



(51) International Patent Classification:

A61K 31/439 (2006.01) *A61K 31/546* (2006.01)
A61K 31/545 (2006.01) *A61P 31/04* (2006.01)

(21) International Application Number:

PCT/IB2016/050282

(22) International Filing Date:

21 January 2016 (21.01.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

249/MUM/2015 24 January 2015 (24.01.2015) IN

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

(72) Inventors: **PATEL, Mahesh Vithalbhai**; Plot No. 157,
Opp. Saint Meera School, N-3, CIDCO, Aurangabad 431
003, MAHARASHTRA, INDIA., Aurangabad 431003
(IN). **BHAGWAT, Sachin**; Row House No.C-2,
"Nilgiris", Khivansara Park(E), Behind Ramayana Cultural
Hall, Ulkanagari, Aurangabad - 431005, MAHA-
RASHTRA, INDIA. Aurangabad 431005 (IN).

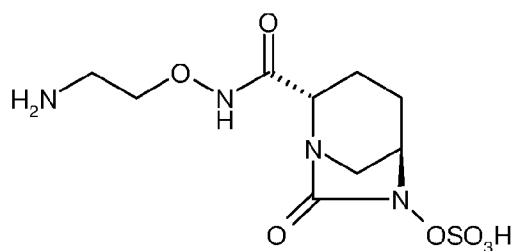
(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG,
MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM,
PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC,
SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ,
TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU,
TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE,
DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,
LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: ANTIBACTERIAL COMPOSITIONS OF A BETA-LACTAMASE INHIBITOR WITH A CEPHALOSPORIN



Formula (I)

(57) Abstract: Pharmaceutical compositions comprising: (a) at least one cephalosporin antibacterial agent and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof are disclosed. Formula (I)

ANTIBACTERIAL COMPOSITIONS OF A BETA-LACTAMASE INHIBITOR WITH A CEPHALOSPORIN

PRIORITY APPLICATION(S)

This application claims priority to Indian Patent Application No. 249/MUM/2015 filed on January 24, 2015, the disclosures of which are incorporated herein by reference in its entirety as if fully rewritten herein.

FIELD OF THE INVENTION

The invention relates to antibacterial compositions and methods for treating or preventing bacterial infections. Particularly, the pharmaceutical compositions comprising cephalosporin antibacterial agent and certain nitrogen containing bicyclic compound are disclosed.

BACKGROUND OF THE INVENTION

Bacterial infections continue to remain one of the major causes contributing towards human diseases. One of the key challenges in treatment of bacterial infections is the ability of bacteria to develop resistance to one or more antibacterial agents over time. Examples of such bacteria that have developed resistance to typical antibacterial agents include: Penicillin-resistant *Streptococcus pneumoniae*, Vancomycin-resistant *Enterococci*, and Methicillin-resistant *Staphylococcus aureus*. The problem of emerging drug-resistance in bacteria is often tackled by switching to newer antibacterial agents, which can be more expensive and sometimes more toxic. Additionally, this may not be a permanent solution as the bacteria often develop resistance to the newer antibacterial agents as well in due course. In general, bacteria are particularly efficient in developing resistance, because of their ability to multiply very rapidly and pass on the resistance genes as they replicate.

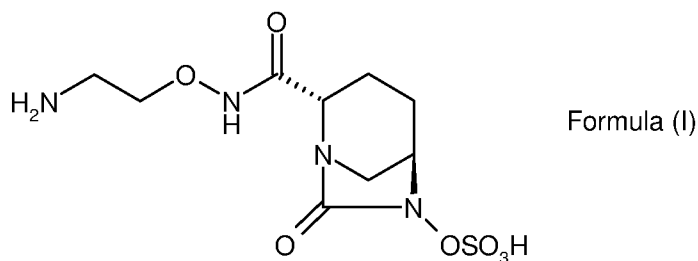
The persistent exposure of bacterial strains to a multitude of beta-lactam antibacterial agents has led to overproduction and mutation of beta-lactamases. These new extended spectrum beta-lactamases (ESBL) are capable of hydrolyzing penicillins, cephalosporins, monobactams and even carbapenems. Such a wide spread resistance to many of the existing beta-lactam antibacterial agents, either used alone or in combination with other agents, is posing challenges in treating serious bacterial infections.

Due to various reasons, the oral therapeutic options for treating bacterial infections (including those caused by ESBL strains) are limited. For example, a combination of amoxicillin and clavulanic acid is effective against Class A ESBLs producing bacteria. However, the usefulness of this combination is compromised against bacteria producing multiple or mixed beta-lactamase enzymes (such as, for example, bacteria producing Class A and Class C ESBLs concurrently), and *Klebsiella pneumoniae* carbapenemases (KPCs). Therefore, oral antibacterial agents or combinations with activity against a range of bacterial strains (including those producing multiple ESBLs and KPCs) are urgently desired.

Cephalosporin antibacterial agents are known for treatment for various bacterial infections. Surprisingly, it has been found that pharmaceutical compositions comprising a cephalosporin antibacterial agent and certain nitrogen containing bicyclic compound (disclosed in PCT/IB2013/053092, PCT/JP2013/064971 and PCT/IB2012/002675) exhibit unexpectedly synergistic antibacterial activity, even against highly resistant bacterial strains.

SUMMARY OF THE INVENTION

Accordingly, there are provided pharmaceutical compositions comprising synergistically effective amount of: (a) at least one cephalosporin antibacterial agent and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof:



In some embodiments, there are provided pharmaceutical compositions comprising synergistically effective amount of: (a) at least one cephalosporin antibacterial agent and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, wherein the weight ratio of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, to a cephalosporin antibacterial agent in the composition is about 1:10 to 10:1.

In some embodiments, there are provided pharmaceutical compositions comprising synergistically effective amount of: (a) at least one cephalosporin antibacterial agent and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, wherein compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof is present in the composition in an amount from about 0.25 gram to about 10 gram per gram of the cephalosporin antibacterial agent.

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

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

effective amount of: (a) at least one cephalosporin antibacterial agent and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof.

In some embodiments, there is provided a method for treating or preventing a bacterial infection in a subject, said method comprising administering to said subject synergistically effective amount of: (a) at least one cephalosporin antibacterial agent and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof; wherein amount of compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and cephalosporin antibacterial agent administered are in a weight ratio of about 1:10 to about 10:1.

