**EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent: 08.03.2006 Bulletin 2006/10

(21) Application number: 01994117.8

(22) Date of filing: 29.11.2001

(54) **ANTIMICROBIAL QUINOLONE DERIVATIVES AND USE OF THE SAME TO TREAT BACTERIAL INFECTIONS**

ANTIMIKROBIELLE CHINOLONDERIVATE UND IHRE VERWENDUNG ZUR BEHANDLUNG BAKTERIELLER INFEKTIONEN

DERIVES ANTIMICROBIENS DE LA QUINOLONE ET LEUR UTILISATION POUR LE TRAITEMENT D'INFECTIONS BACTERIENNES

(84) Designated Contracting States: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR

Designated Extension States: AL LT LV MK RO SI


(43) Date of publication of application: 08.10.2003 Bulletin 2003/41

(73) Proprietor: Pharmacia & Upjohn Company LLC, Kalamazoo, MI 49001 (US)

(72) Inventors:
- GORDEEV, Mikhail, F.
  Castro Valley, CA 94552 (US)
- PATEL, Dinesh, V.
  Fremont, CA 94539 (US)
- BARBACHYN, Michael, R.
  Kalamazoo, MI 49009 (US)
- GAGE, James, R.
  Portage, MI 49002 (US)

(74) Representative: Lane, Graham Mark Hamilton et al

Pfizer Limited,
European Pharma Patent Department
Ramsgate Road
Sandwich, Kent CT13 9NJ (GB)

(56) References cited:

- DE-A- 2 755 061
- WO-A- 94/13649
- DE-A- 19 601 265
- PATENT ABSTRACTS OF JAPAN vol. 014, no. 250
  (C-0723), 29 May 1990 (1990-05-29) & JP 02 069478
  A (SAGAMI CHEM RES CENTER; OTHERS: 01), 8
  March 1990 (1990-03-08)

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).
Description

[0001] The present invention relates to quinolone derivatives substituted with an oxazolidinone, and to their use as broad spectrum antimicrobial agents effective against a number of human and veterinary Gram-positive and Gram-negative pathogens.

BACKGROUND OF THE INVENTION

[0002] The increase in bacterial resistance to existing antibacterial agents is a major clinical problem.

[0003] The 7-substituted quinolone carboxylic acid derivatives, represented by the general formula (II), wherein Y is either C-R₅ or N, and R₁ through R₅ include a wide variety of substituents, are well known as anti-fungal and anti-bacterial agents, and as synthetic intermediates to related compounds. The 7-substituted derivatives of compound (II) include the antibacterials cinoxacin (U.S. Patent No. 3,669,965); ciprofloxacin (U.S. Patent Nos. 4,563,459 and 4,620,007); ofloxacin (U.S. Patent No. 4,382,892); and levofloxacin (U.S. Patent Nos. 4,985,557, 5,053,407, and 5,142,046).

[0004] Oxazolidinones having a general structural formula (III) also are a well known class of orally active, synthetic antibacterial agents. The literature contains numerous references to oxazolidinones (III), wherein R₁ through R₃ include a wide variety of substituents. Oxazolidinones having one or two substituents on the phenyl ring are disclosed in U.S. Patent Nos. 4,705,799; 5,523,403; and 5,654,435, for example. Oxazolidinones (III) include the antibacterial agent designated as DuP 721, see J. Med. Chem., 32, 1673 (1989).

[0005] Oxazolidinones (III) having an arylbenzene substituent on the oxazolidinone ring are disclosed in U.S. Patent Nos. 4,948, 801 and 5,130,316. 3-[(Dis- or fused-ring substituted)phenyl]-2-oxazolidinones are disclosed in U.S. Patent Nos. 4,977,173; 4,921,869; 4,801,600; and 5,164,510. European Patent Applications 0 697 412; 0 694 544; 0 694 543; and 0 693 491, and International Patent Publication No. WO 93/09103, disclose 5- to 9-membered substituted aryl- and heteroaryl-phenol oxazolidinones as antibacterial agents. U.S. Patent No. 5,254,577 discloses aminomethyloxooxazolidinyl arylbenzene derivatives as antibacterial agents. Other references disclosing oxazolidinones include U.S. Patent Nos. 4,801,600 and 4,921,869. Some of the pyridine-substituted phenol oxazolidinone derivatives disclosed in the above patents are effective against Gram positive bacteria, such as Staphylococcus aureus and Streptococcus pneumoniae. However, the oxazolidinones are not active against Gram negative bacteria, such as Escherichia coli, Klebsiella, Proteus, and Seratia marcesens. Moreover, oxazolidinones cannot be administered as an injection solution because their free amino forms are sparingly soluble.

