METHODS FOR TREATING, PREVENTING, OR REDUCING THE RISK OF OPHTHALMIC, OTIC, AND NASAL INFECTIONS

The present invention relates to methods for treating, preventing, or reducing the risk of ophthalmic, otic, and nasal infections by administering antimicrobial compositions to the affected tissues.
METHODS FOR TREATING, PREVENTING, OR REDUCING THE RISK OF
OPHTHALMIC, OTIC, AND NASAL INFECTIONS

RELATED APPLICATIONS

This application claims priority to provisional patent applications U.S.S.N. 60/878,759, filed on January 4, 2007 and U.S.S.N. 60/930,231, filed on May 14, 2007 the disclosure of each is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to methods for treating, preventing, or reducing the risk of microbial infections, such as ophthalmic, otic, and nasal infections, by administering antimicrobial compositions to the affected tissues.

BACKGROUND

The present invention is directed to the provision of topical pharmaceutical compositions for treating ophthalmic, otic, and nasal infections.

Antibiotics have been previously utilized to treat ophthalmic, otic, and nasal infections. For example, a topical ophthalmic composition containing the quinolone ciprofloxacin is marketed by Alcon Laboratories, Inc. under the name Ciloxan™ (Ciprofloxacin 0.3%) Ophthalmic Solution. A topical otic composition containing a combination of ciprofloxacin and hydrocortisone is marketed by Alcon Laboratories, Inc. under the name Cipro™ HC. The following quinolones have also been utilized: norfloxacin, lomefloxacin, moxifloxacin, ofloxacin, and gatifloxacin.

Other antibiotics used for ophthalmic, otic, and nasal indications have included neomycin, polymyxin B, gentamicin and tobramycin, bacitracin, gramicidin, and erythromycin. However, despite the currently available therapies, there is a need for improved compositions and methods of treatment based on the use of antibiotics that are more effective than existing antibiotics against key ophthalmic, otic, and nasal pathogens, and less prone to the development of resistance by those pathogens.

With respect to infections in general there is an increasing incidence of methicillin resistant Staphylococcus aureus infections, including both hospital-associated and
community-associated methicillin resistant *Staphylococcus Aureus* infections, and particularly community-associated methicillin resistant *Staphylococcus aureus* infections. This increasing incidence is also observed for ophthalmic, otic, and nasal infections. Methicillin-resistant *Staphylococcus Aureus* (MRSA) is a type of bacteria that is resistant to certain antibiotics. These antibiotics include methicillin and other more common antibiotics such as oxacillin, penicillin and amoxicillin. *Staphylococcus* infections, also called staph infections, including MRSA, occur most frequently among persons in hospitals and healthcare facilities, such as nursing homes and dialysis centers, who have weakened immune systems. These types of staph infections are referred to as hospital-associated methicillin-resistant *Staphylococcus Aureus* (HA-MRSA) infections. In recent years there has been an increasing incidence of MRSA infections that are acquired by persons who have not been recently (within the past year) hospitalized or had a medical procedure (such as dialysis, surgery, catheters), which are known as community-associated methicillin-resistant *Staphylococcus Aureus* (CA-MRSA) infections. Staph or MRSA infections in the community are usually manifested as skin infections, such as pimples and boils, and occur in otherwise healthy people. CA-MRSA infections can range from minor infections, but can escalate to rapidly fatal, overwhelming pneumonia and sepsis accompanied by the Waterhouse-Friderichsen syndrome (acute adrenal insufficiency due to massive hemorrhage into the adrenal gland). See, R.C. Moellering, The Growing Menace of Community-associated Methicillin-Resistant *Staphylococcus aureus*, Annals of Internal Medicine, volume 144, number 5, 368-370, March 7, 2006.

There is a need for safe, effective, and convenient topical antibiotic compositions, particularly topical antibiotic compositions, and methods for treating ophthalmic, otic, and nasal infections, particularly bacterial infections. Furthermore there is a need for safe, effective, and convenient therapies for treating methicillin resistant *Staphylococcus aureus* infections, including both hospital-associated and community-associated methicillin resistant *Staphylococcus Aureus* infections, and particularly community-associated methicillin resistant *Staphylococcus aureus* infections, particularly when such infections are associated with the eyes, ears, nose, or throat.

**SUMMARY OF THE INVENTION**

The present invention provides a method of treating, preventing, or reducing the risk of ophthalmic, otic, and/or nasal infections. The present invention also provides a method for
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treating, preventing or reducing the risk of such infections associated with surgical or other
invasive medical procedures involving the eye, ear, nose, and related areas such as the throat.
The present invention also provides compositions useful for these methods. The present
invention also provides the use of an antimicrobial compound in the manufacture of a
medicament useful for the methods of the present invention. With respect to these
ophthalmic, otic, and/or nasal infections, the present invention also relates to methods for
treating methicillin resistant Staphylococcus aureus infections, including both hospital-
associated and community-associated methicillin resistant Staphylococcus Aureus infections,
and particularly community-associated methicillin resistant Staphylococcus aureus infections,
using a safe and effective amount of a topically applied antibiotic compound.

The present invention also relates to a method, composition or use wherein said
infection is Staphylococcus aureus infection.

The present invention also relates to a method, composition or use wherein said
infection is a hospital-associated methicillin resistant Staphylococcus aureus infection.

The present invention also relates to a method, composition or use wherein said
infection is a community-associated methicillin resistant Staphylococcus aureus infection.

The present invention also relates to a method, composition or use wherein said
infection is mediated, caused, or associated with Staphylococcus aureus.

The foregoing and other aspects and embodiments of the present invention can be
more fully understood by reference to the following detailed description and claims.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1 shows a powder X-ray diffraction pattern of crystalline D-glucitol 1-(6-
amino-3,5-difluoro-2-pyridinyl)-8-chloro-6-fluoro-1,4-dihydro-7-(3-hydroxy-1-azetidinyl)-4-
oxo-3-quinolinecarboxylate (salt).

FIGURE 2 shows a powder X-ray diffraction pattern of D-glucitol 1-(6-amino-3,5-
difluoro-2-pyridinyl)-8-chloro-6-fluoro-1,4-dihydro-7-(3-hydroxy-1-azetidinyl)-4-oxo-3-
quinoinecarboxylate trihydrate (salt).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides method for treating, preventing, or reducing the risk of
ophthalmic, otic, and/or nasal infections. With respect to these ophthalmic, otic, and/or nasal
infections, the present invention further relates to methods for treating methicillin resistant
*Staphylococcus aureus* infections, including both hospital-associated and community-
associated methicillin resistant *Staphylococcus Aureus* infections, and particularly
community-associated methicillin resistant *Staphylococcus aureus* infections, by topically
applying to a patient a safe and effective amount of an antibiotic, i.e. an antimicrobial,
compound.

1. **Definitions**

   The term "patient", as used herein, means the human or animal (in the case of an
   animal, more typically a mammal, a domestic animal, or a food animal) subject that would be
   considered to be in need of the methods of treating an ophthalmic, otic, or nasal infection.

   As used herein, the phrase "pharmaceutically acceptable" refers to those compounds,
   materials, compositions, carriers, and/or dosage forms which are, within the scope of sound
   medical judgment, suitable for use in contact with the tissues of human beings and animals
   without excessive toxicity, irritation, allergic response, or other problem or complication,
   commensurate with a reasonable benefit/risk ratio.

   The term "treating", as used herein, means to cure an already present ophthalmic, otic,
   or nasal infection in a patient or subject.

   The term "preventing", as used herein means, to completely or almost completely stop
   an ophthalmic, otic, or nasal infection from occurring in a patient or subject, especially when
   the patient or subject is predisposed to such. Preventing can also include inhibiting, i.e.
   arresting the development of, an ophthalmic, otic, or nasal infection.

   The term "reducing the risk of, as used herein, means to lower the likelihood or
   probability of an ophthalmic, otic, or nasal infection from occurring in a patient, especially
   when the patient or subject is predisposed to such occurrence.

   As used herein, the term "pharmaceutically effective amount" refers to an
   amount of a compound, or a combination of compounds, of the present invention effective
   when administered alone or in combination with other active ingredients to treat, prevent, or
   reduce the risk of an ophthalmic, otic, or nasal infection. For example, a pharmaceutically
effective amount refers to an amount of the compound present in a formulation or on a
medical device given to a recipient patient or subject sufficient to elicit biological activity.

   The term "prophylactically effective amount" means an effective amount of a compound, or a
combination of compounds, of the present invention that is administered to prevent or reduce the risk of an ophthalmic, otic, or nasal infection - in other words, an amount needed to provide a preventative or prophylactic effect.

The compounds can be given alone or in combination. The combination of compounds optionally is a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Adv. Enzyme Regul.* vol. 22, pp. 27-55 (1984), occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at sub-optimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased antiproliferative and/or anti-infective effect, or some other beneficial effect of the combination compared with the individual components.

The terms "caused or mediated by" means that the infection has some connection, relation, or etiology to the designated microorganism. "Caused by" means that the designated microorganism is at least partially, but may be fully, responsible for initiation of the infection. "Mediated by" means that the designated microorganism is at least partially, but may be fully, responsible for any worsening of the infection e.g., spread of the infection or increased severity.

Methicillin-resistant *Staphylococcus Aureus* (MRSA) is a type of bacteria that is resistant to certain antibiotics. These antibiotics include methicillin and other more common antibiotics such as oxacillin, penicillin and amoxicillin. Staphylococcus infections, also called staph infections, including MRSA, occur most frequently among persons in hospitals and healthcare facilities, such as nursing homes and dialysis centers, who have weakened immune systems. These types of staph infections are referred to as hospital-associated methicillin-resistant *Staphylococcus Aureus* (HA-MRSA) infections (it should be noted that this term "hospital-associated methicillin-resistant *Staphylococcus Aureus*" infections is supplanting the previously used term "hospital-acquired methicillin-resistant *Staphylococcus Aureus*" infections). However, in recent years there has been an increasing incidence of MRSA infections that are acquired by persons who have not been recently (within the past year) hospitalized or had a medical procedure (such as dialysis, surgery, catheters), which are known as community-associated methicillin-resistant *Staphylococcus Aureus* (CA-MRSA) infections (it should also be noted that this term "community-associated methicillin-resistant *Staphylococcus Aureus*" infections is supplanting the previously used term "community-acquired methicillin-resistant *Staphylococcus Aureus*" infections). Even though a distinction
is made for these lineages of hospital-associated and community-associated infections, it
should be recognized that these lineages are not necessarily distinct, because hospital-
associated infections can be found in the community and community-associated infections
can be found in the hospital. Nonlimiting examples of methicillin-resistant *Staphylococcus
Aureus* (MRSA) infections include both uncomplicated skin and soft tissue infections
(uncomplicated SSTIs), complicated skin and soft tissue infections (complicated SSTIs).
Uncomplicated SSTIs tend to be superficial and do not have other associated secondary sites
of infection, whereas complicated SSTIs are often more invasive and have often spread to
secondary sites or can be more systemic in nature. These infections can progress to
abscesses, sepsis, septic arthritis, septic thrombophlebitis, osteomyelitis, pneumonia, and
Waterhouse-Friderichsen syndrome (acute adrenal insufficiency due to massive hemorrhage
into the adrenal gland).

The terms "topical" and "topically" means that the antibiotic compounds of the
present invention can alternatively be administered or applied to the skin of the patient or
subject, or to other non-internal organs or parts of the patient or subject including, for
example, the hair, fur, feathers, scales, shells, eyes, ears, and nose, particularly the eyes, ears,
and nose.

With respect to the antimicrobial compounds useful in the present invention, the
following terms can be applicable, however, it should be kept in mind that more specific
definitions are also given in the references referred to and incorporated by reference herein:

The chemical compounds described herein can have asymmetric centers. Compounds
of the present invention containing an asymmetrically substituted atom can be isolated in
optically active or racemic forms. It is well known in the art how to prepare optically active
forms, such as by resolution of racemic forms or by synthesis from optically active starting
materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be
present in the compounds described herein, and all such stable isomers are contemplated in
the present invention. Cis and trans geometric isomers of the compounds of the present
invention are described and can be isolated as a mixture of isomers or as separated isomeric
forms. All chiral, diastereomeric, racemic, and geometric isomeric forms of a structure are
intended, unless the specific stereochemistry or isomeric form is specifically indicated. AU
processes used to prepare compounds of the present invention and intermediates made therein
are, where appropriate, considered to be part of the present invention. All tautomers of
shown or described compounds are also, where appropriate, considered to be part of the present invention.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent can be bonded to any atom in the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent can be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, N-methyl glutamic acid (i.e. the acid that would produce the D-gluconate salt), glycolic, glycollyarsanicil, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothentic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, e.g., glycine, alanine, phenylalanine, arginine, etc.

The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 18th ed. (Mack Publishing Company, 1990). For
example, salts can include, but are not limited to, the hydrochloride and acetate salts of the aliphatic amine-containing, hydroxyl amine-containing, and imine-containing compounds of the present invention.

Additionally, the compounds of the present invention, for example, the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Nonlimiting examples of hydrates include monohydrates, dihydrates, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc.

The compounds of the present invention can also be prepared as esters, for example pharmaceutically acceptable esters. For example a carboxylic acid function group in a compound can be converted to its corresponding ester, e.g., a methyl, ethyl, or other ester. Also, an alcohol group in a compound can be converted to its corresponding ester, e.g., an acetate, propionate, or other ester.

The compounds of the present invention can also be prepared as prodrugs, for example pharmaceutically acceptable prodrugs. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention can be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same.

"Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug of the present invention in vivo when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation, and as appropriate, purification from a reaction mixture, and formulation into an efficacious therapeutic agent.
In the specification, the singular forms also include the plural, unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In the case of conflict, the present specification will control.

All percentages and ratios used herein, unless otherwise indicated, are by weight.

Throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that compositions also consist essentially of, or consist of, the recited components. Similarly, where methods or processes are described as having, including, or comprising specific process steps, the processes also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions is immaterial so long as the invention remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

2. Methods of the Invention

The present invention provides a method treating, preventing or reducing the risk of a microbial ophthalmic, otic, or nasal infection in a patient or subject, said method comprising administering a therapeutically effective amount or a prophylactically effective amount of an antimicrobial compound to said patient or subject.

The present invention also provides a method of treating, preventing or reducing the risk of a microbial ophthalmic, otic, or nasal infection in a patient or subject having a surgical or invasive medical procedure, said method comprising administering a therapeutically effective amount or a prophylactically effective amount of an antimicrobial compound to said patient or subject prior to, during, or after said surgical or invasive medical procedure.