In some embodiments, there is provided a method for treating or preventing a bacterial infection in a subject, said method comprising administering to said subject synergistically effective amount of: (a) at least one cephalosporin antibacterial agent and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof; wherein amount of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof administered is from about 0.25 gram to about 10 gram per gram of the cephalosporin antibacterial agent.

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

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

DETAILED DESCRIPTION OF THE INVENTION

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

The inventors have surprisingly discovered that a pharmaceutical composition comprising: (a) at least one cephalosporin antibacterial agent, and (b) a compound of Formula (I)

or a stereoisomer or a pharmaceutically acceptable derivative thereof, exhibits unexpectedly improved antibacterial efficacy, even against highly resistant bacteria, including those producing one or more extended spectrum beta-lactamase enzymes (ESBLs).

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

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

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

The term “administration” or “administering” refers to and includes delivery of a composition, or one or more pharmaceutically active or inert ingredients to a subject, including for example, by any appropriate method, which serves to deliver the composition or its active ingredients, one or more pharmaceutically active or inert 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 (e.g. bacteria) involved, severity of the infection, age and physical condition of the subject and a like. Some non-limiting examples of ways to administer a composition or a pharmaceutically active ingredient to a subject according to this invention include oral, intravenous, topical, intrarespiratory, intraperitoneal, intramuscular, parenteral, sublingual, transdermal, intranasal, aerosol, intraocular, intratracheal, intrarectal, vaginal, gene gun, dermal patch, eye drop and mouthwash. In case of a pharmaceutical composition comprising more than one ingredients (active or inert), one of the ways of administering such composition is by admixing the ingredients (e.g. in the form of a suitable unit dosage form such as tablet, capsule, solution, powder or a like) and then administering the dosage form. Alternatively, the ingredients may also be administered separately (simultaneously or one after the other) as long as these ingredients reach beneficial therapeutic levels such that the composition as a whole provides a synergistic and/or desired effect.

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

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

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

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

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

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

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

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

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

The term “subject” as used herein refers to vertebrate or invertebrate, including a mammal. The term “subject” also includes vertebrate or invertebrate, including a mammal, which is in need of a therapeutic or prophylactic treatment, such as antibacterial treatment. The term “subject” includes human, animal, a bird, a fish, or an amphibian. Typical, non-limiting examples of a “subject” include humans, cats, dogs, horses, sheep, bovine cows, pigs, lambs, rats, mice and guinea pigs.

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

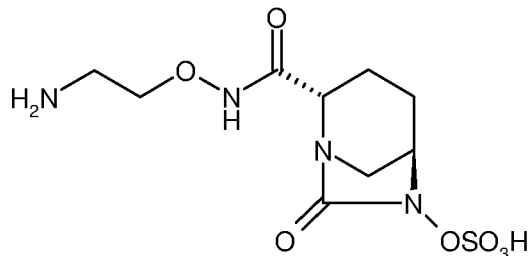
The term “pharmaceutically acceptable salt” as used herein refers to one or more salts of a given compound which possesses desired pharmacological activity of the free compound and which is neither biologically nor otherwise undesirable. In general, the term “pharmaceutically acceptable salts” refer to salts that are suitable for use in contact with the tissues of human and

animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. (J. Pharmaceutical Sciences, 66; 1-19, 1977), incorporated herein by reference in its entirety, describes various pharmaceutically acceptable salts in details.

The term “stereoisomer” as used herein refers to and includes isomeric molecules that have the same molecular formula but differ in positioning of atoms and/or functional groups in the space. The term “stereoisomer” includes enantiomers (where different isomers are mirror-images of each other) and diastereomers (where different isomers are not mirror-images of each other). The term “diastereomers” include isomers such as conformers, meso compounds, cis-trans (E-Z) isomers, and non-enantiomeric optical isomers.

A person of skills in the art would appreciate that various compounds described herein (including, for example a compound of Formula (I), cefixime, cefpodoxime, ceftibuten and cefuroxime) can exist and are often used as their pharmaceutically acceptable derivatives (such as salts, pro-drugs, metabolites, esters, ethers, hydrates, polymorphs, solvates, complexes, and adducts).

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



Formula (I)

Compound of Formula (I), according to the invention can be used in various forms including as such, a stereoisomer or a pharmaceutically acceptable derivative thereof.

The compound of Formula (I) may also be known by different chemical names including the following: (a) “(2*S*, 5*R*)-N-(2-aminoethoxy)-7-oxo-6-(sulfoxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide”, or (b) “sulfuric acid, mono[(1*R*,2*S*,5*R*)-2-[(2-aminoethoxy)amino]carbonyl]-7-oxo-1,6-diazabicyclo[3.2.1]oct-6-yl] ester” [CAS Registry Number: 1452458-86-4]. A reference to a “compound of Formula (I)” is intended to include compounds chemically known as: (a) “(2*S*, 5*R*)-N-(2-aminoethoxy)-7-oxo-6-(sulfoxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide”, and (b) “sulfuric acid, mono[(1*R*,2*S*,5*R*)-2-[(2-aminoethoxy)amino]carbonyl]-7-oxo-1,6-diazabicyclo[3.2.1]oct-6-yl] ester”.

The compound of Formula (I) may also be used in the form of its stereoisomer or a pharmaceutically acceptable derivative thereof. The compound of Formula (I) may also be used in the form of its pharmaceutically acceptable salts such as a sodium, potassium, trifluoroacetate or any other pharmaceutically acceptable salt. Typical, non-limiting examples of suitable pharmaceutically acceptable salts of the compound of Formula (I) include the following:

(a) sodium or potassium salt of sulfuric acid, mono[(1*R*,2*S*,5*R*)-2-[(2-aminoethoxy)amino]carbonyl]-7-oxo-1,6-diazabicyclo[3.2.1]oct-6-yl] ester; or

(b) sulfuric acid, mono[(1*R*,2*S*,5*R*)-2-[(2-aminoethoxy)amino]carbonyl]-7-oxo-1,6-diazabicyclo[3.2.1]oct-6-yl] ester, 2,2,2-trifluoroacetate (1:1) (CAS Registry Number: 1501980-30-8).

Typical, non-limiting examples of Cephalosporin antibacterial agents include Cefazolin, Cefacetile, 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, Oxacephem, Cefepime, Cefozopran, Cefpirome, Cefquinome, Ceftobiprole, Ceftiofur, Cefquinome, Cefovecin, Ceftolozane, Ceftaroline, Ceftobiprole and the like.

