 2.99 (d, J = 12.4 Hz, 1H), 2.81 - 2.74 (m, 2H), 2.50 - 2.46 (m, 2H), 2.05 - 1.72 (m, 4H).	444.3 (M+1) (C ₁₆ H ₂₁ N ₅ O ₈ S)
4		(400MHz, DMSO-d ₆): δ 9.95 (d, J = 6.8 Hz, 1H), 9.60 (s, 1H), 8.14 (s, 1H), 7.25 (d, J = 8.4 Hz, 2H), 6.76 (d, J = 7.6 Hz, 2H), 4.24 (t, J = 6.8 Hz, 1H), 3.99 (s, 1H), 3.80 (d, J = 6.4 Hz, 1H), 3.18 - 3.13 (m, 2H), 2.98 (d, J = 10.0 Hz, 1H), 2.80 - 2.76 (m, 2H), 2.49 - 2.45 (m, 2H), 2.05 - 1.85 (m, 2H), 1.82 - 1.55 (m, 2H)	444.3 (M+1) (C ₁₆ H ₂₁ N ₅ O ₈ S)
5		(400MHz, DMSO-d ₆): δ 9.83 (bs, 2H), 9.28 (s, 1H), 8.91-8.93 (m, 1H), 7.19-7.15 (m, 3H), 6.67-6.74 (m, 2H), 5.31-5.33 (m, 1H), 4.01 (s, 1H), 3.78-3.83 (m, 4H), 3.16-3.18 (m, 1H), 3.01-2.99 (m, 1H), 2.59-2.63 (m, 3H), 2.01-1.64 (m, 5H)	627.2(M+1) (C ₂₂ H ₂₆ N ₈ O ₁₀ S ₂ . Na)
6		(400MHz, DMSO-d ₆): δ 10.02-10.18 (m, 1H), 8.15 (bs, 3H), 4.04 (s, 1H), 3.90-3.77 (m, 4H), 3.16-3.22 (m, 3H), 3.05-3.03 (m, 1H), 2.66-2.56 (m, 2H), 2.12-1.56 (m, 9H)	419.3 (M-1) (C ₁₄ H ₂₄ N ₆ O ₇ S)

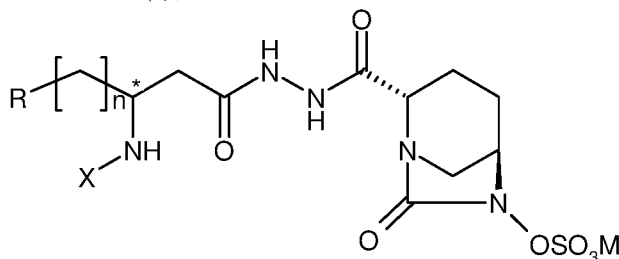
BIOLOGICAL ACTIVITY DATA

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, M07-A9, Volume 32, No. 2, 2012). Molten Mueller Hinton Agar (MHA) (BD, USA) containing serial dilutions of each antibacterial agent were poured on to the plates and allowed to solidify. Appropriate suspensions from the freshly grown cultures were prepared in normal saline so that about 10^4 CFU/spot of the organism was delivered on to the drug containing agar plates using automated multipoint inoculator (Mast, UK). The plates were incubated in Biochemical oxygen demand (BOD) incubator at 37°C for 18 hours and then examined for growth. MICs were read as the lowest concentration of drug that completely inhibited bacterial growth. The Table 2 depicts the antibacterial activity profile of compounds according to present invention against various multidrug resistant bacterial strains.

Table 2. Antibacterial activity of representative compounds according to invention (expressed as MICs (mcg/ml))																
Compounds	KP ATCC 700603	<i>E. coli</i> 13351	<i>E. coli</i> 13352	<i>E. coli</i> 13353	<i>E. coli</i> M 36	<i>E. coli</i> 7 MP	<i>E. coli</i> MI 49	<i>E. coli</i> M 50	<i>E. coli</i> M 138	<i>E. coli</i> S 18	<i>E. coli</i> S 28	<i>K. pneumoniae</i>				
												H 521	H 522	H 523	H 525	
Ceftazidime	16	16	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32	>32
Example 1	>32	2	1	1	2	4	2	2	-	-	-	2	2	2	2	2
Example 2	>32	0.5	0.5	1	0.5	2	4	0.5	0.5	1	-	1	1	1	1	1
Example 3	>32	4	4	2	2	8	8	4	4	4	-	4	4	4	4	2
Example 4	>32	1	1	0.5	0.5	2	2	0.5	0.5	1	-	1	1	1	1	1
Example 5	>32	8	8	8	8	32	32	8	8	8	-	8	8	8	8	8
Example 6	>32	4	4	2	2	-	8	4	4	-	-	4	4	4	4	4
Example 7	>32	1	1	0.5	1	2	4	1	1	-	-	2	2	1	1	1
Example 8	>32	1	1	1	1	4	4	1	1	-	-	2	2	1	1	1
Example 9	>32	0.5	0.5	0.5	0.5	2	2	0.5	0.5	-	-	2	2	1	1	1
Example 10	>32	0.5	0.5	0.5	1	1	2	0.5	0.5	-	-	1	1	1	1	1
Example 11	>32	4	4	2	2	8	8	2	2	-	-	>32	>32	>32	>32	>32