Ophthalmic, otic, and nasal microbial infections are a potentially serious risk for patients. It is found that the compounds and compositions of the present invention are useful for treating, preventing, or reducing the risk of or preventing these microbial infections.

The compounds and compositions of the methods of the present invention are usually administered by direct application to the eyes, ears, nose, or throat. However, the compounds and compositions can be administered by any of the common modes of administration, including, e.g., intravenous administration, oral administration, subcutaneous administration, parenteral administration, intramuscular administration, by inhalation, vaginal
administration, rectal administration, etc. Furthermore, the compounds used in the methods of the present invention are generally provided to the patient or subject by topical administration, including, but not limited to administration to the eyes, ears, throat, skin, hair, fur, feathers, scales, or gils.

With respect to these ophthalmic, otic, and nasal microbial infections, the present invention relates to methods for treating methicillin resistant *Staphylococcus aureus* infections, including both hospital-associated and community-associated methicillin resistant *Staphylococcus Aureus* infections, and particularly community-associated methicillin resistant *Staphylococcus aureus* infections, by topically applying to a patient in need thereof a safe and effective amount of an antibiotic compound.

With respect to these ophthalmic, otic, and nasal microbial infections, the present invention relates to methods for preventing methicillin resistant *Staphylococcus aureus* infections, including both hospital-associated and community-associated methicillin resistant *Staphylococcus Aureus* infections, and particularly community-associated methicillin resistant *Staphylococcus aureus* infections, by topically applying to a patient in need thereof a safe and effective amount of an antibiotic compound.

With respect to these ophthalmic, otic, and nasal microbial infections, the present invention relates to methods for reducing the risk of methicillin resistant *Staphylococcus aureus* infections, including both hospital-associated and community-associated methicillin resistant *Staphylococcus Aureus* infections, and particularly community-associated methicillin resistant *Staphylococcus aureus* infections, by topically applying to a patient in need thereof a safe and effective amount of an antibiotic compound.

As discussed above, methicillin resistant *Staphylococcus aureus* infections, including both hospital-associated and community-associated methicillin resistant *Staphylococcus Aureus* infections, and particularly community-associated methicillin resistant *Staphylococcus aureus* infections pose a risk for patients. It is been found that the antibiotic compounds of the present invention are useful for treating, preventing, or reducing the risk of these microbial infections. The methods of the present invention can be usefully applied to patients, whether human or animal.

In practicing the methods of the present invention, it is desired that the tissue level, or sometimes the blood level in the patient or subject, of the compound used to provide the effect be of an appropriate level for a sufficient time interval. Also, because it often takes a finite amount of time to achieve such blood or tissue levels, it is important that the compound
is administered at some appropriate time. The appropriate time for administration of the
compound will depend upon the pharmacokinetic profile of the compound and its
formulation, route of administration, time required for completing administration, patient
characteristics, desired clinical outcome, etc.

3. Compounds of the Invention

A wide range of antimicrobial compounds can be used in the methods, compositions,
and uses of the present invention. These antimicrobial compounds can provide their
therapeutic effect by a variety of biochemical or biophysical mechanisms. Compounds useful
in the present invention can include those which bind to or modulate ribosomal RNA, for
example bacterial ribosomal RNA. Compounds also useful in the present invention can
include those which bind to or modulate the large ribosomal subunit, for example the large
ribosomal subunit of a bacterial organism. Compounds also useful in the present invention
can include those which bind to or modulate DNA topoisomerases, for example bacterial
DNA topoisomerases. Compounds also useful in the present invention can include those
which bind to or modulate bacterial DNA gyrase, for example bacterial DNA gyrase, i.e.
gyrase being an example of a topoisomerase. Compounds also useful in the present invention
can include those which bind to or modulate bacterial topoisomerase IV.

Useful antimicrobial agents include antibacterial agents (i.e. antibiotic agents),
antifungal agents, anti-viral agents, and anti-parasitic agents. Useful chemical classes of
compounds include those selected from macrolides, ketolides, streptogramin As,
streptogramin Bs, chloramphenicol and chloramphenicol derivatives, fluorfenicol and
fluorfenicol derivatives, glycopeptides, pleuromutilins, aminoglycosides, beta-lactams and
carbapenems (including carbapenems with a 7-acylated imidazo[5-1, b]thiazole-2-yl group
directly attached to the carbapenem moiety of the C-2 position), cephalosporins,
linosamides, quinolones, fluoroquinolones, pyrindencarboxylic acid derivatives,
benzoheterocyclic compounds, aminomethylcycline compounds, dalbavancin, daptomycin,
garenoxacin, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, oritavancin,
oxazolidinones (e.g., linezolid and other oxazolidinones), televancin, and mixtures thereof. It
should be noted that compounds useful herein can in some instances be classified in more
than one way. The description or classification of a compound or compounds is not intended
to limit that compound or compounds, but is being done for the sake of convenience.
The compounds useful in the present invention can include the pharmaceutically acceptable salts, esters, or prodrugs thereof. The invention further provides methods for synthesizing any one of the compounds of the present invention. The invention also provides pharmaceutical compositions comprising an effective amount of one or more of the compounds of the present invention and a pharmaceutically acceptable carrier. The present invention further provides methods for making these pharmaceutical compositions.

a. Pyridone Carboxylic Acid Antimicrobial Agents

The compositions of the present invention comprise a pyridone carboxylic acid antimicrobial agent or a pharmaceutically acceptable salt, ester or prodrug thereof. A wide range of antimicrobial compounds can be used in the methods, compositions, and uses of the present invention. Especially useful herein are pyridonecarboxylic acid derivatives. The compounds useful in the present invention can include the pharmaceutically acceptable salts, esters, or prodrugs thereof. The invention further provides methods for synthesizing any one of the compounds of the present invention. The invention also provides pharmaceutical compositions comprising an effective amount of one or more of the compounds of the present invention and a pharmaceutically acceptable carrier. The present invention further provides methods for making these compounds, carriers, and pharmaceutical compositions.

Pyridonecarboxylic acid derivatives of the methods, compositions, and uses of the present invention include compounds corresponding to the following structure (Pyridonecarboxylic Acid Derivative 1)

Pyridonecarboxylic Acid Derivative 1

wherein $R^1$ represents a hydrogen atom or a carboxyl protective group; $R^2$ represents a hydroxyl group, a lower alkoxy group, or a substituted or unsubstituted amino group; $R^3$ represents a hydrogen atom or a halogen atom; $R^4$ represents a hydrogen atom or a halogen atom; $R^5$ represents a halogen atom or an optionally substituted saturated cyclic amino group; $R^6$ represents a hydrogen atom, a halogen atom, a nitro group, or an optionally protected amino group; $X$, $Y$ and $Z$ may be the same or different and respectively represent a nitrogen atom, CH or CR$^7$ (wherein $R^7$ represents a lower alkyl group, a halogen atom, or a cyano group), with the proviso that at least one of $X$, $Y$ and $Z$ represent a nitrogen atom, and $W$ represents a nitrogen atom or CR$^8$ (wherein $R^8$ represents a hydrogen atom, a halogen atom, or a lower alkyl group), and with the proviso that when $R^1$ represents a hydrogen atom, $R^2$ represents an amino group, $R^3$ and $R^4$ represent a fluorine atom, $R^6$ represents a hydrogen atom, $X$ represents a nitrogen atom, $Y$ represents CR$^7$ (wherein $R^7$ represents a fluorine atom), $Z$ represents CH, and $W$ is CR$^8$ (wherein $R^8$ represents a chlorine atom), then $R^5$ is not a 3-hydroxyazetidin-1-yl group; or a pharmaceutically acceptable salt, ester, or prodrug thereof.

As described in the foregoing paragraph, when $R^1$ is a carboxyl protective group, it may be any carboxylate ester residue which cleaves relatively easily to generate the corresponding free carboxyl group. Exemplary carboxyl protective groups include those which may be eliminated by hydrolysis, catalytic reduction, and other treatments under mild conditions such as lower alkyl groups such as methyl group, ethyl group, n-propyl group, i-
propyl group, n-butyl group, i-butyl group, t-butyl group, pentyl group, hexyl group, and heptyl group; lower alkenyl groups such as vinyl group, allyl group, 1-propenyl group, butenyl group, pentenyl group, hexenyl group, and heptenyl group; aralkyl groups such as benzyl group; and aryl groups such as phenyl group and naphthyl group; and those which may be readily eliminated in the body such as lower alkanoyloxy lower alkyl groups such as acetoxyethyl group and pivaloyloxymethyl group; lower alkoxy carbonyloxy lower alkyl group such as methoxycarbonyloxymethyl group and 1-ethoxycarbonyloxymethyl group; lower alkoxy methyl group such as methoxymethyl group; lactonyl group such as phthalidyl; di-lower alkylamino lower alkyl group such as 1-dimethylaminoethyl group; and (5-methyl-2-oxo-1,3-dioxole-4-yl)methyl group.

It is noted that the substituents R₁, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, A, J₁, J₂, J₃, W, X, Y, Z, e, f, and g are defined herein for convenience with respect to the chemical structure for the pyridonecarboxylic acid derivatives.

In other embodiments, the present invention relates to a method, composition, or use for a pyridonecarboxylic acid derivative of structure Pyridonecarboxylic Acid Derivative 1, wherein W is CR⁸, wherein R⁸ represents a hydrogen atom, a halogen atom, or a lower alkyl group.

In other embodiments, the present invention relates to a method, composition, or use for a pyridonecarboxylic acid derivative of structure Pyridonecarboxylic Acid Derivative 1, wherein R⁵ is a group represented by the following formula (a) or (b):

(a)

(b)

wherein A represents an oxygen atom, sulfur atom or NR⁹ (wherein R⁹ represents hydrogen atom or a lower alkyl group), e represents a number from 3 to 5, f represents a number from 1
to 3, g represents a number from 0 to 2, $J^1$, $J^2$ and $J^3$, which may be the same or different from
one another, represent a hydrogen atom, hydroxyl group, lower alkyl group, amino lower
alkyl group, amino group, lower alkylamino group, lower alkoxy group, or a halogen atom.

In other embodiments, the present invention relates to a method, composition, or use
for a pyridonecarboxylic acid derivative of structure Pyridonecarboxylic Acid Derivative 1.
wherein R$^5$ is a group represented by formula (a).

(a)

In other embodiments, the present invention relates to a method, composition, or use
for a pyridonecarboxylic acid derivative of structure Pyridonecarboxylic Acid Derivative 1.
wherein e in the formula (a) is 3 or 4.

(a)

In other embodiments, the present invention relates to a method, composition, or use
for a pyridonecarboxylic acid derivative of structure Pyridonecarboxylic Acid Derivative 1.
wherein R$^1$ is a hydrogen atom; R$^2$ is an amino group, lower alkylamino group, or a di-lower
alkylamino group; R$^3$ is a halogen atom; R$^4$ is a halogen atom; R$^6$ is hydrogen atom; X is a
nitrogen atom; Y and Z are CH or CR$^7$ (wherein R$^7$ is a lower alkyl group or a halogen atom);
and W is CR$^8$ (wherein R$^8$ is a halogen atom or a lower alkyl group).

In other embodiments, the present invention relates to a method, composition, or use
for a pyridonecarboxylic acid derivative of structure Pyridonecarboxylic Acid Derivative 1.
wherein R$^2$ is amino group; R$^3$ is fluorine atom; R$^4$ is a fluorine atom; Y is CF; Z is CH; W is
CR$^8$ (wherein R$^8$ is a chlorine atom, bromine atom or a methyl group), and e in formula (a) is
3.
In other embodiments, the present invention relates to a method, composition, or use wherein said pyridonecarboxylic acid corresponds to the following structure:

![Chemical Structure]

or a pharmaceutically acceptable salt, ester, or prodrug thereof. This foregoing pyridonecarboxylic acid is also known by the publicly disclosed code names ABT-492 and WQ 3034 and also by the chemical name l-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6-fluoro-1,4-dihydro-7-(3'-hydroxy-1-azetidinyl)-4-oxo-3-quinolinecarboxylic acid or l-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6-fluoro-1,4-dihydro-7-(3'-hydroxyazetidin-1-yl)-4-oxo-3-quinolinecarboxylic acid. This carboxylic acid form of the compound corresponds to the CAS registry number 189279-58-1. Furthermore, WO 2006/042034, cited above discloses the D-glucitol salt of this compound [D-glucitol l-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6-fluoro-1,4-dihydro-7-(3'-hydroxy-1-azetidinyl)-4-oxo-3-quinolinecarboxylate (salt)] and the trihydrate of the D-glucitol salt of this compound [D-glucitol l-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6-fluoro-1,4-dihydro-7-(3'-hydroxy-1-azetidinyl)-4-oxo-3-quinolinecarboxylate trihydrate (salt)]. The D-glucitol salt and the D-glucitol salt trihydrate correspond to the CAS registry numbers 352458-37-8 and 883105-02-0, respectively. D-glucitol corresponds to the CAS registry number 6284-40-8. WO 2006/042034 also discloses a crystalline form of the D-glucitol salt characterized when measured at about 25 °C with Cu-Ka radiation, by the powder diffraction pattern shown in FIGURE 1 (see WO 2006/042034).
and a crystalline form of the D-glucitol salt trihydrate when measured at about 25 °C with Cu-Kα radiation, by the powder diffraction pattern shown in FIGURE 2 (see WO 2006/042034). These D-glucitol salts are useful in the present invention. Also, see A.R. Haight et al., "Synthesis of the Quinolone ABT-492: Crystallizations for Optimal Processing". Organic Process Research & Development (2006), 10(4), 751-756.

b. Benzoheterocyclic Compounds

Benzoheterocyclic compounds useful herein are described, including their synthesis, formulation, and use, in U.S. Patent No. 6,753,333 B2, to De Souza et al., issued June 22, 2004; U.S. Patent No. 6,750,224 Bl, to Patel et al., issued June 15, 2004 and its certificate of correction of November 2, 2004; U.S. Patent No. 6,664,267 Bl, to de Souza et al., issued December 16, 2003; U.S. Patent No. 6,608,078 B2, to De Souza et al., issued August 19, 2003; U.S. Patent No. 6,514,986 B2 to De Souza et al., issued February 4, 2003; U.S. Patent No. 4,552,879 to Ishikawa et al., issued November 12, 1985; and U.S. Patent No. 4,399,134 to Ishikawa et al., issued August 16, 1983.