The active ingredients according to this invention may be used in their free forms or in the form of their pharmaceutically acceptable derivatives (such as salts, pro-drugs, metabolites, esters, ethers, hydrates, polymorphs, solvates, complexes, or adducts). Typical, non-limiting examples of pharmaceutically acceptable derivatives of cefixime include cefixime trihydrate. Typical, non-limiting examples of pharmaceutically acceptable derivatives of cefpodoxime include cefpodoxime proxetil. Typical, non-limiting examples of pharmaceutically acceptable derivatives of ceftibuten include ceftibuten dihydrate. Typical, non-limiting examples of pharmaceutically acceptable derivatives of cefuroxime include cefuroxime axetil and cefuroxime sodium.

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

In some embodiments, the pharmaceutical compositions according to the invention are characterized in that the active ingredients consist of: (a) at least one cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and (b) a compound of Formula (I) or a stereoisomer or a

pharmaceutically acceptable derivative thereof. The pharmaceutical compositions may further comprise one or more pharmaceutically inert ingredients.

Individual amounts of the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and the cephalosporin antibacterial agent in the composition may vary depending on clinical requirements. The specified amount of antibacterial agent and clavulanic acid is calculated on the basis of their equivalent free forms.

In some embodiments, there are provided pharmaceutical compositions comprising synergistically effective amount of: (a) at least one cephalosporin antibacterial agent and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, wherein the weight ratio of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, to a cephalosporin antibacterial agent in the composition is about 1:10 to 10:1.

In some embodiments, there are provided pharmaceutical compositions comprising synergistically effective amount of: (a) at least one cephalosporin antibacterial agent and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, wherein compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof is present in the composition in an amount from about 0.25 gram to about 10 gram per gram of the cephalosporin antibacterial agent.

In some other embodiments, the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof is present in the composition in an amount from about 0.01 gram to about 25 gram. In some other embodiments, the cephalosporin antibacterial agent is present in the composition in an amount from about 0.01 gram to about 25 gram.

In some embodiments, the pharmaceutical composition according to the invention comprises about “x” gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about “y” gram of the cephalosporin antibacterial agent wherein “x” is 0.1, 0.2, 0.25, 0.4, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2 or 4; and “y” is 0.1, 0.2, 0.25, 0.4, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2 or 4.

In some embodiments, there are provided pharmaceutical compositions comprising synergistically effective amount of: (a) at least one cephalosporin antibacterial agent and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, wherein the weight ratio of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, to a cephalosporin antibacterial agent in the composition is about 4:1, 2:1, 1:1, 1:2, 1:4 or 1:8.

In some embodiments, the pharmaceutical composition according to invention comprises: (a) at least one cephalosporin antibacterial agent, and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof in any of the following amounts:

- (i) 0.2 gram of cephalosporin antibacterial agent and 0.8 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (ii) 0.2 gram of cephalosporin antibacterial agent and 0.4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (iii) 0.2 gram of cephalosporin antibacterial agent and 0.2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (iv) 0.2 gram of cephalosporin antibacterial agent and 0.1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (v) 0.4 gram of cephalosporin antibacterial agent and 0.8 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (vi) 0.4 gram of cephalosporin antibacterial agent and 0.4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (vii) 0.4 gram of cephalosporin antibacterial agent and 0.2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (viii) 0.4 gram of cephalosporin antibacterial agent and 0.1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (ix) 0.5 gram of cephalosporin antibacterial agent and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (x) 1 gram of cephalosporin antibacterial agent and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xi) 1 gram of cephalosporin antibacterial agent and 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xii) 1 gram of cephalosporin antibacterial agent and 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xiii) 2 gram of cephalosporin antibacterial agent and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xiv) 2 gram of cephalosporin antibacterial agent and 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xv) 2 gram of cephalosporin antibacterial agent and 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xvi) 2 gram of cephalosporin antibacterial agent and 4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xvii) 4 gram of cephalosporin antibacterial agent and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xviii) 4 gram of cephalosporin antibacterial agent and 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xix) 4 gram of cephalosporin antibacterial agent and 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof; or
- (xx) 4 gram of cephalosporin antibacterial agent and 4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof.

In some embodiments, the pharmaceutical composition according to invention comprises: (a) at least one cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof in any of the following amounts:

(i) 0.2 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 0.8 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;

(ii) 0.2 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 0.4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;

(iii) 0.2 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 0.2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;

(iv) 0.2 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 0.1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;

(v) 0.4 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 0.8 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;

(vi) 0.4 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 0.4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;

(vii) 0.4 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 0.2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;

(viii) 0.4 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 0.1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;

(ix) 0.5 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;

- (x) 1 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xi) 1 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xii) 1 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xiii) 2 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xiv) 2 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xv) 2 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xvi) 2 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xvii) 4 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xviii) 4 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xix) 4 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- or
- (xx) 4 gram of cephalosporin antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof, and 4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof.

In some embodiments, in the compositions and methods according to the invention, the compound of Formula (I) is: “(2*S*, 5*R*)-*N*-(2-aminoethoxy)-7-oxo-6-(sulfoxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide” or a stereoisomer or a pharmaceutically acceptable derivative thereof. In some other embodiments, in the compositions and methods according to the invention, the compound of Formula (I) is: “sulfuric acid, mono[(1*R*,2*S*,5*R*)-2-[(2-aminoethoxy)amino]carbonyl]-7-oxo-1,6-diazabicyclo[3.2.1]oct-6-yl] ester” or a stereoisomer or a pharmaceutically acceptable derivative thereof. In some other embodiments, in the compositions and methods according to the invention, the compound of Formula (I) is present (or

administered) as a sodium, potassium or trifluoroacetate salt of “sulfuric acid, mono[(1*R*,2*S*,5*R*)-2-[[[(2-aminoethoxy)amino]carbonyl]-7-oxo-1,6-diazabicyclo[3.2.1]oct-6-yl] ester” or a stereoisomer thereof.

The pharmaceutical composition and methods according to the invention use active as well as inactive (or inert) ingredients. In some embodiments, the active ingredients consist of: (a) a compound of formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and (b) at least one cephalosporin antibacterial agent. The pharmaceutical compositions according to the invention may include one or more pharmaceutically acceptable inactive ingredients such as carriers or excipients or the like. Typical, non-limiting examples of such carriers or excipients include mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, sodium crosscarmellose, glucose, gelatine, sucrose, magnesium carbonate, wetting agents, emulsifying agents, solubilizing agents, buffering agents, lubricants, preservatives, stabilizing agents, binding agents and the like.

