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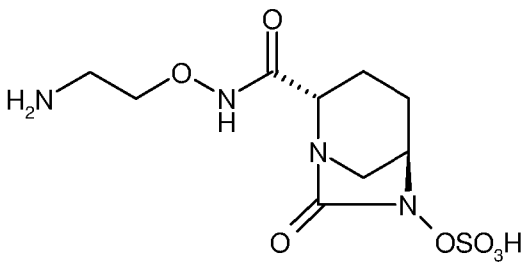


Formula (I)

(57) Abstract: Pharmaceutical compositions comprising sulbactam or a pharmaceutically acceptable derivative, and a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof are disclosed.

PHARMACEUTICAL COMPOSITIONS COMPRISING ANTIBACTERIAL AGENTS

PRIORITY APPLICATION

This application claims priority to Indian Patent Application No. 997/MUM/2015 filed on March 25, 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 sulbactam 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.

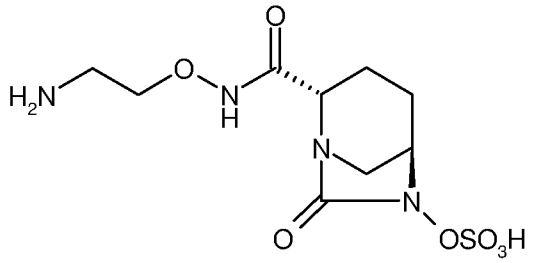
Treatment of infections caused by resistant bacteria remains a key challenge for the clinician community. One example of such challenging pathogen is *Acinetobacter baumannii* (*A. baumannii*), which continues to be an increasingly important and demanding species in healthcare settings. The multidrug resistant nature of this pathogen and its unpredictable susceptibility patterns make empirical and therapeutic decisions more difficult. *A. baumannii* is

associated with infections such as pneumonia, bacteraemia, wound infections, urinary tract infections and meningitis.

Therefore, there is a need for development of newer ways to treat infections that are becoming resistant to known therapies and methods. Surprisingly, it has been found that a compositions comprising sulbactam and certain nitrogen containing bicyclic compounds (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 effective amount of: (a) sulbactam or a pharmaceutically acceptable derivative thereof, and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof:



Formula (I)

In one aspect, there are provided pharmaceutical compositions comprising effective amount of: (a) sulbactam or a pharmaceutically acceptable derivative thereof, 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 sulbactam in the composition is about 1:10 to 10:1.

In some embodiments, there are provided pharmaceutical compositions comprising effective amount of: (a) sulbactam or a pharmaceutically acceptable derivative thereof, and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof; wherein a 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 4 gram per gram of sulbactam or a pharmaceutically acceptable derivative thereof.

In yet another aspect, there is provided a method for treating or preventing a bacterial infection in a subject, the method comprising administering to the subject a pharmaceutical

composition comprising effective amount of: (a) sulbactam or a pharmaceutically acceptable derivative thereof; and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof.

In yet another aspect, there is provided a method for treating or preventing a bacterial infection in a subject, the method comprising administering to the subject an effective amount of: (a) sulbactam 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, there is provided a method for treating or preventing a bacterial infection in a subject, the method comprising administering to the subject an effective amount of: (a) sulbactam or a pharmaceutically acceptable derivative thereof, 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 sulbactam or a pharmaceutically acceptable derivative therefore administered are in a weight ratio of about 1:10 to about 10:1.

In some embodiments, there are provided methods for treating or preventing a bacterial infection in a subject, the method comprising administering to the subject an effective amount of: (a) sulbactam or a pharmaceutically acceptable derivative thereof, and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof; wherein a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof is administered in an amount from about 0.25 gram to about 4 gram per gram of sulbactam or a pharmaceutically acceptable derivative thereof.

In another general aspect, there is provided a method for increasing antibacterial effectiveness of sulbactam or a pharmaceutically acceptable derivative thereof in a subject, the method comprising co-administering the sulbactam 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.