Benzoheterocyclic compounds of the methods, compositions, and uses of the present invention include compounds corresponding to the following structure (Benzoheterocyclic Compound I)

Benzoheterocyclic compound I

wherein R¹ represents a hydrogen atom or a lower alkyl group; R² represents a hydrogen atom or a halogen atom; R³ represents a 1-pyrrolidinyl group which may be substituted with a hydroxymethyl group, a 1,2,5,6-tetrahydro-1-pyridyl group, or a group of the formula

\[
\text{结构式}
\]
where $R^4$ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a hydroxy group, a phenyl-lower alkyl group, a lower alkanoyloxy group, an amino group which may be substituted with a lower alkyl group or a lower alkanoyl group, an oxo group, or a carbamoyl group; $Z$ represents an oxygen atom, a sulfur atom or a methylene group; and $m$ is 1 or 2; and $n$ is an integer of 1 or 2; or a pharmaceutically acceptable salt ester or prodrug thereof.

It is noted that the substituents $R^1, R^2, R^3, R^4, Z, m, n$ are defined herein for convenience with respect to the chemical structure for the benzoheterocyclic compounds, e.g., benzoheterocyclic compound (I) and do not refer to other substituents for other compounds of the present invention.

In other embodiments, the present invention relates to a method, composition, or use for a benzoheterocyclic of structure Benzoheterocyclic Compound I, wherein $n$ is 2.

In other embodiments, the present invention relates to a method, composition, or use for a benzoheterocyclic of structure Benzoheterocyclic Compound I, wherein $n$ is 1.

In other embodiments, the present invention relates to a method, composition, or use for a benzoheterocyclic of structure Benzoheterocyclic Compound I, wherein $R^3$ represents a group of the formula

\[ \text{N} \quad \text{Z} \quad (R^4)_m \]

where $R^4$ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a hydroxy group, a phenyl-lower alkyl group, a lower alkanoyloxy group, an amino group which may be substituted with a lower alkyl group or a lower alkanoyl group, an oxo group, or a carbamoyl group; $Z$ represents an oxygen atom, a sulfur atom or a methylene group; and $m$ is 1 or 2; and $n$ is 1.

In other embodiments, the present invention relates to a method, composition, or use for a benzoheterocyclic of structure Benzoheterocyclic Compound I, wherein $R^3$ represents a 1-pyrrolidinyl group which may be substituted with a hydroxymethyl group or a 1,2,5,6-tetrahydro-1-pyridyl group.

In other embodiments, the present invention relates to a method, composition, or use for a benzoheterocyclic of structure Benzoheterocyclic Compound I, wherein $R^4$ represents a hydrogen atom, a hydroxy group or a lower alkanoyloxy group and the position at which the group of the formula
where $R^4$ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a hydroxy group, a phenyl-lower alkyl group, a lower alkanoyloxy group, an amino group which may be substituted with a lower alkyl group or a lower alkanoyl group, an oxo group, or a carbamoyl group; $Z$ represents an oxygen atom, a sulfur atom or a methylene group; and $m$ is 1 or 2; and $n$ is 1, is attached is the 8-position.

In other embodiments, the present invention relates to a method, composition, or use for a benzoheterocyclic of structure Benzoheterocyclic Compound I, wherein $R^4$ represents a lower alkyl group, a lower alkoxy group, a phenyl-lower alkyl group, an amino group which may be substituted with a lower alkyl group or a lower alkanoyl group, an oxo group, a carbamoyl group, and the position at which the group of the formula

$$\text{N} \quad z \quad (R^4)_m$$

where $R^4$ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a hydroxy group, a phenyl-lower alkyl group, a lower alkanoyloxy group, an amino group which may be substituted with a lower alkyl group or a lower alkanoyl group, an oxo group, or a carbamoyl group; $Z$ represents an oxygen atom, a sulfur atom or a methylene group; and $m$ is 1 or 2; and $n$ is 1, is attached is the 8-position.

In other embodiments, the present invention relates to a method, composition, or use for a benzoheterocyclic of structure Benzoheterocyclic Compound I, wherein $R^2$ represents a halogen atom.

In other embodiments, the present invention relates to a method, composition, or use for a benzoheterocyclic of structure Benzoheterocyclic Compound I, wherein $R^2$ represents a hydrogen atom.

In other embodiments, the present invention relates to a method, composition, or use for a benzoheterocyclic of structure Benzoheterocyclic Compound I, wherein $R^2$ represents a fluorine atom and the position at which the fluorine atom is attached is the 9-position.
In other embodiments, the present invention relates to a method, composition, or use for a benzoheterocyclic of structure Benzoheterocyclic Compound I, wherein \( R^2 \) represents a chlorine atom and the position at which the fluorine atom is attached is the 9-position.

In other embodiments, the present invention relates to a method, composition, or use for a benzoheterocyclic of structure Benzoheterocyclic Compound I, wherein \( R^1 \) represents a lower alkyl group.

In other embodiments, the present invention relates to a method, composition, or use for a benzoheterocyclic of structure Benzoheterocyclic Compound I, wherein \( R^1 \) represents a methyl group.

In other embodiments, the present invention relates to a method, composition, or use for a benzoheterocyclic of structure Benzoheterocyclic Compound I, wherein \( R^2 \) represents a fluorine atom attached to the 9-position and \( R^1 \) represents a methyl group.

In other embodiments, the present invention relates to a method, composition, or use for a benzoheterocyclic of structure Benzoheterocyclic Compound I, wherein \( R^1 \) represents a methyl group, \( R^2 \) represents a fluorine atom attached to the 9-position and the position at which the group represented by \( R^3 \) is attached is the 8-position.

In other embodiments, the present invention relates to a method, composition, or use for a benzoheterocyclic of structure Benzoheterocyclic Compound I, wherein the position at which \( R^3 \) is attached is the 9-position.

In other embodiments, the present invention relates to a method, composition, or use for a benzoheterocyclic of structure Benzoheterocyclic Compound I, wherein \( R^1 \) represents a methyl group, \( R^2 \) represents a fluorine atom attached to the 8-position.

In other embodiments, the present invention relates to a method, composition, or use for a benzoheterocyclic of structure Benzoheterocyclic Compound I, wherein \( R^1 \) represents a methyl group, \( R^2 \) represents a chlorine atom attached to the 8-position.

In other embodiments, the present invention relates to a method, composition, or use wherein said benzoheterocyclic compound is 9-fluoro-8-(4-hydroxy-1-piperidyl)-5-methyl-6,7-dihydro-l-oxo-lH,5H-benzo[ij]quinolizine-2-carboxylic acid or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In other embodiments, the present invention relates to a method, composition, or use wherein said benzoheterocyclic compound is S(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-l-oxo-lH,5H-benzo[ij]quinolizine-2-carboxylic acid or a pharmaceutically acceptable salt, ester, or prodrug thereof. The foregoing compound is also known by the chemical name nadifloxacin.
In other embodiments, the present invention relates to a method, composition, or use where said benzoheterocyclic compound is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[ij]quinolizine-2-carboxylic acid arginine salt.

In other embodiments, the present invention relates to a method, composition, or use wherein said benzoheterocyclic compound is a specific polymorph or crystalline form of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[ij]quinolizine-2-carboxylic acid arginine salt having the following X-ray diffraction data: (2\(\Theta\)) 10.16, 11.78, 12.52, 16.00, 18.94, 19.66, 20.36, 21.28, 21.92, 22.52, 24.74, 25.28, 30.74.

In other embodiments, the present invention relates to a method, composition, or use wherein said benzoheterocyclic compound is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[ij]quinolizine-2-carboxylic acid arginine salt having the following X-ray diffraction data: (2\(\Theta\)) 18.28, 18.8, 19.8, 20.12, 20.62, 21.10, 21.44, 21.88, 22.6, 23.02.

In other embodiments, the present invention relates to a method, composition, or use wherein said benzoheterocyclic compound is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[ij]quinolizine-2-carboxylic acid arginine salt having the following X-ray diffraction data: (20) 14.02+0.2, 14.82+0.2, 19.28+0.2, 22.12+0.2, 22.96+0.2, 23.46+0.2, 28.36+0.2.

With respect to specific polymorph or crystalline forms of the benzoheterocyclic compounds, examples being the arginine salts, a publicly disclosed code name for such a compound is WCK 771.

c. Beta-Lactams

Beta-lactams, for example carbapenems, examples of which are carbapenems with a 7-acylated imidazo[5-1, b]thiazole-2-yl group directly attached to the carbapenem moiety of the C-2 position, useful herein are described, including their synthesis, formulation, and use, in M. Kurazano et al., "In Vitro Activities of ME1036 (CP5609), a Novel Parenteral Carbapenem, Against Methicillin-Resistant Staphylococci", Antimicrobial Agents and Chemotherapy, vol. 48, no. 8, pp. 2831-2837 (August 2004); U.S. Patent Application Publication No. US 2004/0038967 A1, to Kano et al., published February 26, 2004; PCT
Beta-lactam compounds of the methods, compositions, and uses of the present invention include compounds corresponding to the following structure (Beta-Lactam I)

![Beta-Lactam I](image)

wherein \( R^1 \) represents a hydrogen atom or methyl, \( R^2 \) and \( R^3 \), which may be the same or different, each represent a hydrogen atom; a halogen atom; lower alkyl optionally substituted by a halogen atom, cyano, hydroxyl, carbamoyl, amino, formylamino, lower alkylcarbonylamino, aminosulfonlamino, lower alkylthio, lower alkoxy, lower cycloalkyl, N,N-di-lower alkylamino, or N-carbamoyl lower alkyl-N,N-di-lower alkylammonino; lower cycloalkyl; lower alkylcarbonyl wherein the alkyl portion of lower alkylcarbonyl is optionally substituted by a halogen atom, cyano, hydroxyl, carbamoyl, amino, formylamino, lower alkylcarbonylamino, aminosulfonlamino, lower alkylthio, lower alkoxy, lower cycloalkyl, N,N-di-lower alkylamino, or N-carbamoyl lower alkyl-N,N-di-lower alkylammonino; carbamoyl; aryl optionally substituted by amino optionally substituted by one or two lower alkyl groups; lower alkylthio wherein the alkyl portion of lower alkylthio is optionally substituted by amino, hydroxyl, azide, a halogen atom, cyano, carbamoyl, formylamino, lower alkylcarbonylamino, aminosulfonlamino, or lower alkylthio; morpholinyl; lower alkylsulfonyl; or formyl; \( n \) is an integer of 0 to 4, and \( H_y \) represents a four- to seven-membered monocyclic or nine- or ten-membered bicyclic saturated or unsaturated heterocyclic group having one to four hetero-atoms selected from nitrogen, oxygen, and sulfur atoms, the saturated or unsaturated heterocyclic group represented by \( H_y \) is optionally substituted by a halogen atom; cyano; lower alkyl wherein one or more hydrogen atoms on the lower alkyl group are optionally substituted by groups selected from a halogen atom; hydroxyl; carbamoyl; carboxylmethyl-substituted carbamoyl; amino; N,N-di-lower alkylamino; aryl optionally substituted by amino; a monocyclic or bicyclic heterocyclic group containing one or more hetero-atoms selected from nitrogen, oxygen, and sulfur atoms, optionally substituted by aminosulfonyl or carboxyl; carboxyl; imino; lower alkoxy carbonyl;
lower alkylcarbonyl; aminosulfonlamino; amino lower alkylthio; lower alkylsulfonyl; (N,N-di-lower alkylamino)sulfonlamino; N’-(N,N-di-lower alkylamino)sulfonyl-N’-lower alkylamino; halogenated lower alkylcarbonyl; N-aminosulfonylpiperidiny1; and cyano; lower alkylthio wherein one or more hydrogen atoms on the alkyl group are optionally substituted by a group selected from a halogen atom, hydroxyl, carbamoyl, amino, and aryl; lower alkylsulfonyl wherein one or more hydrogen atoms on the alkyl group are optionally substituted by a group selected from a halogen atom, hydroxyl, carbamoyl, amino, 1-iminoethylamino, and aryl; hydroxyl; lower alkoxy; hydroxaminophenyl-substituted lower alkoxy; halogenated lower alkoxy; aminophenyl-substituted lower alkoxy; formyl; lower alkylcarbonyl; arylecarbony1; carboxyl; lower alkoxy carbonyl; carbamoyl; N-lower alkyl carbamoyl; N,N-di-lower alkylaminocarbonyl; amino; N-lower alkylamino; N,N-di-lower alkylamino; formylamino; lower alkylcarbonylamino; aminosulfonlamino; (N-lower alkylamino)sulfonylamin0- ; (N,N-di-lower alkylamino)sulfonylamino; aryl; or a monocyclic or bicyclic heterocyclic group containing one or more hetero-atoms selected from nitrogen, oxygen, and sulfur atoms, optionally substituted by aminosulfonyl or carboxyl, or a pharmaceutically acceptable salt, ester, or pro-drug thereof.

It is noted that the substituents R^1, R^2, R^3, Hy, and n are defined herein for convenience with respect to the chemical structure for the beta-lactams or carbapenems, e.g., Beta-Lactam I and Beta-Lactam II, and do not refer to other substituents for other compounds of the present invention.

In other embodiments, the present invention relates to a method, composition, or use for a beta-lactam of structure Beta-Lactam I, wherein R^1 represents a hydrogen atom or methyl, R^2 and R^3, which may be the same or different, each represent a hydrogen atom; a halogen atom; lower alkyl optionally substituted by a halogen atom, cyano, hydroxyl, carbamoyl, amino, formylamino, lower alkylcarbonylamino, aminosulfonlamino, or lower alkylthio; lower alkylcarbonyl wherein the alkyl portion of lower alkylcarbonyl is optionally substituted by a halogen atom, cyano, hydroxyl, carbamoyl, amino, formylamino, lower alkyl carbonylamino, aminosulfonlamino, or lower alkylthio; carbamoyl; aryl; or lower alkylthio wherein the alkyl portion of lower alkylthio is optionally substituted by a halogen atom, cyano, hydroxyl, carbamoyl, amino, formylamino, lower alkylcarbonylamino, aminosulfonlamino, or lower alkylthio, n is an integer of 0 to 4, and Hy represents a four- to seven-membered monocyclic or nine- or ten-membered bicyclic saturated or unsaturated heterocyclic group containing one to four hetero-atoms selected from nitrogen, oxygen, and sulfur atoms, the saturated or unsaturated heterocyclic group represented by Hy is optionally
substituted by a halogen atom; cyano; lower alkyl wherein one or more hydrogen atoms on
the lower alkyl group are optionally substituted by groups selected from a halogen atom,
hydroxyl, carbamoyl, amino, aryl, and a monocyclic or bicyclic heterocyclic group containing
one or more hetero-atoms selected from nitrogen, oxygen, and sulfur atoms; lower alkylthio
wherein one or more hydrogen atoms on the alkyl group are optionally substituted by groups
selected from a halogen atom, hydroxyl, carbamoyl, amino, and aryl; lower alkylsulfonyl
wherein one or more hydrogen atoms on the alkyl group are optionally substituted by groups
selected from a halogen atom, hydroxyl, carbamoyl, amino, and aryl; hydroxyl; lower alkoxy;
formyl; lower alkylcarbonyl; arylcarbonyl; carboxyl; lower alkoxy carbonyl; carbamoyl; N-
lower alkyl carbamoyl; N,N-di-lower alkylaminocarbonyl; amino; N-lower alkyl amino; N,N-di-
lower alkylamino; formyl amine; lower alkylcarbonylamino; aminosulfonylamino; (N-
lower alkylamino)sulfonylamino; (N,N-di-lower alkylamino)sulfonylamino; aryl; or a
monocyclic or bicyclic heterocyclic group containing one or more hetero-atoms selected from
nitrogen, oxygen, and sulfur atoms.