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

Depending on the requirement, the pharmaceutical compositions according to the invention may also be prepared and packaged in bulk form. Alternatively, the pharmaceutical compositions of the invention may be prepared and packaged in unit dosage form.

In some embodiments, pharmaceutical compositions according to the invention are in the form of a powder or a solution. In some other embodiments, pharmaceutical compositions according to the invention are present in the form of a powder or a solution that can be reconstituted by addition of a compatible reconstitution diluent prior to administration. In some other embodiments, pharmaceutical compositions according to the invention are in the form of a frozen composition that can be diluted with a compatible reconstitution diluent prior to administration. Typical, non-limiting example of suitable compatible reconstitution diluent includes water.

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

In some embodiments, pharmaceutical compositions according to the invention are present in a dosage form suitable for oral administration. Typical, non-limiting examples of dosage forms suitable for oral administration include tablets, capsules, powders, solutions, suspensions, granules, emulsions, syrups, elixirs and the like.

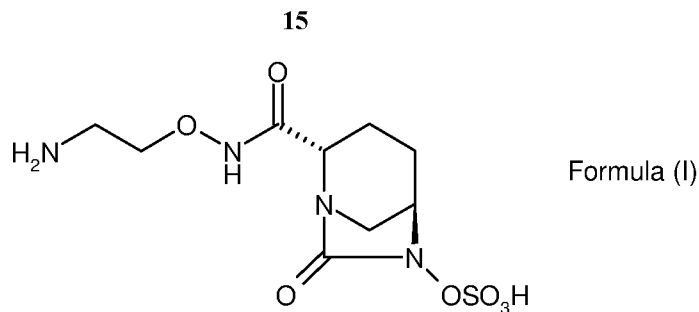
The compositions according to the invention can be formulated into various dosage forms wherein the active ingredients and/or excipients may be present either together (e.g. as an admixture) or as separate components. When the various ingredients in the composition are formulated as a mixture, such compositions 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 (such as 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 reconstituted in suitable reconstitution diluent and 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 cephalosporin antibacterial agent, 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 cephalosporin antibacterial agent, are present in the composition as separate components.

In one general aspect, pharmaceutical compositions according to the invention are used in treatment or prevention of a bacterial infection.

In another general aspect, there are provided methods for treating or preventing a bacterial infection in a subject, said methods comprising administering to said subject effective amount of a pharmaceutical composition according to the invention. In case of dosage forms wherein the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and the cephalosporin antibacterial agent are present in the composition as separate components; the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof may be administered before, after or simultaneously with the administration of the cephalosporin antibacterial agent. In some embodiments, the compositions according to the invention are administered orally or parenterally.

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



In some embodiments, there is provided a method for treating or preventing a bacterial infection in a subject, said method comprising administering to said subject synergistically effective amount of: (a) at least one cephalosporin antibacterial agent, and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof; wherein amount of the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof and a cephalosporin antibacterial agent administered are in weight ratio of about 1:10 to about 10:1.

In some embodiments, there is provided a method for treating or preventing a bacterial infection in a subject, said method comprising administering to said subject synergistically effective amount of: (a) at least one cephalosporin antibacterial agent, and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof; wherein amount of the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof administered is from about 0.25 gram to about 10 gram per gram of the cephalosporin antibacterial agent.

In some embodiments, in the methods according to the invention, the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof is administered in an amount from about 0.01 gram to about 25 gram.

In some other embodiments, in the methods according to the invention, the cephalosporin antibacterial agent is administered in an amount from about 0.01 gram to about 25 gram.

In some embodiments, there is provided a method for treating or preventing a bacterial infection in a subject, said method comprising administering to said subject synergistically effective amount of: (a) at least one cephalosporin antibacterial agent, and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof; wherein amount of the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof and a cephalosporin antibacterial agent administered are in weight ratio of about 4:1, 2:1, 1:1, 1:2, 1:4 or 1:8.

In some embodiments, there is provided a method for treating or preventing a bacterial infection in a subject, said method comprising administering to said subject: (a) a cephalosporin antibacterial agent, and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, in any of the following amounts:

- (i) 0.2 gram of cephalosporin antibacterial agent and 0.8 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (ii) 0.2 gram of cephalosporin antibacterial agent and 0.4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (iii) 0.2 gram of cephalosporin antibacterial agent and 0.2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (iv) 0.2 gram of cephalosporin antibacterial agent and 0.1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (v) 0.4 gram of cephalosporin antibacterial agent and 0.8 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (vi) 0.4 gram of cephalosporin antibacterial agent and 0.4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (vii) 0.4 gram of cephalosporin antibacterial agent and 0.2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (viii) 0.4 gram of cephalosporin antibacterial agent and 0.1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (ix) 0.5 gram of cephalosporin antibacterial agent and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (x) 1 gram of cephalosporin antibacterial agent and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xi) 1 gram of cephalosporin antibacterial agent and 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xii) 1 gram of cephalosporin antibacterial agent and 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xiii) 2 gram of cephalosporin antibacterial agent and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xiv) 2 gram of cephalosporin antibacterial agent and 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xv) 2 gram of cephalosporin antibacterial agent and 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xvi) 2 gram of cephalosporin antibacterial agent and 4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xvii) 4 gram of cephalosporin antibacterial agent and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xviii) 4 gram of cephalosporin antibacterial agent and 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xix) 4 gram of cephalosporin antibacterial agent and 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof; or
- (xx) 4 gram of cephalosporin antibacterial agent and 4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof.

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

In some embodiments, in the methods according to the invention, the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof is administered before, after or simultaneously with the administration of the cephalosporin antibacterial agent.

In some embodiments, there is provided pharmaceutical compositions comprising synergistically effective amount of: (a) compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and (b) cephalosporin antibacterial agent, wherein said composition is administered orally or parenterally.

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 the 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. In some embodiments, the compositions or one or more active ingredients according to the invention are administered orally or parenterally.