This specification discloses a pharmaceutical composition comprising: (a) sulbactam or a pharmaceutically acceptable derivative thereof, and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof; which exhibits unexpectedly improved antibacterial efficacy, even against highly resistant bacteria, including those producing 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 ingredients to a subject, including for example, by any appropriate method, which serves to deliver the composition or its active ingredients or other pharmaceutically active ingredients to the site of infection. The method of administration may vary depending on various factors, such as for example, the components of the pharmaceutical composition or type/nature of the pharmaceutically active or inert ingredients, site of the potential or actual infection, the microorganism involved, severity of the infection, age and physical condition of the subject and a like. Some non-limiting examples of ways to administer a composition or a pharmaceutically active ingredient to a subject according to this invention include oral, intravenous, topical, intrarespiratory, intraperitoneal, intramuscular, parenteral, sublingual, transdermal, intranasal, aerosol, intraocular, intratracheal, intrarectal, vaginal, gene gun, dermal patch, eye drop and mouthwash. In case of a pharmaceutical composition comprising more than one ingredients (active or inert), one of the ways of administering such composition is by admixing the ingredients (e.g. in the form of a suitable unit dosage form such as tablet, capsule, solution, powder or a like) and then administering the dosage form. Alternatively, the ingredients may also be administered separately (simultaneously or one after the other) as long as these ingredients reach beneficial

therapeutic levels such that the composition as a whole provides a synergistic and/or desired effect.

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

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

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

The term "synergistically effective amounts" as used herein refers to amounts of each active component in the treatment which are effective in producing more than additive effect of each component. The term "synergistically effective amounts" also includes the amounts of two or more active agents that provide a synergistic effect.

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-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" 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, carbapenems, monobactams and the like.

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

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

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

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

The term "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.

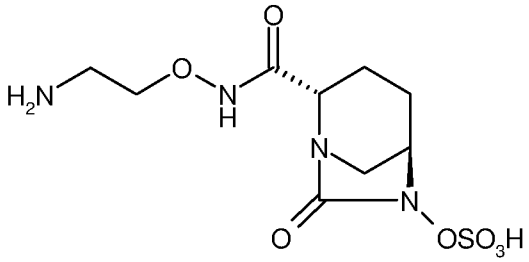
The term "pharmaceutically acceptable salt" as used herein refers to one or more salts of a given compound which possesses desired pharmacological activity of the free compound and which is neither biologically nor otherwise undesirable. In general, the term "pharmaceutically acceptable salts" refer 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. Stereoisomers may further be classified as enantiomers (where different isomers are mirror-images of each other) and diastereomers (where different isomers are not mirror-images of each other). Diastereomers include isomers such as conformers, meso compounds, cis-trans (E-Z) isomers, and non-enantiomeric optical isomers.

The term "about" as used in herein means within a acceptable error range for the particular value as determined by one of the ordinary skilled in the art, which will depend in part on how the value is measured or determined. Alternatively, "about" with respect to the compositions can mean plus or minus a range of up to 10%.

A person of skills in the art would appreciate that various compounds described herein (including, for example a compound of Formula (I) and sulbactam) 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 effective amounts of: (a) sulbactam or a pharmaceutically acceptable derivative thereof, and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof:



Formula (I)

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).

In some embodiments, there is provided a pharmaceutical compositions comprising synergistically effective amounts of: (a) sulbactam 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) sulbactam 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 sulbactam or a pharmaceutically acceptable derivative thereof in the composition may vary depending on clinical requirements. The specified amount of compound of Formula (I) and sulbactam is calculated on the basis of their equivalent free forms.

In one aspect, there are provided pharmaceutical compositions comprising effective amount of: (a) sulbactam or a pharmaceutically acceptable derivative thereof, 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 sulbactam in the composition is about 1:10 to 10:1.

In some embodiments, there are provided pharmaceutical compositions comprising effective amount of: (a) sulbactam or a pharmaceutically acceptable derivative thereof, and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof; wherein a 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 4 gram per gram of sulbactam or a pharmaceutically acceptable derivative thereof.

Both, sulbactam and a compound of Formula (I) may be present in the composition 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).