In other embodiments, the present invention relates to a method, composition, or use
of a beta-lactam of structure Beta-Lactam I wherein R¹ represents a hydrogen atom or methyl,
R² and R³, which may be the same or different, each represent a hydrogen atom, a halogen
atom, optionally substituted lower alkyl, lower cycloalkyl, lower alkyl carbonyl, carbamoyl,
only optionally substituted aryl, optionally substituted lower alkylthio, morpholinyl, lower
alkyl sulfonyl, or formyl, n is an integer of 0 to 2, and Hy represents a group selected from
optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted
tetrahydro pyridinyl, optionally substituted thiazolyl, optionally substituted pyrimidinyl,
only optionally substituted thienyl, optionally substituted quinolinyl, optionally substituted
quinolinium-yl, optionally substituted isoquinolinyl, optionally substituted
dihydro isoquinolinyl, optionally substituted piperazinyl, optionally substituted piperidinyl,
only optionally substituted indolyl, optionally substituted thiomorpholinyl, optionally substituted
imidazolyl, and optionally substituted pyrrolidinyl.

In other embodiments, the present invention relates to a method, composition, or use
of a beta-lactam of structure Beta-Lactam I wherein R¹ represents a hydrogen atom or methyl,
R² and R³, which may be the same or different, each represent a hydrogen atom, a halogen
atom, optionally substituted lower alkyl, optionally substituted lower alkyl carbonyl,
carbamoyl, aryl, or optionally substituted lower alkylthio, n is an integer of 0 to 4, and Hy
represents a group selected from optionally substituted pyridinyl, optionally substituted
pyridinyl, optionally substituted tetrahydro pyridinyl, optionally substituted thiazolyl,
optionally substituted pyrimidinyl, optionally substituted thienyl, optionally substituted quinolinyl, optionally substituted quinolinium-yl, and optionally substituted pyrrolidinyl.

In other embodiments, the present invention relates to Beta-lactam compounds of the methods, compositions, and uses of the present invention include compounds corresponding to the following structure (Beta-Lactam II)

Wherein $R^1$ represents a hydrogen atom or methyl, $R^2$ and $R^3$, which may be the same or different, each represent a hydrogen atom; a halogen atom; lower alkyl optionally substituted by a halogen atom, cyano, hydroxyl, carbamoyl, amino, formylamino, lower alkylcarbonylamino, aminosulfonlamino, lower alkylthio, lower alkoxyl, lower cycloalkyl, N,N-di-lower alkylamino, or N-carbamoyl lower alkyl-N,N-di-lower alkylammonio; lower cycloalkyl; lower alkylcarbonyl wherein the alkyl portion of lower alkylcarbonyl is optionally substituted by a halogen atom, cyano, hydroxyl, carbamoyl, amino, formylamino, lower alkylcarbonylamino, aminosulfonlamino, lower alkylthio, lower alkoxyl, lower cycloalkyl, N,N-di-lower alkylamino, or N-carbamoyl lower alkyl-N,N-di-lower alkylammonio; carbamoyl; aryl optionally substituted by amino optionally substituted by one or two lower alkyl groups; lower alkylthio wherein the alkyl portion of lower alkylthio is optionally substituted by amino, hydroxyl, azide, a halogen atom, cyano, carbamoyl, formylamino, lower alkylcarbonylamino, aminosulfonlamino, or lower alkylthio; morpholinyl; lower alkylsulfonyl; or formyl; $n$ is an integer of 0 to 4, and $H_y$ represents a four- to seven-membered monocyclic or nine- or ten-membered bicyclic saturated or unsaturated heterocyclic group having one to four hetero-atoms selected from nitrogen, oxygen, and sulfur atoms, the saturated or unsaturated heterocyclic group represented by $H_y$ is optionally substituted by a halogen atom; cyano; lower alkyl wherein one or more hydrogen atoms on the lower alkyl group are optionally substituted by groups selected from a halogen atom; hydroxyl; carbamoyl; carboxymethyl-substituted carbamoyl; amino; N,N-di-lower alkylamino; aryl optionally substituted by amino; a monocyclic or bicyclic heterocyclic group containing one or more hetero-atoms selected from nitrogen, oxygen, and sulfur atoms,
optionally substituted by aminosulfonyl or carboxyl; carboxyl; imino; lower alkoxy carbonyl; lower alkylcarbonyl; aminosulfonylamino; amino lower alkylthio; lower alkylsulfonyl; (N,N-di-lower alkylamino)sulfonylamino; N’-(N,N-di-lower alkylamino)sulfonyl-N’-lower alkylamino; halogenated lower alkylcarbonyl; N-aminosulfonylpiperidinyl; and cyano; lower alkylthio wherein one or more hydrogen atoms on the alkyl group are optionally substituted by a group selected from a halogen atom, hydroxyl, carbamoyl, amino, and aryl; lower alkylsulfonyl wherein one or more hydrogen atoms on the alkyl group are optionally substituted by a group selected from a halogen atom, hydroxyl, carbamoyl, amino, 1-iminoethylamino, and aryl; hydroxyl; lower alkoxyl; hydroxyaminophenyl-substituted lower alkoxy; halogenated lower alkoxy; aminophenyl-substituted lower alkoxy; formyl; lower alkylcarbonyl; arylcarbonyl; carboxyl; lower alkoxy carbonyl; carbamoyl; N-lower alkylcarbamoyl; N,N-di-lower alkylaminocarbonyl; amino; N-lower alkylaminocarbonyl; N,N-di-lower alkylaminoformyl; lower alkylcarbonylamino; aminosulfonylamino; (N-lower alkylamino)sulfonylamino- ; (N,N-di-lower alkylamino)sulfonylamino; aryl; or a monocyclic or bicyclic heterocyclic group containing one or more hetero-atoms selected from nitrogen, oxygen, and sulfur atoms, optionally substituted by aminosulfonyl or carbonyl, or a pharmaceutically acceptable salt, ester, or pro-drug thereof.

In other embodiments, the present invention relates to a method, composition, or use of a beta-lactam of structure Beta-Lactam II, wherein R₁ represents a hydrogen atom or methyl, R² and R³, which may be the same or different, each represent a hydrogen atom, a halogen atom, lower alkyl optionally substituted by a halogen atom, cyano, hydroxyl, carbamoyl, amino, formylamino, lower alkylcarbonylamino, aminosulfonylamino, or lower alkylthio; lower alkylcarbonyl wherein the alkyl portion of lower alkylcarbonyl is optionally substituted by a halogen atom, cyano, hydroxyl, carbamoyl, amino, formylamino, lower alkylcarbonylamino, aminosulfonylamino, or lower alkylthio; carbamoyl; aryl; or lower alkylthio wherein the alkyl portion of lower alkylthio is optionally substituted by a halogen atom, cyano, hydroxyl, carbamoyl, amino, formylamino, lower alkylcarbonylamino, aminosulfonylamino, or lower alkylthio, n is an integer of 0 to 4, and Hy represents a four- to seven-membered monocyclic or nine- or ten-membered bicyclic saturated or unsaturated heterocyclic group containing one to four hetero-atoms selected from nitrogen, oxygen, and sulfur atoms, the saturated or unsaturated heterocyclic group represented by Hy is optionally substituted by a halogen atom; cyano; lower alkyl wherein one or more hydrogen atoms on the lower alkyl group are optionally substituted by groups selected from a halogen atom, hydroxyl, carbamoyl, amino, aryl, and a monocyclic or bicyclic heterocyclic group.
containing one or more hetero-atoms selected from nitrogen, oxygen, and sulfur atoms; lower alkylthio wherein one or more hydrogen atoms on the alkyl group are optionally substituted by groups selected from a halogen atom, hydroxyl, carbamoyl, amino, and aryl; lower alkylsulfonyl wherein one or more hydrogen atoms on the alkyl group are optionally substituted by groups selected from a halogen atom, hydroxyl, carbamoyl, amino, and aryl; hydroxyl; lower alkoxy; formyl; lower alkylcarbonyl; arylcarbonyl; carboxyl; lower alkoxy carbonyl; carbamoyl; N-lower alkyl carbamoyl; N,N-di-lower alkylaminocarbonyl; amino; N-lower alkylamino; N,N-di-lower alkylamino; formylamino; lower alkylcarbonylamino; aminosulfonylamino; (N-lower alkylamino)sulfonylamino; (N,N-di-lower alkylamino)sulfonylamino; aryl; or a monocyclic or bicyclic heterocyclic group containing one or more hetero-atoms selected from nitrogen, oxygen, and sulfur atoms.

In other embodiments, the present invention relates to a method, composition, or use of a beta-lactam of structure Beta-Lactam I or Beta-Lactam II, wherein the substituent on the lower alkyl and lower alkylcarbonyl groups optionally represented by R² and R³ is hydroxyl, lower alkoxy, N,N-di-lower alkylamino, or N-carbamoyl lower alkyl-N,N-di-lower alkylammonino, the substituent on the aryl group optionally represented by R² and R³ is N,N-di-lower alkylamino, the substituent on the lower alkylthio group optionally represented by R² and R³ is amino, hydroxyl, or azide, and the substituent on the saturated or unsaturated heterocyclic ring represented by Hy is lower alkyl optionally substituted by carboxylmethyl-substituted carbamoyl, carbamoyl, phenyl, aminophenyl, N,N-di-lower alkylamino, amino, hydroxyl, morpholinyl, pyrrolidinyl, carboxyl, imino, amino lower alkylthio, lower alkoxy carbonyl, lower alkyl carbonyl, aminosulfonylamino, piperidinyl, lower alkylsulfonyl, (N,N-di-lower alkylamino)sulfonylamino, N'-(N,N-di-lower alkylamino)sulfonyl-N'-lower alkylamino, halogenated lower alkylcarbonyl, N-aminosulfonyl piperidinyl, or cyano; carbamoyl; pyridinyl; N-aminosulfonylpyrrolidinyl; 2-carboxy pyrrolidinyl; phenyl; hydroxyl; lower alkoxy; hydroxyaminophenyl-substituted lower alkoxy; halogenated lower alkoxy; aminophenyl-substituted lower alkoxy; amino; carboxyl; lower alkylthio optionally substituted by amino; amino lower alkylthio; amino lower alkylsulfonyl; or 1-iminoethylamino lower alkylsulfonyl.

In other embodiments, the present invention relates to a method, composition, or use of a beta-lactam of structure Beta-Lactam I or Beta-Lactam II, wherein R¹ represents a hydrogen atom or methyl, R² and R³ represent a hydrogen atom, n is 0 (zero), and Hy represents pyridinium-yl having carbamoylmethyl at its 1-position.

In other embodiments, the present invention relates to a method, composition, or use
of a beta-lactam of structure Beta-Lactam I or Beta-Lactam II, wherein n is 0 (zero).

In other embodiments, the present invention relates to a method, composition, or use of a beta-lactam of structure Beta-Lactam I or Beta-Lactam II, wherein R1 represents methyl, and R2 and R3 represent a hydrogen atom.

In other embodiments, the present invention relates to a method, composition, or use of a beta-lactam of structure Beta-Lactam I or Beta-Lactam II, wherein R1 represents methyl, R2 and R3 represent a hydrogen atom, n is 0 (zero), and Hy represents pyridinium-3-yl which optionally has carbamoyl lower alkyl, carboxyl lower alkyl, or aminosulfonylamino lower alkyl at its 1-position and amino lower alkylthio at other position than the 1-position.

In other embodiments, the present invention relates to a method, composition, or use of a beta-lactam of structure Beta-Lactam I or Beta-Lactam II, wherein R1 represents methyl, R2 and R3 represent a hydrogen atom, n is 0 (zero), and Hy represents pyridin-3-yl.

In other embodiments, the present invention relates to a method, composition, or use of a beta-lactam of structure Beta-Lactam I or Beta-Lactam II, wherein R1, R2 and R3 represent a hydrogen atom, n is 0 (zero), and Hy represents 1-carbamoylmethylpyridinium-3-yl.

In other embodiments, the present invention relates to a method, composition, or use of a beta-lactam of structure Beta-Lactam I or Beta-Lactam II, wherein R1, R2 and R3 represent a hydrogen atom, n is 0 (zero), and Hy represents 1-carbamoylmethyl-5-phenylpyridinium-3-yl.

In other embodiments, the present invention relates to a method, composition, or use of a beta-lactam of structure Beta-Lactam I or Beta-Lactam II, wherein R1 represents methyl, R2 and R3 represent a hydrogen atom, n is 0 (zero), and Hy represents (2S)-pyrrolidin-2-yl.

In other embodiments, the present invention relates to a method, composition, or use of a beta-lactam of structure Beta-Lactam I or Beta-Lactam II, wherein R1 represents methyl, R2 and R3 represent a hydrogen atom, n is 0 (zero), and Hy represents 1-carboxymethylpyridinium-3-yl.

In other embodiments, the present invention relates to a method, composition, or use of a beta-lactam of structure Beta-Lactam I or Beta-Lactam II, wherein R1 represents methyl,
R² and R³ represent a hydrogen atom, n is 0 (zero), and H_y represents 1-(2-aminosulfonylaminoethyl)pyridinium-3-yl.