In some embodiments, there is provided a method for increasing antibacterial effectiveness of an cephalosporin antibacterial agent in a subject, said method comprising co-administering the cephalosporin antibacterial agent, with the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof. In some other embodiments, there is provided a method for increasing antibacterial effectiveness of a cephalosporin antibacterial agent, said method comprising co-administering the cephalosporin antibacterial agent with the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, wherein the amount of the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and cephalosporin antibacterial agent administered are in weight ratio of about 1:10 to about 10:1. In some other embodiments, there is provided a method for increasing antibacterial effectiveness of a cephalosporin antibacterial agent, said method comprising co-administering the cephalosporin antibacterial agent with the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, wherein the amount of the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof is from about 0.25 gram to about 10 gram per gram of the

cephalosporin antibacterial agent. In some embodiments, the said cephalosporin antibacterial agent is selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof.

A wide variety of bacterial infections can be treated or prevented using compositions and methods according to the invention. Typical, non-limiting examples of bacterial infections that can be treated or prevented using methods and/or pharmaceutical compositions according to the invention include *E. coli* infections, *Yersinia pestis* (pneumonic plague), staphylococcal infection, mycobacteria infection, bacterial pneumonia, Shigella dysentery, Serratia infections, Candida infections, Cryptococcal infection, anthrax, tuberculosis or infections caused by *Pseudomonas aeruginosa*, *Acinetobacter baumannii* or methicillin resistant *Staphylococcus aureus* (MRSA) etc.

The pharmaceutical compositions and methods according to the invention are useful in treatment or prevention of several infections, including for example, skin and soft tissue infections, febrile neutropenia, urinary tract infection, intraabdominal infections, respiratory tract infections, pneumonia (nosocomial), bacteremia meningitis, surgical infections and the like.

In some embodiments, pharmaceutical compositions and methods according to the invention are used in treatment or prevention of infections caused by resistant bacteria. In some other embodiments, the compositions and methods according to the invention are used in treatment or prevention of infections caused by bacteria producing one or more beta-lactamase enzymes.

In some embodiments, pharmaceutical compositions and methods according to the invention are used in treatment or prevention of infections caused by resistant bacteria producing Class C beta-lactamase enzymes.

In some other embodiments, pharmaceutical compositions and methods according to the invention are used in treatment or prevention of infections caused by resistant bacteria producing carbapenem hydrolyzing beta-lactamase enzymes. In some embodiments, pharmaceutical compositions and methods according to the invention are used in treatment or prevention of infections caused by resistant bacteria producing *Klebsiella pneumoniae* carbapenemases (KPCs).

In general, the pharmaceutical compositions and methods disclosed herein are also effective in preventing or treating infections caused by bacteria that are considered to 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*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Enterobacter*, *Klebsiella*, *Citrobacter* and the like.

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.

The killing effect of the combinations according to invention was studied by performing time kill studies. In a typical time kill study, the freshly grown cultures were diluted to the required cell density (initial starting inoculum) in Cation adjusted Muller Hinton broth medium (BD, USA). The antibacterial agents (either alone or in combination) at the required concentrations were added into the culture-containing medium. The samples were incubated under shaking condition (120 rpm) at 37°C. Enumeration of viable bacterial count was done every 2 hour by diluting in normal saline and plating on to the Tryptic Soya Agar plates (BD, USA). The plates were incubated for 24 hours to arrive at the viable bacterial count. The results are expressed in terms of log₁₀ CFU per ml. In general, the decrease of 1 log₁₀ CFU/ml corresponds to 90% killing of bacteria. Similarly, 2 log₁₀ CFU/ml reductions indicates to 99% killing of bacteria and 3 log₁₀ CFU/ml reductions is equal to 99.9% killing of bacteria.

Example 1

The results on the antibacterial activity of the antibacterial agent selected from cefixime, cefpodoxime, ceftibuten or cefuroxime; alone and in combination with a compound of Formula (I), against *E. coli* M50 are given in Table 1. *E. coli* M50 produces resistant CMY 6, DHA-1/2 beta-lactamase enzymes. As can be seen from the data in Table 1, cefixime, cefpodoxime, ceftibuten, cefuroxime and compound of Formula (I), when used alone, did not reduce the bacterial counts throughout the duration of the study. However, surprisingly, it has been observed that presence of a compound of Formula (I), the antibacterial agent selected from cefixime, cefpodoxime, ceftibuten or cefuroxime, significantly reduced the bacterial counts throughout the duration of the study. For example, a combination of cefixime (1 mcg/ml or 2 mcg/ml or 4 mcg/ml) and compound of Formula (I) (4 mcg/ml); and a combination of cefpodoxime (1 mcg/ml or 2 mcg/ml or 4 mcg/ml) and compound of Formula (I) (4 mcg/ml), exhibited potent antibacterial activity against highly resistant strains of *E. coli* even at the end 8 hours of the study. In comparison to this, Imipenem (1 mcg/ml) did not exhibit antibacterial activity at the end of 8 hours of study. Thus, it appears from the data of Table 1, that the combination of the antibacterial agent selected from cefixime, cefpodoxime, ceftibuten or cefuroxime, and a compound of Formula (I) exhibited synergistic antibacterial activity.

Example 2

The results on antibacterial activity of the antibacterial agent selected from cefixime, cefpodoxime, ceftibuten or cefuroxime alone and in combination with a compound of Formula (I) against *K. pneumoniae* H521 are given in Table 2. *K. pneumoniae* H521 produces resistant KPC, SHV and TEM beta-lactamase enzymes. As can be seen from the data in the Table 2, cefixime, cefpodoxime, ceftibuten, cefuroxime and compound of Formula (I), when used alone, did not reduce the bacterial counts throughout the duration of the study. However, surprisingly, it has been observed that presence of a compound of Formula (I) in combination with the antibacterial agent selected from cefixime, cefpodoxime, ceftibuten or cefuroxime, significantly reduced the bacterial counts throughout the duration of the study. For example, the combination of ceftibuten (4 mcg/ml) and a compound of Formula (I) (4 mcg/ml) was found to be effective against the resistant strains of *K. pneumoniae* H521.

The results given in the Tables 1 and 2, clearly demonstrate the surprisingly potent antibacterial activity of the combination comprising at least one antibacterial agent selected from cefixime, cefpodoxime, ceftibuten or cefuroxime, and a compound of Formula (I), even against highly resistant bacterial strains producing multiple beta-lactamase enzymes. Thus, combination of the antibacterial agent selected from cefixime, cefpodoxime, ceftibuten or cefuroxime, and a compound of Formula (I) has tremendous beneficial effect in inhibiting highly resistant bacterial strains demonstrating the noteworthy therapeutic advance in the treatment of infections caused by resistant bacteria.