Individual amounts of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and sulbactam or a pharmaceutically acceptable derivative thereof in the composition may vary depending on clinical requirements. In some embodiments, a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof in the composition is present in an amount from about 0.01 gram to about 10 gram. In some other embodiments, sulbactam or a pharmaceutically acceptable derivative thereof in the composition is present in an amount from about 0.01 gram to about 10 gram.

In some embodiments, there are provided pharmaceutical compositions comprising effective amount of: (a) sulbactam or a pharmaceutically acceptable derivative thereof, 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 the sulbactam in the composition is about 1:8, 1:4, 1:2, 1:1, 2:1, 4:1 or 8:1.

In some embodiments, the pharmaceutical composition according to the invention comprises about 4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 4 gram of sulbactam or a pharmaceutically acceptable derivative thereof.

In some other embodiments, the pharmaceutical composition according to the invention comprises about 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 4 gram of sulbactam or a pharmaceutically acceptable derivative thereof.

In some embodiments, the pharmaceutical composition according to the invention comprises about 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 4 gram of sulbactam or a pharmaceutically acceptable derivative thereof.

In some embodiments, the pharmaceutical composition according to the invention comprises about 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 4 gram of sulbactam or a pharmaceutically acceptable derivative thereof.

In some embodiments, the pharmaceutical composition according to the invention comprises about 4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 2 gram of sulbactam or a pharmaceutically acceptable derivative thereof.

In some embodiments, the pharmaceutical composition according to the invention comprises about 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically

acceptable derivative thereof, and about 2 gram of sulbactam or a pharmaceutically acceptable derivative thereof.

In some embodiments, the pharmaceutical composition according to the invention comprises about 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 2 gram of sulbactam or a pharmaceutically acceptable derivative thereof.

In some embodiments, the pharmaceutical composition according to the invention comprises about 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 2 gram of sulbactam or a pharmaceutically acceptable derivative thereof.

In some embodiments, the pharmaceutical composition according to the invention comprises about 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 1 gram of sulbactam or a pharmaceutically acceptable derivative thereof.

In some embodiments, the pharmaceutical composition according to the invention comprises about 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 1 gram of sulbactam or a pharmaceutically acceptable derivative thereof.

In some embodiments, the pharmaceutical composition according to the invention comprises about 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 1 gram of sulbactam or a pharmaceutically acceptable derivative thereof.

In some embodiments, the pharmaceutical composition according to the invention comprises about 0.25 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 1 gram of sulbactam or a pharmaceutically acceptable derivative thereof.

In some embodiments, the pharmaceutical composition according to the invention comprises about 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically

acceptable derivative thereof, and about 0.5 gram of sulbactam or a pharmaceutically acceptable derivative thereof.

In some embodiments, the pharmaceutical composition according to the invention comprises about 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 0.5 gram of sulbactam or a pharmaceutically acceptable derivative thereof.

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 diluents, wetting agents, emulsifying agents, suspending agents, solubilizing agents, buffering agents, lubricants, preservatives, stabilizing agents, binding agents, disintegrants, colorants, flavorants, lubricants and the like.

The pharmaceutical compositions according to invention are prepared according to standard literature procedures. 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, injectable preparations 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.

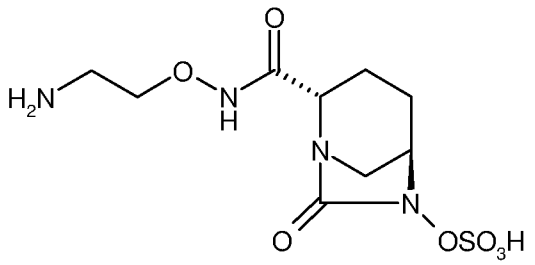
The compositions according to the invention can be formulated into various dosage forms wherein the active ingredients and/or excipients may be present either together (e.g. as an admixture) or as separate components. When the various ingredients in the composition are formulated as a mixture, such compositions 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 a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and sulbactam or a pharmaceutically acceptable derivative thereof, are present in the composition as admixture or as a separate components. In some other embodiments, pharmaceutical compositions according to the invention are formulated into a dosage form such that a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and sulbactam or a pharmaceutically acceptable derivative thereof, 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, the method comprising administering to the subject therapeutically effective amount of a pharmaceutical composition according to the invention. In case of dosage forms wherein a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and sulbactam or a pharmaceutically acceptable derivative thereof, are present in the composition as separate components; a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof may be administered before, after or simultaneously with the administration of sulbactam or a pharmaceutically acceptable derivative thereof.