In other embodiments, the present invention relates to a method, composition, or use wherein said beta-lactam or carbapenem corresponds to the following structure:

![Chemical structure image]

or a pharmaceutically acceptable salt, ester, or prodrug thereof. This foregoing beta-lactam or carbapenem is also known by the publicly disclosed code names ME1036 and CP5609.

d. Aminomethylcycline Compounds


e. Dalbavancin


f. Daptomycin

Daptomycin and its pharmaceutically acceptable salts, esters, and prodrugs thereof, can be used in the methods, compositions, and uses of the present invention. Daptomycin is sold under the tradename or proprietary Cubicin. See U.S. Patent No. 6,852,689 B2, to Oleson, Jr. et al., issued February 8, 2005; U.S. Patent No. 6,468,967 BI, to Oleson, Jr. et al., issued October 22, 2002; and U.S. Patent No. 5,912,226, to Baker et al., issued June 15, 1999; and PCT Application No. WO 00/18419, to Cubist Pharmaceuticals, Inc., published April 6, 2000.
g. Garenoxacin

Garenoxacin and its pharmaceutically acceptable salts, esters, and prodrugs thereof, can be used in the methods, compositions, and uses of the present invention. Garenoxacin is also known as 1-cyclopropyl-8-(difluoromethoxy)-7-(1R)-(1-methyl-2,3-dihydro-lH-5-isoinodiy)-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid methanesulfonate monohydrate and by the publicly disclosed code names T-381 l and BM 284756. See M. Takahata et al., "In Vitro and In Vivo Antimicrobial Activities of T-381 IME, a Novel Des-F(6)-Quinolone", Antimicrobial Agents and Chemotherapy, vol. 43, no. 5, pp. 1077-1084 (1999); U.S. Patent No. 6,025,370, to Todo et al., issued February 15, 2000; and U.S. Patent 5,935,952, to Todo et al., issued August 10, 1999 and its certificate of correction of December 5, 2000.

h. Gatifloxacin

Gatifloxacin and its pharmaceutically acceptable salts, esters, and prodrugs thereof, can be used in the methods, compositions, and uses of the present invention. Gatifloxacin is sold under the tradename or proprietary Tequin. See U.S. Patent No. 6,589,955 B2, to Raghavan et al., issued July 8, 2003; U.S. Patent No. 5,880,283, to Matsumoto et al., issued March 9, 1999; and U.S. Patent No. 4,980,470, to Masuzawa et al., issued December 25, 1990 and its certificate of correction of August 11, 1992.

i. Gemifloxacin

Gemifloxacin and its pharmaceutically acceptable salts, esters, and prodrugs thereof, can be used in the methods, compositions, and uses of the present invention. Gemifloxacin is sold under the tradename or proprietary Factive. See U.S. Patent No. 6,803,376 B1, to Appelbaum et al., issued October 12, 2004; U.S. Patent No. 6,723,734 B2, to Kim et al., issued April 20, 2004; U.S. Patent No. 6,455,540 B1, to Citron et al., issued September 24, 2002; U.S. Patent No. 6,340,689 B1, to Dubois et al., issued January, 22, 2002 and its certificate of correction of June 18, 2002; U.S. Patent No. 6,331,550 B1, to Citron et al., issued December 18, 2001; U.S. Patent No. 6,262,071 B1, to Crabb et al., issued July 17, 2001; U.S. Patent No. 5,962,468, to Hong et al., issued October 5, 1999 and its certificate of correction of May 9, 2000; U.S. Patent No. 5,776,944, to Hong et al., issued July 7, 1998; and U.S. Patent No. 5,633,262, to Hong et al., issued May 27, 1997.
j. Levofloxacin

Levofloxacin and its pharmaceutically acceptable salts, esters, and prodrugs thereof, can be used in the methods, compositions, and uses of the present invention. Levofloxacin is sold under the tradename or proprietary Levaquin. See U.S. Patent No. 5,053,407, to Hayakawa et al., issued October 1, 1991 and its certificate of correction of September 27, 1994.

k. Moxifloxacin

Moxifloxacin and its pharmaceutically acceptable salts, esters, and prodrugs thereof, can be used in the methods, compositions, and uses of the present invention. Moxifloxacin is sold under the tradename or proprietary Avelox. See U.S. Patent No. 5,849,752, to Grunenberg et al., issued December 15, 1998; U.S. Patent No. 5,607,942, to Petersen et al., issued March 4, 1997; and U.S. Patent No. 4,990,517, to Petersen et al., issued February 5, 1991 and its certificate of correction of April 25, 1995.

l. Oritavancin


m. Oxazolidinones


Other nonlimiting examples of oxazolidinones include those selected from the group consisting of the following compounds:
or a pharmaceutically acceptable salt, ester, or prodrug thereof. An example of a salt would be the monohydrochloride salt of the four foregoing oxazolidinones A, B, C, and D.

<table>
<thead>
<tr>
<th>A</th>
<th>(5S)-N-(3-{2-Fluoro-4'-{[3-fluoro-propylamino]-methyl]-biphenyl-4-yl}-2-oxo-oxazolidin-5-ylmethyl)-acetamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>(5S)-N-[3-{2-Fluoro-4'-{[(3-fluoro-propyl)-hydroxy-amino]-methyl}-biphenyl-4-yl}-2-oxo-oxazolidin-5-ylmethyl]-acetamide</td>
</tr>
<tr>
<td>C</td>
<td>N-[3-{2-Fluoro-4'-{[(3H-[1,2,3]triazol-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl}-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide</td>
</tr>
<tr>
<td>D</td>
<td>3-{2-Fluoro-4'-{[(3H-[1,2,3]triazol-4-ylmethyl)-amino]-methyl}-biphenyl-4-yl}-5-(R)-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one</td>
</tr>
</tbody>
</table>
n. Televancin

Televancin and its pharmaceutically acceptable salts, esters, and prodrugs thereof, can be used in the methods, compositions, and uses of the present invention. Televancin, which is a peptidoglycan, can be prepared by the sequential reduction amination of vancomycin and reaction with aminomethylphosphonic acid. Televancin can also be prepared by the reductive alkylation of vancomycin with N-decyl-N-fluoroaryl-methyloxycarbonyl-2-aminoacetaldehyde via sodium cyano-borohydride and trifluoroacetic acid, and modification of the resorcinol position via Mannich aminomethylation. Televancin can also be prepared from vancomycin or its analogues by the sequential reaction with a protected amino-aldehyde, an amine and then an aminoalkylphosphonic acid in the presence of formaldehyde. See U.S. Patent No. 6,887,976 B2, to Leadbetter et al., issued May 3, 2005; U.S. Patent No. 6,878,686 B2, to Marquess et al., issued April 12, 2005; U.S. Patent No. 6,872,804 B2, to Mu, issued March 29, 2005; U.S. Patent No. 6,872,701 B2, to Leadbetter et al., issued March 29, 2005; U.S. Patent No. 6,858,584 B2, to Judice et al., issued February 22, 2005; U.S. Patent No. 6,831,150 B2, to Linsell, issued December 14, 2004; U.S. Patent No. 6,828,299 B2, to Yang et al., issued December 7, 2004; U.S. Patent 6,770,621 B2, to Linsell et al., issued August 3, 2004; U.S. Patent No. 6,635,618 B2, to Leadbetter et al., issued October 21, 2003; U.S. Patent No. 6,620,781 B2, to Linsell et al., issued September 16, 2003; U.S. Patent No. 6,518,242 B1, to Chen et al. issued February 11, 2003; and U.S. Patent No. 6,455,669 B1, to Judice et al., issued September 24, 2002; and PCT Application No. WO 03/029270, to Theravance, Inc., published April 10, 2003.

o. DK-507k

The compound DK-507k and its pharmaceutically acceptable salts, esters, and prodrugs thereof, can be used in the methods, compositions, and uses of the present invention. DK-507k can be described as a fluoroquinolone. DK-507k is also known by the chemical name (-)-7-[(7S)-7-amino-5-azaspiro[2.4]heptan-5-yl]-6-fluoro-l-[(IR, 2S)-2-fluoro-1-cyclopropyl]-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid monohydrochloride monohydrate. See Otani et al., In Vitro and In Vivo antibacterial Activities ofDK-507k, a Novel Fluoroquinolone, Antimicrobial Agents and Chemotherapy, Vol. 47, no. 12, pages 3750-3759 (2003); Japanese Patent No. JP 2004244380 A2, to Daiichi Seiyaku Co., Ltd., Japan, September 2, 2004; PCT Application No. WO 2004/058261, to Daiichi Pharmaceutical Co., Ltd., Japan, published July 15, 2004; PCT Patent Application No., WO 2003/076248, to
DK-507k can be represented by the following formula;

![Chemical Structure]

The compound can also be obtained as crystals exhibiting characteristic peaks in the vicinity of angles of diffraction (20) of 6.9, 10.5, 14.4, 23.1, 26.9, and 27.8° when subjected to powder X-ray diffractometry.

The anhydrous free acid of the above compound, as well as other salts, esters, and prodrugs, and also hydrates of the compounds can be prepared and used in the present invention. Also other crystal forms of the foregoing can be prepared and used in the present invention.

p. Other Aspects of the Compounds of the Present Invention

Compounds designed, selected and/or optimized for use in the present invention, after being produced, can be characterized using a variety of assays known to those skilled in the art to determine whether the compounds have biological activity. For example, the compounds can be characterized by conventional assays, including but not limited to those...
assays described below, to determine whether the compounds have a predicted activity, binding activity and/or binding specificity.

Furthermore, high-throughput screening can be used to speed up analysis using such assays. As a result, it can be possible to screen rapidly the molecules described herein for activity, for example, as anti-cancer, anti-bacterial, anti-fungal, anti-parasitic or anti-viral agents. Also, it can be possible to assay how the compounds interact with a ribosome or ribosomal subunit and/or are effective as modulators (for example, inhibitors) of protein synthesis using techniques known in the art. General methodologies for performing high-throughput screening are described, for example, in Devlin, *High Throughput Screening*, (Marcel Dekker, 1998); and U.S. Patent No. 5,763,263. High-throughput assays can use one or more different assay techniques including, but not limited to, those described below.

(1) *Surface Binding Studies.* A variety of binding assays can be useful in screening new molecules for their binding activity. One approach includes surface plasmon resonance (SPR) that can be used to evaluate the binding properties of molecules of interest with respect to a ribosome, ribosomal subunit or a fragment thereof.

SPR methodologies measure the interaction between two or more macromolecules in real-time through the generation of a quantum-mechanical surface plasmon. One device, (BIAcore Biosensor RTM from Pharmacia Biosensor, Piscatawy, NJ.) provides a focused beam of polychromatic light to the interface between a gold film (provided as a disposable biosensor "chip") and a buffer compartment that can be regulated by the user. A 100 nm thick "hydrogel" composed of carboxylated dextran that provides a matrix for the covalent immobilization of analytes of interest is attached to the gold film. When the focused light interacts with the free electron cloud of the gold film, plasmon resonance is enhanced. The resulting reflected light is spectrally depleted in wavelengths that optimally evolved the resonance. By separating the reflected polychromatic light into its component wavelengths (by means of a prism), and determining the frequencies that are depleted, the BIAcore establishes an optical interface which accurately reports the behavior of the generated surface plasmon resonance. When designed as above, the plasmon resonance (and thus the depletion spectrum) is sensitive to mass in the evanescent field (which corresponds roughly to the thickness of the hydrogel). If one component of an interacting pair is immobilized to the hydrogel, and the interacting partner is provided through the buffer compartment, the interaction between the two components can be measured in real time based on the accumulation of mass in the evanescent field and its corresponding effects of the plasmon
resonance as measured by the depletion spectrum. This system permits rapid and sensitive real-time measurement of the molecular interactions without the need to label either component.

(2) Fluorescence Polarization. Fluorescence polarization (FP) is a measurement technique that can readily be applied to protein-protein, protein-ligand, or RNA-ligand interactions in order to derive IC50S and Kds of the association reaction between two molecules. In this technique one of the molecules of interest is conjugated with a fluorophore. This is generally the smaller molecule in the system (in this case, the compound of interest). The sample mixture, containing both the ligand-probe conjugate and the ribosome, ribosomal subunit or fragment thereof, is excited with vertically polarized light. Light is absorbed by the probe fluorophores, and re-emitted a short time later. The degree of polarization of the emitted light is measured. Polarization of the emitted light is dependent on several factors, but most importantly on viscosity of the solution and on the apparent molecular weight of the fluorophore. With proper controls, changes in the degree of polarization of the emitted light depends only on changes in the apparent molecular weight of the fluorophore, which in-turn depends on whether the probe-ligand conjugate is free in solution, or is bound to a receptor. Binding assays based on FP have a number of important advantages, including the measurement of IC50S and Kds under true homogenous equilibrium conditions, speed of analysis and amenity to automation, and ability to screen in cloudy suspensions and colored solutions.

(3) Protein Synthesis. It is contemplated that, in addition to characterization by the foregoing biochemical assays, the compound of interest can also be characterized as a modulator (for example, an inhibitor of protein synthesis) of the functional activity of the ribosome or ribosomal subunit.

Furthermore, more specific protein synthesis inhibition assays can be performed by administering the compound to a whole organism, tissue, organ, organelle, cell, a cellular or subcellular extract, or a purified ribosome preparation and observing its pharmacological and inhibitory properties by determining, for example, its inhibition constant (IC50) for inhibiting protein synthesis. Incorporation of 3H leucine or 35S methionine, or similar experiments can be performed to investigate protein synthesis activity. A change in the amount or the rate of protein synthesis in the cell in the presence of a molecule of interest indicates that the molecule is a modulator of protein synthesis. A decrease in the rate or the amount of protein synthesis indicates that the molecule is an inhibitor of protein synthesis.
Furthermore, the compounds can be assayed for antiproliferative or anti-infective properties on a cellular level. For example, where the target organism is a microorganism, the activity of compounds of interest can be assayed by growing the microorganisms of interest in media either containing or lacking the compound. Growth inhibition can be indicative that the molecule could be acting as a protein synthesis inhibitor. More specifically, the activity of the compounds of interest against bacterial pathogens can be demonstrated by the ability of the compound to inhibit growth of defined strains of human pathogens. For this purpose, a panel of bacterial strains can be assembled to include a variety of target pathogenic species, some containing resistance mechanisms that have been characterized. Use of such a panel of organisms permits the determination of structure-activity relationships not only in regards to potency and spectrum, but also with a view to obviating resistance mechanisms. The assays can be performed in microtiter trays according to conventional methodologies as published by The National Committee for Clinical Laboratory Standards (NCCLS) guidelines (NCCLS. M7-A5-Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Fifth Edition. NCCLS Document M100-S12/M7 (ISBN 1-56238-394-9)).

4. Formulation and Administration

The methods of the present invention can be practiced by delivering the compounds of the present invention using any suitable carrier. The dose of active compound, mode of administration and use of suitable carrier will depend upon the intended patient or subject and the targeted microorganism, e.g., the target bacterial organism. The formulations, both for human medical use and veterinary use, of compounds according to the present invention typically include such compounds in association with a pharmaceutically acceptable carrier. The carrier(s) should be "acceptable" in the sense of being compatible with compounds of the present invention and not deleterious to the recipient. Pharmaceutically acceptable carriers, in this regard, are intended to include any and all solvents, dispersion media, coatings, absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds (identified or designed according to the invention and/or known in the art) also can be incorporated into the compositions. The formulations can conveniently be presented
in dosage unit form and can be prepared by any of the methods well known in the art of pharmacy/microbiology. In general, some formulations are prepared by bringing the compound into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

A pharmaceutical composition of the invention should be formulated to be compatible with its intended route of administration. In certain embodiments of the present invention, the intended routes of administration include, for example: ophthalmic administration, i.e. administration to or via the eye; otic administration, i.e. administration to or via the ear; nasal administration, i.e. administration to or via the nose; and oral administration, i.e. administration to or via the mouth. Solutions or suspensions can include the following components: a sterile diluent such as water, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzy alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose.