A few other representative compositions were prepared comprising about “x” gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about “y” gram of the antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof; wherein “x” is 0.1, 0.2, 0.25, 0.4, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2 or 4; and “y” is 0.1, 0.2, 0.25, 0.4, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2 or 4. These composition were formulated as powders (the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and the antibacterial agent selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof were present as separate components or in admixture with each other).

Table 1. Antibacterial activity of various antibacterial agents and the compound of Formula (I) (alone or in combination with each other) against clinical isolate of *E. coli* M50 producing CMY 6, DHA – 1/2 beta-lactamase enzymes.

Sr.	Combinations	Bacterial count (Log ₁₀ CFU/ml)					Change in Log ₁₀ CFU/ml over 0 hour count after 8 hours*
		0 hour	2 hour	4 hour	6 hour	8 hour	
1.	Control (No active ingredient)	7.14	8.74	8.70	8.88	8.81	1.67
2.	Cefixime (4 mcg/ml)	7.14	8.95	8.40	8.90	8.65	1.51
3.	Cefpodoxime (4 mcg/ml)	7.14	8.18	8.88	8.95	8.40	1.26
4.	Ceftibuten (4 mcg/ml)	7.14	7.90	8.40	8.98	8.93	1.79
5.	Cefuroxime (4 mcg/ml)	7.14	8.33	8.54	9.20	8.65	1.51
6.	Compound of Formula (I) (4 mcg/ml)	7.14	6.40	5.32	5.32	5.34	-1.8
7.	Cefixime (1 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.14	5.81	4.04	3.93	3.90	-3.24
8.	Cefixime (2 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.14	5.70	4.11	3.78	3.74	-3.40
9.	Cefixime (4 mcg/ml)+ Compound of Formula (I) (4 mcg/ml)	7.14	5.11	3.74	3.40	3.74	-3.40
10.	Cefpodoxime (1 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.14	6.90	4.79	4.30	4.16	-2.98
11.	Cefpodoxime (2 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.14	6.20	4.85	4.10	4.08	-3.06
12.	Cefpodoxime (4 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.14	5.45	4.16	4.11	3.90	-3.24
13.	Ceftibuten (1 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.14	6.13	5.15	4.90	4.50	-2.64
14.	Ceftibuten (2 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.14	6.28	4.74	4.34	4.32	-2.82
15.	Ceftibuten (4 mcg/ml)+ Compound of Formula (I) (4 mcg/ml)	7.14	6.18	4.85	4.26	4.17	-2.97
16.	Cefuroxime (1 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.14	6.26	4.88	4.78	4.90	-2.24
17.	Cefuroxime (2 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.14	6.24	4.93	4.78	4.26	-2.88
18.	Cefuroxime (4 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.14	6.14	4.87	4.23	4.30	-2.84
19.	Imipenem (1 mcg/ml)	7.14	4.25	4.60	6.04	7.34	0.2

Note: Positive value indicates increase in bacterial count over 0 hour count; and negative value indicates reduction in bacterial count over 0 hour count.

Table 2. Antibacterial activity of various antibacterial agents and the compound of Formula (I) (alone or in combination with each other) against clinical isolate of *K. pneumoniae* H521 producing KPC, SHV and TEM beta-lactamase enzymes.

Sr.	Combinations	Bacterial count (Log ₁₀ CFU/ml)					Change in Log ₁₀ CFU/ml over 0 hour count after 8 hours*
		0 hour	2 hour	4 hour	6 hour	8 hour	
1.	Control (No active ingredient)	7.18	8.69	8.65	8.81	8.85	1.67
2.	Cefixime (4 mcg/ml)	7.18	8.26	8.85	8.98	8.95	1.77
3.	Cefpodoxime (4 mcg/ml)	7.18	8.60	8.74	8.93	8.81	1.63
4.	Ceftibuten (4 mcg/ml)	7.18	8.18	8.88	8.40	8.60	1.42
5.	Cefuroxime (4 mcg/ml)	7.18	8.48	8.70	8.78	8.60	1.42
6.	Compound of Formula (I) (4 mcg/ml)	7.18	7.98	8	8.37	8.04	0.86
7.	Cefixime (1 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.18	5.70	4.81	4.54	4.06	-3.12
8.	Cefixime (2 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.18	5.20	4.81	4.22	3.81	-3.37
9.	Cefixime (4 mcg/ml)+ Compound of Formula (I) (4 mcg/ml)	7.18	4.81	4.40	4.22	3.90	-3.28
10.	Cefpodoxime (1 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.18	6.90	6.78	6.40	5.85	-1.33
11.	Cefpodoxime (2 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.18	6.93	5.98	5.54	5.30	-1.88
12.	Cefpodoxime (4 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.18	6.88	6.18	5.41	5.70	-1.48
13.	Ceftibuten (1 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.18	5.30	4.65	4.30	3.93	-3.25
14.	Ceftibuten (2 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.18	5.48	4.60	4.78	4.18	-3.0
15.	Ceftibuten (4 mcg/ml)+ Compound of Formula (I) (4 mcg/ml)	7.18	4.91	4.60	4.54	3.54	-3.64
16.	Cefuroxime (1 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.18	6.88	5.74	5.65	5.40	-1.78
17.	Cefuroxime (2 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.18	6.60	5.06	5.27	5.23	-1.95
18.	Cefuroxime (4 mcg/ml) + Compound of Formula (I) (4 mcg/ml)	7.18	6.09	5.30	5.48	5.23	-1.95
19.	Imipenem (8 mcg/ml)	7.18	8.10	8.81	8.70	9.11	1.93

Note: Positive value indicates increase in bacterial count over 0 hour count; and negative value indicates reduction in bacterial count over 0 hour count.

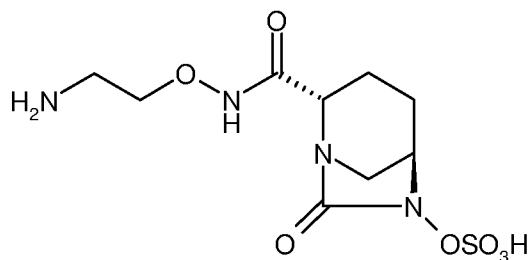
Example 3

Manufacturing Procedure: The compound of Formula (I), ceftibuten, microcrystalline cellulose, croscarmellose sodium were weighed, sifted, and mixed in a Rapid Mixer Granulator. The above mass was granulated by spraying aqueous solution of povidone. The granules were dried in a fluidized bed drier, sifted and milled. The resulting granules were blended with sifted microcrystalline cellulose, croscarmellose sodium, talc and magnesium stearate. The lubricated granules were compressed into tablets using suitable tooling. The tablets were coated with aqueous dispersion of opadry. The composition is shown in Table 3.