CLAIMS

1. A compound of Formula (I),



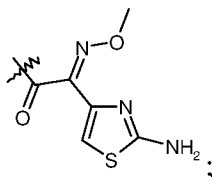
Formula (I)

or a stereoisomer or a pharmaceutically acceptable salt thereof.

wherein R is:

- (a) heterocycloalkyl optionally substituted, with one or more substituents independently selected from OH, NH₂, CN, halogen, or
- (b) aryl optionally substituted, with one or more substituents independently selected from OH, NH₂, CN, halogen;

X is hydrogen or



n is 0, 1, 2, 3 or 4; and

M is hydrogen or a cation.

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

(2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(4-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(4-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(4-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-{(3*RS*)-3-amino-3-[(2*S*)-pyrrolidin-2-yl]propanoyl}-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-{(3*S*)-3-amino-3-[(2*S*)-pyrrolidin-2-yl]propanoyl}-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-{(3*R*)-3-amino-3-[(2*S*)-pyrrolidin-2-yl]propanoyl}-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

(2*S*,5*R*)-*N*-[(3*S*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(2-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(2-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(2-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(3-hydroxyphenyl)propanoyl]-7-oxo-6-hydroxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(3-hydroxyphenyl)propanoyl]-7-oxo-6-hydroxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(3-hydroxyphenyl)propanoyl]-7-oxo-6-hydroxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(3-aminophenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(3-aminophenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(3-aminophenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(2,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(2,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(2,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(2-chloro-3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(2-chloro-3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(2-chloro-3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

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*)-*N*-[(3*RS*)-3-amino-3-(4-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 Sodium salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(4-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 Sodium salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(4-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 Sodium salt of (2*S*,5*R*)-*N*-{(3*RS*)-3-amino-3-[(2*S*)-pyrrolidin-2-yl]propanoyl}-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 Sodium salt of (2*S*,5*R*)-*N*-{(3*S*)-3-amino-3-[(2*S*)-pyrrolidin-2-yl]propanoyl}-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 Sodium salt of (2*S*,5*R*)-*N*-{(3*R*)-3-amino-3-[(2*S*)-pyrrolidin-2-yl]propanoyl}-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
 Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(2-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(2-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(2-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(3-hydroxyphenyl)propanoyl]-7-oxo-6-hydroxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(3-hydroxyphenyl)propanoyl]-7-oxo-6-hydroxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(3-hydroxyphenyl)propanoyl]-7-oxo-6-hydroxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and di-trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(3-aminophenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and di-trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(3-aminophenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and di-trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(3-aminophenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(2,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(2,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(2,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(2-chloro-3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(2-chloro-3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(2-chloro-3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide; or a stereoisomer thereof.

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

5. The pharmaceutical composition according to Claim 4, further comprising at least one antibacterial agent or a pharmaceutically acceptable derivative thereof.

6. The pharmaceutical composition according to Claim 5, wherein the antibacterial agent is a beta-lactam antibacterial agent.

7. The pharmaceutical composition according to Claim 5, wherein the antibacterial agent is at least one selected from a group consisting of Ansamycin, Carbacephem, Carbapenam,

Carbapenem, Cephalosporin, Cephamycin, Cephem, Lincosamide, Lipopeptide, Macrolide, Ketolide, Monobactam, Nitrofurantoin, Oxacephem, Oxapenam, Oxazolidinone, Penam, Penem, Penicillin, Polypeptide, Quinolone, Sulfonamide, or Tetracycline antibacterial agents.

8. The pharmaceutical composition according to Claim 5, wherein the antibacterial agent is at least one selected from a group consisting of cefacetrile, cefaclor, cefadroxil, cefalexin, cefaloglycin, cefalonium, cefaloridine, cefalotin, cefamandole, cefapirin, cefatrizine, cefazaflur, cefazedone, cefazolin, cefbuparazone, cefcapene, cefcladin, cefdaloxime, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefluprenam, cefmenoxime, cefmetazole, cefminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefoselis, cefotaxime, cefotetan, cefotiam, cefovecin, cefoxitin, cefoxitin, cefozopran, cefpimizole, cefpiramide, cefpirome, cefpodoxime, cefprozil, cefquinome, cefradine, cefroxadine, cefsulodin, ceftaroline, ceftazidime, cefteteram, ceftazolidine, ceftibuten, ceftiofur, ceftiolene, ceftizoxime, ceftobiprole, ceftolozane, ceftriaxone, cefuroxime, cefuzonam, cephaloridine, cephradine, CXA-101, flomoxef, latamoxef, loracarbef, moxalactam, or a pharmaceutically acceptable derivative thereof.