In yet another general aspect, there is provided a method for treating or preventing bacterial infections in a subject, the method comprising administering to the subject an effective amount of: (a) sulbactam or a pharmaceutically acceptable derivative thereof, and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof:



Formula (I)

In one aspect, there is provided a method for treating or preventing a bacterial infection in a subject, the method comprising administering to the subject effective amount of: (a) sulbactam or a pharmaceutically acceptable derivative thereof, 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 sulbactam 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 bacterial infections in a subject, the method comprising administering to the subject an effective amount of: (a) sulbactam or a pharmaceutically acceptable derivative thereof, 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 4 gram per gram of sulbactam or a pharmaceutically acceptable derivative thereof.

In some embodiments, there is provided a method for treating or preventing a bacterial infection in a subject, the method comprising administering to the subject effective amount of: (a) sulbactam or a pharmaceutically acceptable derivative thereof, 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 sulbactam administered are in weight ratio of about 1:8, 1:4, 1:2, 1:1, 2:1, 4:1 or 8:1.

In some embodiments, there is provided a method for treating or preventing a bacterial infection in a subject, the method comprising administering to the subject: (a) sulbactam 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) about 4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 4 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(ii) about 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 4 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(iii) about 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 4 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(iv) about 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 4 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(v) about 4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 2 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(vi) about 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 2 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(vii) about 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 2 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(viii) about 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 2 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(ix) about 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 1 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(x) about 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 1 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(xi) about 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 1 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(xii) about 0.25 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 1 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(xiii) about 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 0.5 gram of sulbactam or a pharmaceutically acceptable derivative thereof; or

(xiv) about 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 0.5 gram of sulbactam or a pharmaceutically acceptable derivative thereof.

In some embodiments, in the methods according to the invention, 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 10 gram. In some other embodiments, in the methods according to the invention, sulbactam or a pharmaceutically acceptable derivative thereof is administered in an amount from about 0.01 gram to about 10 gram.

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

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, intrarespiratory, 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 parenterally or orally.

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.

In some embodiments, in the compositions and methods according to the invention, sulbactam is present as sulbactam sodium.

In some embodiments, there is provided a method for increasing antibacterial effectiveness of sulbactam or a pharmaceutically acceptable derivative thereof in a subject, the method comprising co-administering sulbactam or a pharmaceutically acceptable derivative thereof, with a 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 sulbactam or a pharmaceutically acceptable derivative thereof in a subject, the method comprising co-administering the sulbactam 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 sulbactam 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 sulbactam or a pharmaceutically acceptable derivative thereof in a subject, the method comprising co-administering sulbactam or a pharmaceutically acceptable derivative thereof, with a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, wherein the amount of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof is from about 0.25 gram to about 4 gram per gram of sulbactam 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, the compositions and methods according to the invention are used in treatment or prevention of infections caused by bacteria producing one or more extended spectrum 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 a like.

EXAMPLES

The following examples illustrate 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 embodiments of the invention.

The antibacterial activity of combinations according to the invention against resistant bacterial strains was investigated. Minimum Inhibitory Concentration (MIC) for the combinations according to invention was determined in Muller Hinton Agar (MHA) (BD, USA) according to Clinical and Laboratory Standards Institute (CLSI) recommendations (Clinical and Laboratory Standards Institute (CLSI), Performance Standards for Antimicrobial Susceptibility Testing, 20th Informational Supplement, M 100-S20, Volume 30, No. 1, 2010). Typically, the test strains were adjusted to deliver about 10^4 CFU per spot with a multipoint inoculator (Applied Quality Services, UK). The plates were pored with MHA containing doubling concentration range of the test combinations according to invention. The plates were inoculated and were incubated at 35ºC for 18 hours. MICs were read as the lowest concentration of drug that completely inhibited bacterial growth.