The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide.

Although ophthalmic, otic, and oral formulations and administration methods are generally intended, other formulations and administration methods can also be considered. A wide variety of formulations and administration methods, including, e.g., intravenous formulations and administration methods can be found in S.K. Niazi, ed., Handbook of Pharmaceutical Formulations, Vols. 1-6 [Vol. 1 Compressed Solid Products, Vol. 2 Uncompressed Drug Products, Vol. 3 Liquid Products, Vol. 4 Semi-Solid Products, Vol. 5 Over the Counter Products, and Vol. 6 Sterile Products], CRC Press, April 27, 2004.

Useful solutions for oral or parenteral administration can be prepared by any of the methods well known in the pharmaceutical art, described, for example, in Remington's Pharmaceutical Sciences, 18th ed. (Mack Publishing Company, 1990). Formulations for parenteral administration can also include glycocholate for buccal administration, methoxysalicylate for rectal administration, or citric acid for vaginal administration. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Suppositories for rectal administration also can be prepared by mixing the drug with a non-irritating excipient such as cocoa butter, other glycerides, or other compositions which are solid at room temperature and liquid at body temperatures. Formulations also can include, for example, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, and hydrogenated naphthalenes. Formulations for direct administration can include glycerol and other compositions of high viscosity. Other potentially useful parenteral carriers for these drugs include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation administration can contain as excipients, for example, lactose, or can be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Retention enemas also can be used for rectal delivery.

Formulations of the present invention suitable for oral administration can be in the form of: discrete units such as capsules, gelatin capsules, sachets, tablets, troches, or lozenges, each containing a predetermined amount of the drug; a powder or granular composition; a solution or a suspension in an aqueous liquid or non-aqueous liquid; or an oil-in-water emulsion or a water-in-oil emulsion. The drug can also be administered in the form of a bolus, electuary or paste. A tablet can be made by compressing or molding the drug optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the drug in a free-flowing form such as a powder or
granules, optionally mixed by a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets can be made by molding, in a suitable machine, a mixture of the powdered drug and suitable carrier moistened with an inert liquid diluent.

Oral compositions generally include an inert diluent or an edible carrier. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients. Oral compositions prepared using a fluid carrier for use as a mouthwash include the compound in the fluid carrier and are applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose; a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filter sterilization. Generally, dispersions are
prepared by incorporating the active compound into a sterile vehicle which contains a basic
dispersion medium and the required other ingredients from those enumerated above. In the
case of sterile powders for the preparation of sterile injectable solutions, methods of
preparation include vacuum drying and freeze-drying which yields a powder of the active
ingredient plus any additional desired ingredient from a previously sterile-filtered solution
thereof.

Formulations suitable for intra-articular administration can be in the form of a sterile
aqueous preparation of the drug that can be in microcrystalline form, for example, in the form
of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable
polymer systems can also be used to present the drug for both intra-articular and ophthalmic
administration.

Formulations suitable for topical administration, including eye treatment, include
liquid or semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or
water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such
as drops. Formulations for topical administration to the skin surface can be prepared by
dispersing the drug with a dermatologically acceptable carrier such as a lotion, cream,
ointment or soap. Useful are carriers capable of forming a film or layer over the skin to
localize application and inhibit removal. For topical administration to internal tissue
surfaces, the agent can be dispersed in a liquid tissue adhesive or other substance known to
enhance adsorption to a tissue surface. For example, hydroxypropylcellulose or
fibrinogen/thrombin solutions can be used to advantage. Alternatively, tissue-coating
solutions, such as pectin-containing formulations can be used.

For inhalation treatments, inhalation of powder (self-propelling or spray formulations)
dispensed with a spray can, a nebulizer, or an atomizer can be used. Such formulations can
be in the form of a fine powder for pulmonary administration from a powder inhalation
device or self-propelling powder-dispensing formulations. In the case of self-propelling
solution and spray formulations, the effect can be achieved either by choice of a valve having
the desired spray characteristics (i.e., being capable of producing a spray having the desired
particle size) or by incorporating the active ingredient as a suspended powder in controlled
particle size. For administration by inhalation, the compounds also can be delivered in the
form of an aerosol spray from pressured container or dispenser which contains a suitable
propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

Systemic administration also can be by transmucosal or transdermal means. For
transmucosal or transdermal administration, penetrants appropriate to the barrier to be
permeated are used in the formulation. Such penetrants generally are known in the art, and include, for example, for transmucosal administration, detergents and bile salts. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds typically are formulated into ointments, salves, gels, or creams as generally known in the art.

The active compounds can be prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. Liposomal suspensions can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

Oral or parenteral compositions can be formulated in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals. Furthermore, administration can be by periodic injections of a bolus, or can be made more continuous by intravenous, intramuscular or intraperitoneal administration from an external reservoir (e.g., an intravenous bag).

Where adhesion to a tissue surface is desired the composition can include the drug dispersed in a fibrinogen-thrombin composition or other bioadhesive. The compound then can be painted, sprayed or otherwise applied to the desired tissue surface. Alternatively, the drugs can be formulated for parenteral or oral administration to humans or other mammals, for example, in effective amounts, e.g., amounts that provide appropriate concentrations of the drug to target tissue for a time sufficient to induce the desired effect.

Where the active compound is to be used as part of a transplant procedure, it can be provided to the living tissue or organ to be transplanted prior to removal of tissue or organ from the donor. The compound can be provided to the donor host. Alternatively or, in addition, once removed from the donor, the organ or living tissue can be placed in a
preservation solution containing the active compound. In all cases, the active compound can be administered directly to the desired tissue, as by injection to the tissue, or it can be provided systemically, either by oral or parenteral administration, using any of the methods and formulations described herein and/or known in the art. Where the drug comprises part of a tissue or organ preservation solution, any commercially available preservation solution can be used to advantage. For example, useful solutions known in the art include Collins solution, Wisconsin solution, Belzer solution, Eurocollins solution and lactated Ringer's solution.

In conjunction with the methods of the present invention, pharmacogenomics (i.e., the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) can be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician can consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to administer a drug as well as tailoring the dosage and/or therapeutic regimen of treatment with the drug.

Generally, an effective amount of dosage of active compound will be in the range of from about 0.001 mg to about 100 mg/kg of body weight/day. In other embodiments an effective amount of dosage of active compound will be in the range of from about 1.0 to about 50 mg/kg of body weight/day. The amount administered will also likely depend on such variables as the exact mode of administration, the overall health status of the patient, the relative biological efficacy of the compound delivered the formulation of the drug, the presence and types of excipients in the formulation. Also, it is to be understood that the initial dosage administered can be increased beyond the above upper level in order to rapidly achieve the desired blood-level or tissue level, or the initial dosage can be smaller than the optimum.

Nonlimiting doses of active compound comprise from about 0.1 to about 1500 mg per dose. Nonlimiting examples of doses, which can be formulated as a unit dose for convenient administration to a patient include: about 0.10 mg, about 0.15 mg, about 0.20 mg, about 0.25 mg, about 0.30 mg, about 0.35 mg, about 0.40 mg, about 0.45 mg, about 0.5 mg, about 0.75 mg, about 1 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 7.5 mg, about 10 mg, about 12.5 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 60 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, about 100 mg, about 120 mg, about 125 mg,
about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 175 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 225 mg, about 230 mg, about 240 mg, about 250 mg, about 275 mg, about 300 mg, about 325, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050, mg, about 1075 mg, about 1100 mg, about 1125 mg, about 1150 mg, about 1175 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, and about 1500 mg. The foregoing doses are useful for administering the compounds of the present invention according to the methods of the present invention. The foregoing doses are particularly useful for administering the pyridone carboxylic acid compounds of the present invention, particularly the compound known by the names ABT-492 and WQ 3034 and also by the chemical name 1-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6-fluoro-1,4-dihydro-7-(3-hydroxy-1-azetidinyl)-4-oxo-3-quinolinecarboxylic acid, and pharmaceutically acceptable salts, esters and prodrugs thereof.

The compounds and compositions of the present invention can be administered for the treatment or prevention of infections associated with surgical or invasive medical procedures. With respect to administration in connection with surgical or invasive medical procedures, the compounds of the present invention and the doses disclosed in the previous paragraph can be administered to the patient from about 24 hours prior to up to immediately before the surgical or invasive medical procedure. Other times of administration are from about 12 hours prior to up to immediately before the surgical or invasive medical procedure, from about 11 hours prior to up to immediately before the surgical or invasive medical procedure, from about 10 hours prior to up to immediately before the surgical or invasive medical procedure, from about 9 hours prior to up to immediately before the surgical or invasive medical procedure, from about 8 hours prior to up to immediately before the surgical or invasive medical procedure, from about 7 hours prior to up to immediately before the surgical or invasive medical procedure, from about 6 hours prior to up to immediately before the surgical or invasive medical procedure, from about 5.5 hours prior to up to immediately before the surgical or invasive medical procedure, from about 5 hours prior to up to immediately before the surgical or invasive medical procedure, from about 4.5 hours prior to
up to immediately before the surgical or invasive medical procedure, from about 4 hours prior to up to immediately before the surgical or invasive medical procedure, from about 3.5 hours prior to up to immediately before the surgical or invasive medical procedure, from about 3 hours prior to up to immediately before the surgical or invasive medical procedure, from about 2.5 hours prior to up to immediately before the surgical or invasive medical procedure, from about 2 hours prior to up to immediately before the surgical or invasive medical procedure, from about 1.5 hours prior to up to immediately before the surgical or invasive medical procedure, from about 1 hour prior to up to immediately before the surgical or invasive medical procedure, from about 30 minutes (0.5 hours) prior to up to immediately before the surgical or invasive medical procedure.

As is understood by one of ordinary skill in the art, generally, when dosages are described for a pharmaceutical active, the dosage is given on the basis of the parent or active moiety. Therefore, if a salt, hydrate, or another form of the parent or active moiety is used, a corresponding adjustment in the weight of the compound is made, although the dose is still referred to on the basis of the parent or active moiety delivered. As a nonlimiting example, if the parent or active moiety of interest is a monocarboxylic acid having a molecular weight of 250, and if the monosodium salt of the acid is desired to be delivered to be delivered at the same dosage, then an adjustment is made recognizing that the monosodium salt would have a molecular weight of approximately 272 (i.e. minus 1H or 1.008 atomic mass units and plus 1 Na or 22.99 atomic mass units). Therefore, a 250 mg dosage of the parent or active compound would correspond to about 272 mg of the monosodium salt, which would also deliver 250 mg of the parent or active compound. Said another way, about 272 mg of the monosodium salt would be equivalent to a 250 mg dosage of the parent or active compound.

Using ABT-492 as a nonlimiting example, an example of a composition useful in the methods of the present invention can be about 100 mg of 1-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6-fluoro-1,4-dihydro-7-(3-hydroxy-1-azetidinyl)-4-oxo-3-quinolinecarboxylic acid, or a pharmaceutically acceptable salt, ester or prodrugs thereof, for administration to a patient from about 1 hour prior to up to immediately before a surgical or invasive medical procedure.

See, e.g., PCT Application No. WO 2005/019211 A2, published, March 3, 2005, which describes various aspects useful in the present invention.

EXAMPLES

The following examples further describe and demonstrate embodiments within the
scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention. The formulation examples are made using standard mixing techniques familiar to one of ordinary skill in the art. These formulations are useful for ophthalmic, oral, or nasal administration.

Ingredients are identified by chemical, USP, NF, or CTFA name. Q.S. means "as needed" to achieve a final 100% formulation.

**EXAMPLE 1**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount (total or weight %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial Compound</td>
<td>0.1 - 1500 total mg</td>
</tr>
<tr>
<td>Dextrose, USP</td>
<td>50 mg/ml</td>
</tr>
<tr>
<td>Sodium citrate, USP</td>
<td>1.60-1.75 mg/ml</td>
</tr>
<tr>
<td>Citric Acid, USP</td>
<td>0.80-0.90 mg/ml</td>
</tr>
<tr>
<td>Water, USP</td>
<td>q.s. 100</td>
</tr>
</tbody>
</table>

**EXAMPLE 2**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount (WT %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial Compound</td>
<td>0.1 - 1500 total mg</td>
</tr>
<tr>
<td>Sodium Acetate</td>
<td>0.03%</td>
</tr>
<tr>
<td>Acetic Acid</td>
<td>0.04%</td>
</tr>
<tr>
<td>Mannitol</td>
<td>4.60%</td>
</tr>
<tr>
<td>EDTA</td>
<td>0.05%</td>
</tr>
<tr>
<td>Benzalkonium Chloride</td>
<td>0.06%</td>
</tr>
<tr>
<td>Water, USP</td>
<td>q.s. 100</td>
</tr>
</tbody>
</table>
### EXAMPLE 3

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount (WT %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial Compound</td>
<td>0.1 - 1500 total mg</td>
</tr>
<tr>
<td>Dexamethasone, Micronized USP</td>
<td>0.10%</td>
</tr>
<tr>
<td>Benzalkonium Chloride</td>
<td>0.01%</td>
</tr>
<tr>
<td>Edetate Disodium, USP</td>
<td>0.01%</td>
</tr>
<tr>
<td>Sodium Chloride, USP</td>
<td>0.3%</td>
</tr>
<tr>
<td>Sodium Sulfate, USP</td>
<td>1.2%</td>
</tr>
<tr>
<td>Tyloxapol, USP</td>
<td>0.05%</td>
</tr>
<tr>
<td>Hydroxyethylcellulose</td>
<td>0.25%</td>
</tr>
<tr>
<td>Sulfuric Acid and/or Sodium Hydroxide, N.F.</td>
<td>q.s. for pH adjustment to 5.5Sodium</td>
</tr>
<tr>
<td>Sodium Water, USP</td>
<td>q.s. 100</td>
</tr>
</tbody>
</table>

The term "q.s." above means the amount which is needed.