9. Use of a compound according to any one of the Claims 1 to 3, in treating or preventing a bacterial infection.

10. Use of a pharmaceutical composition according to any one of the Claims 4 to 8, in treating or preventing a bacterial infection.

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

12. A method for treating or preventing bacterial infection in a subject, said method comprising administering to said subject a pharmaceutical composition according to any one of the Claims 4 to 8.

13. A method for treating or preventing a bacterial infection in a subject, said method comprising administering to said subject: (a) a compound of Formula (I) according to Claim 1 or a stereoisomer or a pharmaceutically acceptable salt thereof, and (b) at least one antibacterial agent or a pharmaceutically acceptable derivative thereof.

14. The method according to Claim 13, wherein the compound of Formula (I) is selected from:

(2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(4-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;

(2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(4-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;

(2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(4-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;

(2*S*,5*R*)-*N*-{(3*RS*)-3-amino-3-[(2*S*)-pyrrolidin-2-yl]propanoyl}-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;

(2*S*,5*R*)-*N*-{(3*S*)-3-amino-3-[(2*S*)-pyrrolidin-2-yl]propanoyl}-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;

(2*S*,5*R*)-*N*-{(3*R*)-3-amino-3-[(2*S*)-pyrrolidin-2-yl]propanoyl}-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;

(2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;

(2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;

(2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*RS*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*S*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(2-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(2-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(2-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(3-hydroxyphenyl)propanoyl]-7-oxo-6-hydroxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(3-hydroxyphenyl)propanoyl]-7-oxo-6-hydroxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(3-hydroxyphenyl)propanoyl]-7-oxo-6-hydroxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(3-aminophenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(3-aminophenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(3-aminophenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(2,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(2,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(2,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(2-chloro-3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(2-chloro-3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;
(2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(2-chloro-3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

or a stereoisomer or a pharmaceutically acceptable derivative thereof.

15. The method according to Claim 13, wherein the compound of Formula (I) is selected from:

Sodium salt of (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(4-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(4-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(4-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

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

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

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

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(2-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(2-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(2-hydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(3-hydroxyphenyl)propanoyl]-7-oxo-6-hydroxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(3-hydroxyphenyl)propanoyl]-7-oxo-6-hydroxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(3-hydroxyphenyl)propanoyl]-7-oxo-6-hydroxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and di-trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(3-aminophenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and di-trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(3-aminophenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and di-trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(3-aminophenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1] octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(2,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(2,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(2,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*RS*)-3-amino-3-(2-chloro-3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*S*)-3-amino-3-(2-chloro-3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide;

Sodium and trifluoroacetate salt of (2*S*,5*R*)-*N*-[(3*R*)-3-amino-3-(2-chloro-3,4-dihydroxyphenyl)propanoyl]-7-oxo-6-sulfooxy-1,6-diazabicyclo[3.2.1]octane-2-carbonylhydrazide; or a stereoisomer thereof.

16. The method according to any one of the Claims 13 to 15, wherein the antibacterial agent is a beta-lactam antibacterial agent.

17. The method according to any one of the Claims 13 to 15, wherein the antibacterial agent is at least one selected from a group consisting of Ansamycins, Carbacephems, Carbapenams,

Carbapenems, Cephalosporins, Cephameycins, Cephems, Lincosamides, Lipopeptides, Macrolides, Ketolides, Monobactams, Nitrofurans, Oxacephems, Oxapenams, Oxazolidinones, Penams, Penems, Penicillins, Polypeptides, Quinolones, Sulfonamides, Tetracyclines antibacterial agents.

18. The method according to any one of the Claims 13 to 15, wherein the antibacterial agent is at least one selected from a group consisting of cefacetrile, cefaclor, cefadroxil, cefalexin, cefaloglycin, cefalonium, cefaloridine, cefalotin, cefamandole, cefapirin, cefatrizine, cefazaflur, cefazedone, cefazolin, cefbuperazone, cefcapene, cefclidin, cefdaloxime, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefluprenam, cefmenoxime, cefmetazole, cefminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefoselis, cefotaxime, cefotetan, cefotiam, cefovecin, cefoxitin, cefoxitin, cefozopran, cefpimizole, cefpiramide, cefpirome, cefpodoxime, cefprozil, cefquinome, cefradine, cefroxadine, cefsulodin, ceftaroline, ceftazidime, cefteram, ceftezole, ceftibuten, ceftiofur, ceftiolene, ceftizoxime, ceftobiprole, ceftolozane, ceftriaxone, cefuroxime, cefuzonam, cephaloridine, cephradine, CXA-101, flomoxef, latamoxef, loracarbef, moxalactam, or a pharmaceutically acceptable derivative thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/053585

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/08 A61K31/551 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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	EP 2 857 401 A1 (MEIJI SEIKA PHARMA CO LTD [JP]) 8 April 2015 (2015-04-08) claims 1, 8-15 -----	1-18



Further documents are listed in the continuation of Box C.



See patent family annex.

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"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

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Fink, Dieter

INTERNATIONAL SEARCH REPORT

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