The killing effect of the combinations according to invention was studied using time kill studies. In a typical time kill study, 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 37ºC. 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 Log_{10} CFU per ml. In general, the decrease of 1 Log_{10} CFU/ml, corresponds to 90% killing of bacteria. Similarly, 2 Log_{10} CFU/ml reductions indicates 99% killing of bacteria and 3 Log_{10} CFU/ml reductions is equal to 99.9% killing of bacteria.

Example 1

The results on antibacterial activity of sulbactam, imipenem and compound of Formula (I) against highly resistant strains of *A. baumannii* are given in Table 1. The strains of *A. baumannii* selected in this study produced carbapenem hydrolyzing beta-lactamase enzymes. As can be seen in Table 1, the MIC values of sulbactam were significantly lowered in the presence of a compound of Formula (I). The lowered MIC values suggest that the combination according

to the invention exhibited good antibacterial activity against highly resistant strains of *A. baumannii*.

Example 2

Table 1. Antibacterial activity of various antibacterial agents

Sr.	Strain	Carbapenem Hydrolyzing Beta-Lactamase Enzymes	MIC (mcg/ml)			
			Sulbactam	Imipenem	Compound of Formula (I)	MIC of Sulbactam in presence of a Compound of Formula (I) (4 mcg/ml)
1.	*A. baumannii* NCTC 13301	OXA 23	8	64	> 32	2
2.	*A. baumannii* NCTC 13302	OXA 24	16	128	> 32	2
3.	*A. baumannii* NCTC 13304	OXA 27	16	64	> 32	4
4.	*A.baumannii* S 410	OXA family	8	16	> 32	4
5.	*A. baumannii* Q1338384	OXA family	8	32	> 32	2
6.	*A. baumannii* M1	OXA family	64	32	> 32	1

The results on antibacterial activity of sulbactam and a compound of Formula (I) (alone and in combination with each other) against *A. baumannii* NCTC 13304 (producing carbapenem hydrolyzing OXA-27 beta-lactamase enzyme) are given in Table 2. As can be seen from the data in Table 2, sulbactam or a compound of Formula (I), when used alone, did not reduce the bacterial counts throughout the duration of the study. However, surprisingly, a combination of sulbactam and a compound of Formula (I) reduced the bacterial counts significantly throughout the duration of the study. The combination of sulbactam (at 4 mcg/ml) and a compound of Formula (I) (at 8 mcg/ml) reduced the bacterial count from 6.40 Log_{10} CFU/ml to 4.77 Log_{10} CFU/ml at the end of 6 hours (about 99% killing). Alternatively, the combination of sulbactam (at 8 mcg/ml) and a compound of Formula (I) (at 16 mcg/ml) reduced the bacterial count from 6.40 Log_{10} CFU/ml to 3.30 Log_{10} CFU/ml at the end of 6 hours (about 99.9% killing). These reduced bacterial counts suggest enhanced antibacterial activity of the combination according to invention.

The results given in the Tables 1 and 2, demonstrate the surprisingly potent antibacterial activity of a combination of sulbactam and a compound of Formula (I) against even highly resistant strains of *A. baumannii*. Both, sulbactam and a compound of Formula (I), when used alone, did not exhibit significant antibacterial activity. However, a combination of sulbactam and a compound of Formula (I) exhibited unusual and unexpected synergistic antibacterial activity even against highly resistant *A. baumannii*. Thus, combination of sulbactam and a compound of Formula (I) offered beneficial effect in inhibiting highly resistant bacterial strains demonstrating the noteworthy therapeutic advance in the treatment of infections caused by bacteria.