### EXAMPLE 4

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount (WT %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial Compound</td>
<td>0.1 - 1500 total mg</td>
</tr>
<tr>
<td>Mineral Oil, USP</td>
<td>2.0%</td>
</tr>
<tr>
<td>White Petrolatum, USP</td>
<td>q.s. 100</td>
</tr>
</tbody>
</table>

### EXAMPLE 5

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amount (WT %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial Compound</td>
<td>0.1 - 1500 total mg</td>
</tr>
<tr>
<td>Fluorometholone acetate, USP</td>
<td>0.1%</td>
</tr>
<tr>
<td>Chlorobutanol, anhydrous, N.F.</td>
<td>0.5%</td>
</tr>
<tr>
<td>Mineral Oil, USP</td>
<td>5.0%</td>
</tr>
<tr>
<td>White Petrolatum, USP</td>
<td>q.s. 100</td>
</tr>
</tbody>
</table>

The term "q.s." above means the amount which is needed.
The foregoing formulations are also specifically prepared with the compound, 1-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6-fluoro-1,4-dihydro-7-(3-hydroxy-1-azetidinyl)-4-oxo-3-quinolinecarboxylic acid, or a pharmaceutically acceptable salt or ester thereof.

INCORPORATION BY REFERENCE

The entire disclosure of each of the patent documents, including certificates of correction, patent application documents, scientific articles, governmental reports, websites, and other references referred to herein is incorporated by reference in its entirety for all purposes.

EQUIVALENTS

The invention can be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.
WHAT IS CLAIMED IS:

1. A method of treating, preventing or reducing the risk of an ophthalmic, otic, or nasal infection in a patient in need thereof comprising administering a therapeutically effective amount or a prophylactically effective amount of an antimicrobial compound to said patient.

2. A method of treating, preventing or reducing the risk of an ophthalmic, otic, or nasal infection in a patient undergoing or having undergone a surgical or invasive medical procedure comprising administering a therapeutically effective amount or a prophylactically effective amount of an antimicrobial compound to said patient.

3. A composition for treating, preventing or reducing the risk of an ophthalmic, otic, or nasal infection in a patient in need thereof comprising a prophylactically effective amount or a therapeutically effective amount of an antimicrobial compound.

4. The use of an antimicrobial compound in the manufacture of a medicament for treating, preventing, or reducing the risk of an ophthalmic, otic, or nasal infection in a patient comprising administering a therapeutically effective amount or a prophylactically effective amount of said compound to said patient.

5. A method, composition, or use according to any of Claims 1-4 wherein said ophthalmic, otic, or nasal infection is a bacterial infection.

6. A method, composition, or use according to any of Claims 1-4 wherein said infection is a viral infection.

7. A method, composition, or use according to any of Claims 1-4 wherein said infection is a fungal infection.
8. A method, composition, or use according to any of Claims 1-7 wherein said patient is a mammal.

9. A method, composition, or use according to any of Claims 1-8 wherein said patient is a human.

10. A method, composition, or use according to any of Claims 1-9 wherein said compound is administered ophthalmically, namely to the eye.

11. A method, composition, or use according to any of Claims 1-9 wherein said compound is administered otically or otically, namely to the ear.

12. A method, composition, or use according to any of Claims 1-9 wherein said compound is administered nasally, namely to the nose.

13. A method, composition, or use according to any of Claims 1-9 wherein said compound is administered intravenously.

14. A method, composition, or use according to any of Claims 1-9 wherein said compound is administered orally.

15. A method, composition, or use according to any of Claims 1-9 wherein said compound is administered subcutaneously.

16. A method, composition, or use according to any of Claims 1-9 wherein said compound is administered parenterally.
17. A method, composition or use according to any of Claims 1-9 wherein said compound is administered intramuscularly.

18. A method, composition, or use according to any of Claims 1-17 wherein said antimicrobial agent is selected from a compound that binds to or modulates ribosomal RNA.

19. A method, composition, or use according to any of Claims 1-17 wherein said antimicrobial agent is selected from a compound that binds to or modulates bacterial ribosomal RNA.

20. A method, composition, or use according to any of Claims 1-17 wherein said antimicrobial agent is selected from a compound that binds to or modulates the large ribosomal subunit.

21. A method, composition, or use according to any of Claims 1-17 wherein said antimicrobial agent is selected from a compound that binds to or modulates the large ribosomal subunit of a bacterial organism.

22. A method, composition, or use according to any of Claims 1-17 wherein said antimicrobial agent is selected from a compound that binds to or modulates DNA topoisomerases.

23. A method, composition, or use according to any of Claims 1-17 wherein said antimicrobial agent is selected from a compound that binds to or modulates bacterial DNA topoisomerases.

24. A method, composition, or use according to any of Claims 1-17 wherein said antimicrobial agent is selected from a compound that binds to or modulates bacterial DNA gyrase.
25. A method, composition, or use according to any of Claims 1-17 wherein said antimicrobial agent is selected from a compound that binds to or modulates bacterial topoisomerase IV.

26. A method, composition, or use according to any of Claims 1-25 wherein said antimicrobial agent is selected from macrolides, ketolides, streptogramin As, streptogramin Bs, chloramphenicol, chloramphenicol derivatives, fluorfenicol, fluorfenicol derivatives, glycopeptides, pleuromutilins, aminoglycosides, beta-lactams and carbapenems, cephalosporins, lincosamides, quinolones, fluoroquinolones, pyridonecarboxylic acid derivatives, benzoheterocyclic compounds, aminomethylcyclohexane compounds, dalbavancin, daptomycin, garenoxacin, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, oritavancin, oxazolidinones, televancin, DK-507k, and mixtures thereof.

27. A method, composition, or use according to any of Claims 1-26 wherein said compound is a pyridonecarboxylic acid derivative.

28. A method, composition, or use according to any of Claim 27 wherein said compound is selected from a pyridonecarboxylic acid derivative corresponding to the following structure

\[
\text{Pyridonecarboxylic Acid Derivative 1}
\]

wherein \( R^1 \) represents a hydrogen atom or a carboxyl protective group; \( R^2 \) represents a hydroxyl group, a lower alkoxy group, or a substituted or unsubstituted amino group; \( R^3 \)
represents a hydrogen atom or a halogen atom; \( R^4 \) represents a hydrogen atom or a halogen atom; \( R^5 \) represents a halogen atom or an optionally substituted saturated cyclic amino group; \( R^6 \) represents a hydrogen atom, a halogen atom, a nitro group, or an optionally protected amino group; \( X, Y \) and \( Z \) may be the same or different and respectively represent a nitrogen atom, \( \text{CH} \) or \( \text{CR}^7 \) (wherein \( \text{CR}^7 \) represents a lower alkyl group, a halogen atom, or a cyano group), with the proviso that at least one of \( X, Y \) and \( Z \) represent a nitrogen atom, and \( W \) represents a nitrogen atom or \( \text{CR}^8 \) (wherein \( \text{CR}^8 \) represents a hydrogen atom, a halogen atom, or a lower alkyl group), and with the proviso that when \( R^1 \) represents a hydrogen atom, \( R^2 \) represents an amino group, \( R^3 \) and \( R^4 \) represent a fluorine atom, \( R^6 \) represents a hydrogen atom, \( X \) represents a nitrogen atom, \( Y \) represents \( \text{CR}^7 \) (wherein \( \text{CR}^7 \) represents a fluorine atom), \( Z \) represents \( \text{CH} \), and \( W \) is \( \text{CR}^8 \) (wherein \( \text{CR}^8 \) represents a chlorine atom), then \( R^5 \) is not a 3-hydroxyazetidine-1-yl group;

or a pharmaceutically acceptable salt, ester, or prodrug thereof; with the proviso that \( R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, W, X, Y, \) and \( Z \) are defined with respect to this Claim 28 and any such claims on which this Claim 28 depends, or a pharmaceutically acceptable salt, ester, or prodrug thereof.

29. A method, composition, or use according to any of Claims 1-28 wherein said compound is selected from a pyridonecarboxylic acid corresponding to the following structure

or a pharmaceutically acceptable salt, ester, or prodrug thereof.
30. A method, composition, or use according to any of claims 1-29 wherein said compound is D-glucitol 1-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6-fluoro-1,4-dihydro-7-(3-hydroxy-1-azetidinyl)-4-oxo-3-quinolinecarboxylate (salt).

31. A method, composition, or use according to claim 30 wherein said compound is crystalline D-glucitol 1-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6-fluoro-1,4-dihydro-7-(3-hydroxy-1-azetidinyl)-4-oxo-3-quinolinecarboxylate (salt) characterized, when measured about 25 °C with Cu-Ka radiation, by the powder diffraction pattern shown in FIGURE 1.

32. A method, composition, or use according to any of claims 1-29 wherein said compound is D-glucitol 1-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6-fluoro-1,4-dihydro-7-(3-hydroxy-1-azetidinyl)-4-oxo-3-quinolinecarboxylate trihydrate (salt).

33. A method, composition, or use according to claim 32 wherein said compound is crystalline D-glucitol 1-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6-fluoro-1,4-dihydro-7-(3-hydroxy-1-azetidinyl)-4-oxo-3-quinolinecarboxylate trihydrate (salt) characterized, when measured about 25 °C with Cu-Ka radiation, by the powder diffraction pattern shown in FIGURE 2.

34. A method, composition, or use according to any of claims 1-26 wherein said compound is a benzoheterocyclic compound.

35. A method, composition, or use according to any of claim 34 wherein said compound is selected from a benzoheterocyclic compound corresponding to the formula Benzoheterocyclic Compound I.
wherein $R_1$ represents a hydrogen atom or a lower alkyl group; $R_2$ represents a hydrogen atom or a halogen atom; $R_3$ represents a 1-pyrrolidinyl group which may be substituted with a hydroxymethyl group, a 1,2,5,6-tetrahydro-l-pyridyl group, or a group of the formula

\[
\begin{align*}
\text{N} & \quad \text{Z} \\
(R^4)_m & \\
\end{align*}
\]

where $R^4$ represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a hydroxy group, a phenyl-lower alkyl group, a lower alkanoyloxy group, an amino group which may be substituted with a lower alkyl group or a lower alkanoyl group, an oxo group, or a carbamoyl group; $Z$ represents an oxygen atom, a sulfur atom or a methylene group; and $m$ is 1 or 2; and $n$ is an integer of 1 or 2; or a pharmaceutically acceptable salt ester or prodrug thereof; with the proviso that $R_1$, $R_2$, $R_3$, $R_4$, $Z$, $m$, and $n$ are defined with respect to this Claim 40 and any such claims on which this Claim 40 depends.

36. A method, composition, or use according to Claim 34 wherein said compound is 9-fluoro-8-(4-hydroxy-l-piperidyl)-5-methyl-6,7-dihydro-l-oxo-lH,5H-benzo[lj]quinolizine-2-carboxylic acid or a pharmaceutically acceptable salt, ester, or prodrug thereof.

37. A method, composition, or use according to Claim 36 wherein said compound is S-(->)9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[lj]quinolizine-2-carboxylic acid or a pharmaceutically acceptable salt, ester, or prodrug thereof.
38. A method, composition or use according to Claim 37 wherein said compound is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[ij]quinolizine-2-carboxylic acid arginine salt.

39. A method, composition or use according to Claim 38 wherein said compound is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[ij]quinolizine-2-carboxylic acid arginine salt having the following X-ray diffraction data: (2Θ): 10.16, 11.78, 12.52, 16.00, 18.94, 19.66, 20.36, 21.28, 21.92, 22.52, 24.74, 25.28, 30.74.

40. A method, composition or use according to Claim 38 wherein said compound is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[ij]quinolizine-2-carboxylic acid arginine salt having the following X-ray diffraction data: (2Θ): 18.28, 18.8, 19.8, 20.12, 20.62, 21.10, 21.44, 21.88, 22.6, 23.02.

41. A method, composition or use according to Claim 38 wherein said compound is S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[ij]quinolizine-2-carboxylic acid arginine salt having the following X-ray diffraction data: (2Θ): 14.02±0.2, 14.82±0.2, 19.28±0.2, 22.12±0.2, 22.96±0.2, 23.46±0.2, 28.36±0.2.

42. A method, composition, or use according to any of Claims 1-26 wherein said compound is a beta-lactam.

43. A method, composition, or use according to Claims 1-26 wherein said compound is a carbapenem.

44. A method, composition, or use according to Claims 1-26 wherein said compound is a carbapenem with a 7-acylated imidazo[5,1-b]thiazole-2-yl group directly attached to the carbapenem moiety of the C-2 position.
A method, composition, or use according to any of Claims 42-44 wherein said compound is a beta-lactam corresponding to the following structure (Beta-Lactam I)

\[
\text{Beta-Lactam I}
\]

wherein \( R^1 \) represents a hydrogen atom or methyl, \( R^2 \) and \( R^3 \), which may be the same or different, each represent a hydrogen atom; a halogen atom; lower alkyl optionally substituted by a halogen atom, cyano, hydroxyl, carbamoyl, amino, formylamino, lower alkylcarbonylamino, aminosulfonylamino, lower alkylthio, lower alkoxy, lower cycloalkyl, N,N-di-lower alkylamino, or N-carbamoyl lower alkyl-N,N-di-lower alkylammonino; lower cycloalkyl; lower alkylcarbonyl wherein the alkyl portion of lower alkylcarbonyl is optionally substituted by a halogen atom, cyano, hydroxyl, carbamoyl, amino, formylamino, lower alkylcarbonylamino, aminosulfonylamino, lower alkylthio, lower alkoxy, lower cycloalkyl, N,N-di-lower alkylamino, or N-carbamoyl lower alkyl-N,N-di-lower alkylammonino; carbamoyl; aryl optionally substituted by amino optionally substituted by one or two lower alkyl groups; lower alkylthio wherein the alkyl portion of lower alkylthio is optionally substituted by amino, hydroxyl, azide, a halogen atom, cyano, carbamoyl, formylamino, lower alkylcarbonylamino, aminosulfonylamino, or lower alkylthio; morpholinyl; lower alkylsulfonyl; or formyl; \( n \) is an integer of 0 to 4, and \( H_y \) represents a four- to seven-membered monocyclic or nine- or ten-membered bicyclic saturated or unsaturated heterocyclic group having one to four hetero-atoms selected from nitrogen, oxygen, and sulfur atoms, the saturated or unsaturated heterocyclic group represented by \( H_y \) is optionally substituted by a halogen atom; cyano; lower alkyl wherein one or more hydrogen atoms on the lower alkyl group are optionally substituted by groups selected from a halogen atom; hydroxyl; carbamoyl; carboxylmethyl-substituted carbamoyl; amino; N,N-di-lower alkylamino; aryl optionally substituted by amino; a monocyclic or bicyclic heterocyclic group containing one or more hetero-atoms selected from nitrogen, oxygen, and sulfur atoms, optionally substituted by aminosulfonyl or carboxyl; carboxyl; imino; lower alkoxy carbonyl;
- 60 -

lower alkylcarbonyl; aminosulfonlamino; amino lower alkylthio; lower alkylsulfonfyl; (N,N-di-lower alkylamino)sulfonlamino; N'-lower alkylthio wherein one or more hydrogen atoms on the alkyl group are optionally substituted by a group selected from a halogen atom, hydroxyl, carbamoyl, amino, and aryl; lower halogenated alkylcarbonyl; N-aminosulfonfylpiperidinyl; and cyano; lower alkylthio wherein one or more hydrogen atoms on the alkyl group are optionally substituted by a group selected from a halogen atom, hydroxyl, carbamoyl, amino, and aryl; lower alkylsulfonfyl wherein one or more hydrogen atoms on the alkyl group are optionally substituted by a group selected from a halogen atom, hydroxyl, carbamoyl, amino, 1-iminoethylamino, and aryl; hydroxyl; lower alkoxy; hydroxyaminophenyl-substituted lower alkylcarbonyl; arylcarbonyl; carboxyl; lower alkoxy carbonyl; carbamoyl; N-lower alkylcarbamoyl; N,N-di-lower alkylaminocarbonyl; amino; N-lower alkylamino; N,N-di-lower alkylaminolamino; formylamino; lower alkylcarbonylamino; aminosulfonlamino; (N-lower alkylamino)sulfonlamino- ; (N,N-di-lower alkylamino)sulfonlamino; aryl; or a monocyclic or bicyclic heterocyclic group containing one or more hetero-atoms selected from nitrogen, oxygen, and sulfur atoms, optionally substituted by aminosulfonfyl or carboxyl, or a pharmaceutically acceptable salt, ester or pro-drug thereof, with the proviso that R\(^1\), R\(^2\), R\(^3\), Hy, and n are defined with respect to this Claim 45 and any such claims on which this Claim 45 depends.