Table 3. Pharmaceutical compositions according to the invention			
Sr.	Ingredients	mg/Tablet	
		Formulation 1	Formulation 2
INTRAGRANULAR			
1	Compound of Formula (I)	200.0	200.0
2	Ceftibuten	200.0	400.0
3	Microcrystalline Cellulose (Avicel PH 101)	80.0	160.0
4	Croscarmesllose Sodium (Ac-Di-Sol)	7.0	14.0
5	Povidone K30 (Kollidone K30)	8.75	17.50
6	Purified water USP	q.s.	q.s.
EXTRAGRANULAR			
7	Microcrystalline cellulose (Avicel PH 102)	31.25	62.50
8	Croscarmesllose Sodium (Ac-Di-Sol)	13.0	26.0
9	Talc	3.50	7.00
10	Magnesium stearate	3.0	6.0
CORE TABLET (mg)		350.0	700.0
FILM COATING			
11	Opadry Yellow (03B28796)	10.5	21.0
12	Purified Water USP	q.s.	q.s.
Total (Coated Tablet Weight) mg		560.50	921.0

CLAIMS

1. A pharmaceutical composition comprising synergistically effective amount of: (a) at least one cephalosporin antibacterial agent and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof:



Formula (I)

2. A pharmaceutical composition according to Claim 1, wherein the weight ratio of compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, to a cephalosporin antibacterial agent in the composition is from about 1:10 to about 10:1.

3. A pharmaceutical composition according to any one of Claims 1 or 2, wherein weight ratio of compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, to a cephalosporin antibacterial agent in the composition is about 4:1, 2:1, 1:1, 1:2, 1:4 or 1:8.

4. A pharmaceutical composition according to any one of Claim 1 to 3, wherein the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof is present in the composition in an amount from about 0.25 gram to about 10 gram per gram of the cephalosporin antibacterial agent.

5. A pharmaceutical composition according to any of the Claims 1 to 4, wherein the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof is present in the composition in an amount from about 0.01 gram to about 25 gram.

6. A pharmaceutical composition according to any of the Claims 1 to 4, wherein the cephalosporin antibacterial agent is present in the composition in an amount from about 0.01 gram to about 25 gram.

7. A pharmaceutical composition according to any one of Claims 1 to 4, comprising any one of following amounts:

(i) 0.2 gram of cephalosporin antibacterial agent and 0.8 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;

(ii) 0.2 gram of cephalosporin antibacterial agent and 0.4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;

- (iii) 0.2 gram of cephalosporin antibacterial agent and 0.2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (iv) 0.2 gram of cephalosporin antibacterial agent and 0.1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (v) 0.4 gram of cephalosporin antibacterial agent and 0.8 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (vi) 0.4 gram of cephalosporin antibacterial agent and 0.4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (vii) 0.4 gram of cephalosporin antibacterial agent and 0.2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (viii) 0.4 gram of cephalosporin antibacterial agent and 0.1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (ix) 0.5 gram of cephalosporin antibacterial agent and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (x) 1 gram of cephalosporin antibacterial agent and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xi) 1 gram of cephalosporin antibacterial agent and 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xii) 1 gram of cephalosporin antibacterial agent and 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xiii) 2 gram of cephalosporin antibacterial agent and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xiv) 2 gram of cephalosporin antibacterial agent and 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xv) 2 gram of cephalosporin antibacterial agent and 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xvi) 2 gram of cephalosporin antibacterial agent and 4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xvii) 4 gram of cephalosporin antibacterial agent and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xviii) 4 gram of cephalosporin antibacterial agent and 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xix) 4 gram of cephalosporin antibacterial agent and 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof; or
- (xx) 4 gram of cephalosporin antibacterial agent and 4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof.

8. A pharmaceutical composition according to any one of the Claims 1 to 7, wherein the compound of Formula (I) is: “(2*S*, 5*R*)-N-(2-aminoethoxy)-7-oxo-6-(sulfoxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide” or a stereoisomer or a pharmaceutically acceptable derivative thereof.

9. A pharmaceutical composition according to any one of the Claims 1 to 7, wherein the compound of Formula (I) is: “sulfuric acid, mono[(1*R*,2*S*,5*R*)-2-[(2-aminoethoxy)amino]carbonyl]-7-oxo-1,6-diazabicyclo[3.2.1]oct-6-yl] ester” or a stereoisomer or a pharmaceutically acceptable derivative thereof.

10. A pharmaceutical composition according to any one of the Claims 1 to 7, wherein the compound of Formula (I) is present as a sodium or a potassium salt of “sulfuric acid, mono[(1*R*,2*S*,5*R*)-2-[(2-aminoethoxy)amino]carbonyl]-7-oxo-1,6-diazabicyclo[3.2.1]oct-6-yl] ester” or a stereoisomer thereof.

11. A pharmaceutical composition according to any one of the Claims 1 to 7, wherein the cephalosporin antibacterial agent is selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof.

12. A pharmaceutical composition according to any of one the Claims 1 to 11, wherein the composition is formulated into a dosage form such that the compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and the cephalosporin antibacterial agent are present in the composition as admixture or as separate components.

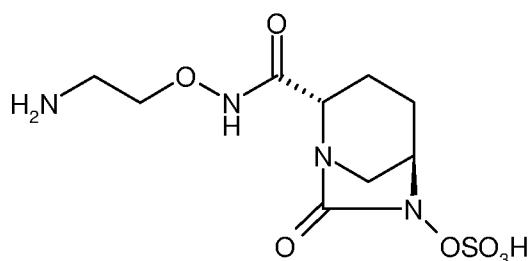
13. A pharmaceutical composition according to any of the Claims 1 to 12, wherein the composition is in the form of a powder or a solution.

14. A pharmaceutical composition according to any of the Claims 1 to 13, wherein the composition is formulated into a dosage form suitable for oral or parenteral administration.

15. A pharmaceutical composition according to any of the Claims 1 to 14 for use in treatment or prevention of a bacterial infection.