Table 2. Antibacterial activity of Sulbactam and Compound of Formula (I) (alone and in combination with each other) against *A. baumannii* NCTC 13304 producing carbapenem hydrolyzing OXA-27 beta-lactamase enzyme

Sr.	Combination	Bacterial count (Log_{10} CFU/ml)				Change in Log_{10} CFU/ml over 0 hour count after 24 hours*
		0 hour	2 hours	4 hours	6 hours	
1.	Control (No active ingredient)	6.40	7.81	8.69	8.00	1.60
2.	Sulbactam (4 mcg/ml)	6.40	7.77	8.21	8.02	1.62
3.	Sulbactam (8 mcg/ml)	6.40	7.11	8.00	8.03	1.63
4.	Compound of Formula (I) (8 mcg/ml)	6.40	7.90	8.52	8.69	2.29
5.	Compound of Formula (I) (16 mcg/ml)	6.40	7.80	8.11	8.32	1.92
6.	Sulbactam (4 mcg/ml) + Compound of Formula (I) (8 mcg/ml)	6.40	6.36	4.84	4.77	-1.63
7.	Sulbactam (8 mcg/ml) + Compound of Formula (I) (16 mcg/ml)	6.40	5.34	3.87	3.30	-3.1

*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

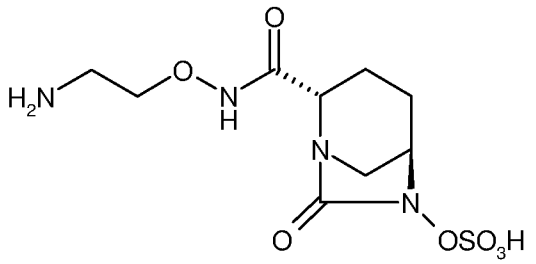
Manufacturing Procedure: The compound of Formula (I), sulbactam sodium, microcrystalline cellulose, crosscarmellose sodium were weighed, sifted, and mixed in a Rapid Mixer Granulator. The above mass was granulated by spraying aqueous solution of povidone. The granules were dried in a fluidized bed drier, sifted and milled. The resulting granules were blended with sifted microcrystalline cellulose, crosscarmellose 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)	500.0	1000.0
2	Sulbactam sodium	1094	1094
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)		1744.0	2394.0
FILM COATING			
11	Opadry Yellow (03B28796)	10.5	21.0
12	Purified Water USP	q.s.	q.s.
Total (Coated Tablet Weight) mg		**1754.5**	**2415.0**

CLAIMS

1. A pharmaceutical composition comprising effective amount of: (a) sulbactam or a pharmaceutically acceptable derivative thereof; and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof:



Formula (I)

2. The 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 sulbactam or a pharmaceutically acceptable derivative thereof in the composition is from about 1:10 to about 10:1.

3. The pharmaceutical composition according to Claim 2, wherein weight ratio of compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, to sulbactam or a pharmaceutically acceptable derivative thereof in the composition is about 1:8, 1:4, 1:2, 1:1, 2:1, 4:1, 8:1.

4. The pharmaceutical composition according to Claim 1, 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 4 gram per gram of the sulbactam.

5. The pharmaceutical composition according to Claim 1, 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 10 gram.

6. The pharmaceutical composition according to Claim 1, wherein the sulbactam or pharmaceutically acceptable derivative thereof is present in the composition in an amount from about 0.01 gram to about 10 gram.

7. The pharmaceutical composition according to Claim 1, comprising any one of following amounts:

(i) about 4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 4 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(ii) about 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 4 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(iii) about 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 4 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(iv) about 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 4 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(v) about 4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 2 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(vi) about 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 2 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(vii) about 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 2 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(viii) about 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 2 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(ix) about 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 1 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(x) about 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 1 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(xi) about 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 1 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(xii) about 0.25 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 1 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(xiii) about 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 0.5 gram of sulbactam or a pharmaceutically acceptable derivative thereof; or

(xiv) about 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 0.5 gram of sulbactam or a pharmaceutically acceptable derivative thereof.

8. The pharmaceutical composition according to Claim 1, 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.

9. The pharmaceutical composition according to Claim 1, 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.

10. The pharmaceutical composition according to Claim 1, wherein the sulbactam is present as sulbactam sodium.

11. The pharmaceutical composition according to Claim 1, 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 sulbactam or a pharmaceutically acceptable derivative thereof are present in the composition as admixture or as separate components.