46. A method, composition, or use according to any of Claims 42-44 wherein said compound is a beta-lactam corresponding to the following structure (Beta-Lactam II)

\[
\text{Beta-Lactam} \pi
\]

wherein R\(^1\) represents a hydrogen atom or methyl, R\(^2\) and R\(^3\), which may be the same or different, each represent a hydrogen atom; a halogen atom; lower alkyl optionally substituted by a halogen atom, cyan, hydroxyl, carbamoyl, amino, formylamino, lower alkylcarbonylamino, aminosulfonfylamino, lower alkylthio, lower alkoxy, lower cycloalkyl, N,N-di-lower alkylamino, or N-carbamoyl lower alkyl-N,N-di-lower alkylammonino; lower
cycloalkyl; lower alkylcarbonyl wherein the alkyl portion of lower alkylcarbonyl is optionally
substituted by a halogen atom, cyano, hydroxyl, carbamoyl, amino, formylamino, lower
alkylcarbonylamino, aminosulfonylamino, lower alkylthio, lower alkoxy, lower cycloalkyl,
N,N-di-lower alkylamino, or N-carbamoyl lower alkyl-N,N-di-lower alkylammonino;
carbamoyl; aryl optionally substituted by amino optionally substituted by one or two lower
alkyl groups; lower alkylthio wherein the alkyl portion of lower alkylthio is optionally
substituted by amino, hydroxyl, azide, a halogen atom, cyano, carbamoyl, formylamino, lower
alkylcarbonylamino, aminosulfonylamino, or lower alkylthio; morpholinyl; lower
alkylsulfonyl; or formyl; n is an integer of 0 to 4, and Hy represents a four- to seven-
membered monocyclic or nine- or ten-membered bicyclic saturated or unsaturated
heterocyclic group having one to four hetero-atoms selected from nitrogen, oxygen, and sulfur
atoms, the saturated or unsaturated heterocyclic group represented by Hy is optionally
substituted by a halogen atom; cyano; lower alkyl wherein one or more hydrogen atoms on
the lower alkyl group are optionally substituted by groups selected from a halogen atom;
hydroxyl; carbamoyl; carboxymethyl-substituted carbamoyl; amino; N,N-di-lower
alkylamino; aryl optionally substituted by amino; a monocyclic or bicyclic heterocyclic group
containing one or more hetero-atoms selected from nitrogen, oxygen, and sulfur atoms,
optionally substituted by aminosulfonyl or carboxyl; carbamoyl; imino; lower alkoxy Carbonyl;
lower alkylcarbonyl; aminosulfonylamino; amino lower alkylthio; lower alkylsulfonyl; (N,N-
di-lower alkylamino)sulfonylamino; N’-(N,N-di-lower alkylamino)sulfonyl-N’-lower
alkylamino; halogenated lower alkylcarbonyl; N-aminosulfonylpiperidinyl; and cyano; lower
alkylthio wherein one or more hydrogen atoms on the alkyl group are optionally substituted
by a group selected from a halogen atom, hydroxyl, carbamoyl, amino, and aryl; lower
alkylsulfonyl wherein one or more hydrogen atoms on the alkyl group are optionally
substituted by a group selected from a halogen atom, hydroxyl, carbamoyl, amino, 1-
iminoethylamino, and aryl; hydroxyl; lower alkoxy; hydroxylaminophenyl-substituted lower
alkoxy; halogenated lower alkoxy; aminophenyl-substituted lower alkoxy; formyl; lower
alkylcarbonyl; arylcarbonyl; carboxyl; lower alkoxy carbonyl; carbamoyl; N-lower
alkylcarbamoyl; N,N-di-lower alkylaminocarbonyl; amino; N-lower alkylamino; N,N-di-
lower alkylamino; formylamino; lower alkylcarbonylamino; aminosulfonylamino; (N-lower
alkylamino)sulfonylamino-; (N,N-di-lower alkylamino)sulfonylamino; aryl; or a monocyclic
or bicyclic heterocyclic group containing one or more hetero-atoms selected from nitrogen,
oxygen, and sulfur atoms, optionally substituted by aminosulfonyl or carboxyl, or a
pharmaceutically acceptable salt, ester, or pro-drug thereof, with the proviso that R₁, R², R³,
Hy, and n are defined with respect to this Claim 46 and any such claims on which this Claim 46 depends.

47. A method, composition, or use according to any of Claims 42-44 wherein said compound is selected from a beta-lactam corresponding to the following structure

![Chemical Structure](image)

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

48. A method, composition, or use according to any one of Claims 1-26 wherein said compound is an aminomethylcycline compound.

49. A method, composition, or use according to Claim 48 wherein said aminomethylcycline compound is 7-methylamino-9-(2,2-dimethylpropyl)aminomethylcycline or a pharmaceutically acceptable salt, ester, or prodrug thereof.

50. A method, composition, or use according to any of Claims 1-26 wherein said compound is dalbavancin or a pharmaceutically acceptable salt, ester, or prodrug thereof.

51. A method, composition, or use according to any of Claims 1-26 wherein said compound is daptomycin or a pharmaceutically acceptable salt, ester, or prodrug thereof.

52. A method, composition, or use according to any of Claims 1-26 wherein said compound is garenoxacin or a pharmaceutically acceptable salt, ester, or prodrug thereof.
53. A method, composition, or use according to any of Claims 1-26 wherein said compound is gatifloxacin or a pharmaceutically acceptable salt, ester, or prodrug thereof.

54. A method, composition, or use according to any of Claims 1-26 wherein said compound is gemifloxacin or a pharmaceutically acceptable salt, ester, or prodrug thereof.

55. A method, composition, or use according to any of Claims 1-26 wherein said compound is levofloxacin or a pharmaceutically acceptable salt, ester, or prodrug thereof.

56. A method, composition, or use according to any of Claims 1-26 wherein said compound is moxifloxacin or a pharmaceutically acceptable salt, ester, or prodrug thereof.

57. A method, composition, or use according to any of Claims 1-26 wherein said compound is oritavancin or a pharmaceutically acceptable salt, ester, or prodrug thereof.

58. A method, composition, or use according to any of Claims 1-26 wherein said compound is televancin or a pharmaceutically acceptable salt, ester, or prodrug thereof.

59. A method, composition, or use according to any one of Claims 1-26 wherein said compound is an oxazolidinone.

60. A method, composition, or use according to Claim 59 wherein said oxazolidinone is linezolid or a pharmaceutically acceptable salt, ester, or prodrug thereof.

61. A method, composition, or use according to Claim 59 wherein said oxazolidinone is selected from the group consisting of the following compounds
or a pharmaceutically acceptable salt, ester, or prodrug thereof.

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<th>A</th>
<th>![Chemical Structure]</th>
<th>(5S)-N-(3-(2-Fluoro-4'-(3-fluoro-propylamino)-methyl)biphenyl-4-yl)-2-oxo-oxazolidin-5-ylmethyl)-acetamide</th>
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<td>B</td>
<td>![Chemical Structure]</td>
<td>(5S)-N-[3-(2-Fluoro-4'-[[3-fluoro-propyl]-hydroxy-amino]-methyl)-biphenyl-4-yl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide</td>
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<td>C</td>
<td>![Chemical Structure]</td>
<td>N-[3-(2-Fluoro-4'-'-[[3H-[1,2,3]triazol-4-ylmethyl]-amino]-methyl]-biphenyl-4-yl]-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide</td>
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<td>D</td>
<td>![Chemical Structure]</td>
<td>3-(2-Fluoro-4'-'-[[3H-[1,2,3]triazol-4-ylmethyl]-amino]-methyl)-biphenyl-4-yl)-5-(R)-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one</td>
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</table>
62. A method, composition, or use according to any of Claims 1-26 wherein said compound is televancin or a pharmaceutically acceptable salt, ester, or prodrug thereof.

63. A method, composition, or use according to any one of Claims 1-26 wherein said compound corresponds to the following structure or a salt, ester, or prodrug thereof:

![Chemical Structure]

64. A method, composition, or use according to Claim 63 wherein said compound is:

![Chemical Structure]

65. A method, composition, or use according to any of Claims 63 or 64, wherein said compound is a crystalline compound exhibiting characteristic peaks in the vicinity of angles of diffraction (2θ) of 6.9, 10.5, 14.4, 23.1, 26.9, and 27.8(°) when subjected to powder X-ray diffractometry.

66. A method, composition, or use according to any of Claims 1-65, wherein said compound comprises from about 0.1 to about 1500 mg.
67. A method, composition, or use according to any of claims 1-66, wherein said compound comprises about 0.10 mg, about 0.15 mg, about 0.20 mg, about 0.25 mg, about 0.30 mg, about 0.35 mg, about 0.40 mg, about 0.45 mg, about 0.5 mg, about 0.75 mg, about 1 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 7.5 mg, about 10 mg, about 12.5 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 60 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, about 120 mg, about 125 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 175 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 225 mg, about 230 mg, about 240 mg, about 250 mg, about 275 mg, about 300 mg, about 325, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050, mg, about 1075 mg, about 1100 mg, about 1125 mg, about 1150 mg, about 1175 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, and about 1500 mg.

68. A method, composition or use according to any of claims 1-67 wherein said infection is Staphylococcus aureus infection.

69. A method, composition or use according to any of claims 1-68 wherein said infection is a hospital-associated methicillin resistant Staphylococcus aureus infection.

70. A method, composition or use according to any of claims 1-68 wherein said infection is a community-associated methicillin resistant Staphylococcus aureus infection.

71. A method, composition or use according to any of claims 1-10 wherein said infection is mediated, caused, or associated with Staphylococcus aureus.
**INTERNATIONAL SEARCH REPORT**

**International application No**
PCT/US2008/000153

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**A. CLASSIFICATION OF SUBJECT MATTER**

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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 practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>WADA TOMOYUKI ET AL: &quot;Treatment of rabbit corneal infections with ophthalmic gatifloxacin: A concentration dependence study&quot; ADVANCES IN THERAPY, vol. 21, no. 1, January 2004 (2004-01), pages 1-12, XP009099166 ISSN: 0741-238X pages 1,3,10</td>
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**X** Further documents are listed in the continuation of Box C.

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**X** See patent family annex.

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

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Date of the actual completion of the international search
7 May 2008

Date of mailing of the international search report
21/05/2008

Name and mailing address of the ISA/ European Patent Office, PB. 5818 Patentlaan 2 NL-2280 Hl RhoonTel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016

Authorized officer
Albayrak, Timur

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Form PCT/ISA/210 (second sheet) (April 2005)
**INTERNATIONAL SEARCH REPORT**

**DOCUMENTS CONSIDERED TO BE RELEVANT**

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| X         | ROSS J ET AL: "TOPICAL VANOCYCYIN FOR THE TREATMENT OF STAPHYLOCOCCUS EPIDERMIDIS AND METHICILLIN-RESISTANT STAPHYLOCOCCUS AEREUS CONJUNCTIVITIS"  
DICP, HARVEY WHITNEY BOOKS, CINCINNATI, OH, US, vol. 24, no. 11, November 1990 (1990-11), pages 1050-1053, XP009066866  
the whole document | 1-71 |
cl aims 1-5 | 1-71 |
| X         | WO 2004/058262 A (SAOJI DILIP G [IN]; NAGORI RAJENDRA N [IN]; SHUKLA MILIND C [IN]; BHAG) 15 July 2004 (2004-07-15)  
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c l aims 1-37 | 1-71 |
| X         | DAJCS JOSEPH J ET AL: "Effectiveness of ciprofloxacin, levofloxacin, or moxifloxacin for treatment of experimental Staphylococcus aureus keratitis"  
ISSN: 0066-4804  
the whole document | 1-71 |
| X         | KURAZONO MIZUYO ET AL: "In vitro activities of ME1036 (CP5609), a novel parenteral carbapenem, against methicillin-resistant staphylococci"  
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 48, no. 8, August 2004 (2004-08), pages 2831-2837, XP002477978  
ISSN: 0066-4804  
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| X         | WO 00/12048 A (MERCK & CO INC [US]; DORSO KAREN L [US]; GILL CHARLES J [US]; JACKSON) 9 March 2000 (2000-03-09)  
cl aims 1-23  
page 2, line 9 - line 18 | 1-71 |
paragraph [0060] | 1-71 |
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<td>HANNA C: &quot;DELIVERY OF ANTIBIOTICS TO THE EYE&quot; LIFE SCIENCES, PERGAMON PRESS, OXFORD, GB, vol. 27, no. 25/26, December 1980 (1980-12), pages 2509-2512, XP000866504 ISSN: 0024-3205 the whole document</td>
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<td>wo 01/08689 A (ALLERGAN SALES INC [US]) 8 February 2001 (2001-02-08) claim 9</td>
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<td>GB 794 488 A (UPJOHN CO) 7 May 1958 (1958-05-07) page 5, left-hand column, line 31 - line 35 page 1, left-hand column, line 11 - line 15</td>
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