16. A method for preventing or treating a bacterial infection in a subject, said method comprising administering to said subject an effective amount of a pharmaceutical composition according to any of the Claims 1 to 14.

17. A method for treating or preventing a bacterial infection in a subject, said method comprising administering to said subject a synergistically effective amount of: (a) at least one cephalosporin antibacterial agent, and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof:



Formula (I)

18. A method according to Claim 17, wherein amount of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof and a cephalosporin antibacterial agent administered are in a weight ratio of about 1:10 to about 10:1.

19. A method according to Claim 17, wherein amount of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof and a cephalosporin antibacterial agent administered are in a weight ratio of about 4:1, 2:1, 1:1, 1:2, 1:4 or 1:8.

20. A method according to any one of the Claims 17 to 19, wherein a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof administered is in an amount from about 0.25 gram to about 10 gram per gram of the cephalosporin antibacterial agent.

21. A method according to any one of the Claims 17 to 20, wherein a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof is administered in an amount from about 0.01 gram to about 25 gram.

22. A method according to any one of the Claims 17 to 20, wherein the cephalosporin antibacterial agent is administered in an amount from about 0.01 gram to about 25 gram.

23. A method according to any of the Claims 17 to 20, wherein the cephalosporin antibacterial agent and a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof are administered in any of the following amounts:

- (i) 0.2 gram of cephalosporin antibacterial agent and 0.8 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (ii) 0.2 gram of cephalosporin antibacterial agent and 0.4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (iii) 0.2 gram of antibacterial agent cephalosporin antibacterial agent and 0.2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (iv) 0.2 gram of cephalosporin antibacterial agent and 0.1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (v) 0.4 gram of cephalosporin antibacterial agent and 0.8 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (vi) 0.4 gram of cephalosporin antibacterial agent and 0.4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (vii) 0.4 gram of cephalosporin antibacterial agent and 0.2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (viii) 0.4 gram of cephalosporin antibacterial agent and 0.1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (ix) 0.5 gram of cephalosporin antibacterial agent and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;

- (x) 1 gram of cephalosporin antibacterial agent and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xi) 1 gram of cephalosporin antibacterial agent and 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xii) 1 gram of cephalosporin antibacterial agent and 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xiii) 2 gram of cephalosporin antibacterial agent and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xiv) 2 gram of cephalosporin antibacterial agent and 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xv) 2 gram of cephalosporin antibacterial agent and 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xvi) 2 gram of cephalosporin antibacterial agent and 4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xvii) 4 gram of cephalosporin antibacterial agent and 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xviii) 4 gram of cephalosporin antibacterial agent and 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof;
- (xix) 4 gram of cephalosporin antibacterial agent and 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof; or
- (xx) 4 gram of cephalosporin antibacterial agent and 4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof.

24. A method according to any of the Claims 17 to 23, wherein a compound of Formula (I) is: “(2*S*, 5*R*)-N-(2-aminoethoxy)-7-oxo-6-(sulfoxy)-1,6-diazabicyclo [3.2.1] octane-2-carboxamide” or a stereoisomer or a pharmaceutically acceptable derivative thereof.

25. A method according to any of the Claims 17 to 23, wherein a compound of Formula (I) is: “sulfuric acid, mono[(1*R*,2*S*,5*R*)-2-[(2-aminoethoxy)amino]carbonyl]-7-oxo-1,6-diazabicyclo[3.2.1]oct-6-yl] ester” or a stereoisomer or a pharmaceutically acceptable derivative thereof.

26. A method according to any of the Claims 17 to 23, wherein a compound of Formula (I) is present as a sodium or potassium salt of “sulfuric acid, mono[(1*R*,2*S*,5*R*)-2-[(2-aminoethoxy)amino]carbonyl]-7-oxo-1,6-diazabicyclo[3.2.1]oct-6-yl] ester” or a stereoisomer thereof.

27. A method according to any one of Claims 17 to 23, wherein a cephalosporin antibacterial agent is selected from cefixime, cefpodoxime, ceftibuten, cefuroxime or a pharmaceutically acceptable derivative thereof.

28. A method for increasing antibacterial effectiveness of cephalosporin antibacterial agent in a subject, said method comprising coadministering at least one cephalosporin

antibacterial agent, with a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof.

29. A method according to Claim 28, wherein amount of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof and a cephalosporin antibacterial agent administered are in a weight ratio of about 1:10 to about 10:1.

30. A method according to any one of Claims 28 or 29, wherein amount of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof administered is from about 0.25 gram to about 10 gram per gram of cephalosporin antibacterial agent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/050282

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/439 A61K31/545 A61K31/546 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) A61K		
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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2013/225554 A1 (MAITI SAMARENDRA N [CA] ET AL) 29 August 2013 (2013-08-29) paragraphs [0003], [0004], [0013], [0094], [0107], [05521581], [1912]; table 5	1-30
X	----- WO 2013/180197 A1 (MEIJI SEIKA PHARMA CO LTD [JP]) 5 December 2013 (2013-12-05) cited in the application see passages of EP2857401 which is a publication of the earliest family member of WO 2013/180197 in Japanese, and is assumed to refer to the same content & EP 2 857 401 A1 (MEIJI SEIKA PHARMA CO LTD [JP]) 8 April 2015 (2015-04-08) cited in the application paragraphs [0019], [0025] - [0028], [0109] - [0111], [0124], [0438] - [0444] paragraphs [0660], [0066]; claims -----	1-30
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 23 March 2016		Date of mailing of the international search report 31/03/2016
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 Leherte, Chantal

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2016/050282

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2013225554 A1	29-08-2013	US 2013225554 A1	29-08-2013
		US 2013281359 A1	24-10-2013
		US 2014221341 A1	07-08-2014

WO 2013180197 A1	05-12-2013	AR 091222 A1	21-01-2015
		AU 2013268415 A1	04-12-2014
		CA 2874279 A1	05-12-2013
		CL 2014003035 A1	30-01-2015
		CN 104334559 A	04-02-2015
		CO 7151513 A2	29-12-2014
		EP 2857401 A1	08-04-2015
		HK 1206746 A1	15-01-2016
		HK 1208862 A1	18-03-2016
		JP WO2013180197 A1	21-01-2016
		KR 20150015523 A	10-02-2015
		PH 12014502683 A1	26-01-2015
		TW 201408668 A	01-03-2014
		US 2015141401 A1	21-05-2015
		US 2016024090 A1	28-01-2016
		WO 2013180197 A1	05-12-2013