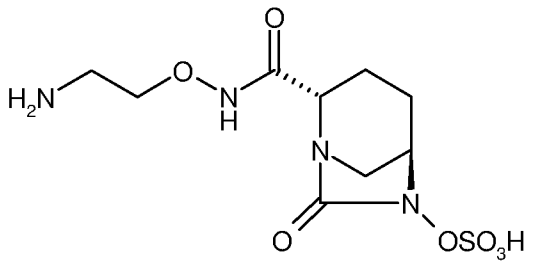
12. The pharmaceutical composition according to Claim 1, wherein the composition is in the form of a powder or a solution.

13. The pharmaceutical composition according to Claim 1, wherein the composition is formulated into a dosage form suitable for oral or parenteral administration.

14. The pharmaceutical composition according to any of the Claims 1 to 13 for use in treatment or prevention of a bacterial infection.

15. The method for preventing or treating a bacterial infection in a subject, the method comprising administering to the subject a pharmaceutical composition according to any of the Claims 1 to 13.

16. A method for treating or preventing a bacterial infection is a subject, the method comprising administering to the subject an effective amount of: (a) sulbactam or a pharmaceutically acceptable derivative thereof, and (b) a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof:



Formula (I)

17. The method according to Claim 16, wherein amount of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof and sulbactam or a pharmaceutically acceptable derivative thereof administered are in a weight ratio of about 1:10 to about 10:1.

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

19. The method according to Claim 16, 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 4 gram per gram of the sulbactam or a pharmaceutically acceptable derivative thereof.

20. The method according to Claim 16, 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 10 gram.

21. The method according to Claim 16, wherein the sulbactam or a pharmaceutically acceptable derivative thereof is administered in an amount from about 0.01 gram to about 10 gram.

22. The method according to Claim 16, wherein the sulbactam or a pharmaceutically acceptable derivative thereof and a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof are administered in any of the following amounts:

(i) about 4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 4 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(ii) about 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 4 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(iii) about 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 4 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(iv) about 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 4 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(v) about 4 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 2 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(vi) about 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 2 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(vii) about 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 2 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(viii) about 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 2 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(ix) about 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 1 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(x) about 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 1 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(xi) about 0.5 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 1 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(xii) about 0.25 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 1 gram of sulbactam or a pharmaceutically acceptable derivative thereof;

(xiii) about 1 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 0.5 gram of sulbactam or a pharmaceutically acceptable derivative thereof; or

(xiv) about 2 gram of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof, and about 0.5 gram of sulbactam or a pharmaceutically acceptable derivative thereof.

23. The method according to Claim 16, 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.

24. The method according to Claim 16, 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.

25. A method for increasing antibacterial effectiveness of sulbactam in a subject, the method comprising co-administering sulbacam or a pharmaceutically acceptable derivative

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

26. The method according to Claim 25, wherein amount of a compound of Formula (I) or a stereoisomer or a pharmaceutically acceptable derivative thereof and sulbacam or a pharmaceutically acceptable derivative thereof administered are in a weight ratio of about 1:10 to about 10:1.

27. The method according to Claim 25, 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 4 gram per gram of sulbacam or a pharmaceutically acceptable derivative thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/051718

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/43 A61K31/439 A61P31/04 A61K45/06
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 A61P

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, EMBASE, SCISEARCH, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 8 877 743 B2 (MAITI SAMARENDRA N [CA] ET AL) 4 November 2014 (2014-11-04) claims; table 4	1-27
Y	WO 2013/030733 A1 (WOCKHARDT LTD [IN]; PATEL MAHESH VITHALBHAI [IN]; DESHPANDE PRASAD KES) 7 March 2013 (2013-03-07) claims; tables 7,8	1-27
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Y,P	WO 2015/136387 A1 (WOCKHARDT LTD [IN]) 17 September 2015 (2015-09-17) claims; examples	1-27

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[X] Further documents are listed in the continuation of Box C.

[X] 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

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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

Date of the actual completion of the international search	Date of mailing of the international search report
17 June 2016	30/06/2016

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/051718

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/IB2016/051718

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