[0006] Antibacterial oxazolidinones are disclosed in European Patent Application 0 390 215.
SUMMARY OF THE INVENTION

[0007] One aspect of the present invention is substituted quinolone derivatives of formula I

or a pharmaceutically acceptable salt thereof;
wherein L is a bond or \(-\text{NR}^8(\text{CR}^9)^2\text{NR}^8\);
R\(^1\) is selected from H, C\(_1\)-C\(_4\) alkyl, C\(_3\)-C\(_5\) cycloalkyl, C\(_1\)-C\(_4\) haloalkyl and halophenyl; and
R\(^2\) is selected from H, alkyl, C\(_1\)-C\(_2\) alkoxy, halo and haloalkoxy; or
R\(^1\) and R\(^2\) taken together form a 5- or 6-membered, optionally substituted, heteroalkyl or heteroaryl ring;
R\(^3\) is H or F;
R\(^8\) is selected from H, methyl, hydroxy and halo;
each R\(^8\) is independently H or C\(_1\)-C\(_4\) alkyl, or the R\(^8\) groups are taken together to form a 4- to 9-membered, optionally substituted, heteroalkyl or heteroaryl ring;
each R\(^8\) is independently H or C\(_1\)-C\(_4\) alkyl, or the R\(^8\) groups are taken together to form a 4- to 9-membered heterocyclic or heterobicyclic ring optionally substituted with C\(_1\)-C\(_2\) alkyl, haloalkyl or methoximino;
R\(^11\) is selected from H, C\(_1\)-C\(_7\) alkyl, C\(_3\)-C\(_5\) cycloalkyl, hydroxymethyl, haloalkyl, CH\(_2\)SMe, N(R\(^{12}\))\(_2\), C\(_1\)-C\(_4\) alkoxy and aryloxy; and
R\(^{12}\) is C\(_1\)-C\(_4\) alkyl.

[0008] Another aspect of the present invention is a pharmaceutical composition containing a compound of the invention and a pharmaceutical acceptable carrier, diluent, or excipient.

[0009] A further aspect of the present invention is the use of a compound of the invention for the manufacture of a medicament for treating a microbial infection in a warm-blooded animal.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0010] As used herein, the terms and phrases have the meanings and definitions known in the art. Some of the more commonly used phrases are described in more detail below.
[0011] "Alkyl" refers to a cyclic, branched, or straight chain chemical group containing only carbon and hydrogen atoms, for example methyl, pentyl and adamantyl. Alkyl groups can be unsubstituted or substituted with one or more substituents, e.g., halogen, alkoxy, acyloxy, amino, hydroxyl, mercapto, carboxy, benzylxoy, phenyl and benzyl. Alkyl groups can be saturated or unsaturated (e.g., containing alkenyl or alkynyl subunits), at one or several positions. Typically, alkyl groups contain 1 to 12 carbon atoms, for example 1 to 10, or 1 to 8, carbon atoms.
[0012] "Heteroalkyl" refers to a cyclic, branched, or straight chain chemical group containing carbon, hydrogen and at least one heteroatom. Heteroalkyl includes bicyclic compounds. The heteroatom typically is nitrogen, oxygen, or sulfur. Heteroalkyl groups can be unsubstituted or substituted with one or more substituents, e.g., halogen, alkoxy, acyloxy, amino, hydroxyl, mercapto, carboxy, benzylxoy, phenyl and benzyl. When the heteroalkyl group contains a nitrogen atom, the nitrogen atom can be primary, secondary, tertiary, or quaternary, or can be in various forms such as an amide or sulfonamide. Heteroalkyl groups can contain one or more unsaturated (e.g., alkenyl or alkynyl) subunits. Typically, heteroalkyl groups contain 1 to about 12 atoms, for example 1 to about 8, or 1 to about 4 carbon atoms.
[0013] "Heteroaryl" refers to a monovalent aromatic group having a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizyl or benzothienyl) containing carbon atoms and having at least one heteroatom within the ring. The heteroatom preferably is nitrogen, oxygen or sulfur. Heteroaryl groups can be optionally unsubstituted or substituted with amino, hydroxyl, alkyl, heteroalkyl, alkoxy, halo, mercapto, and other substituents. In one embodiment, the heteroaryl group is substituted pyridyl.
[0014] The term "halo" or "halogen" is defined herein to include fluorine, bromine, chlorine, and iodine.
The term "haloalkyl" is defined herein as an alkyl group substituted with one or more halo substituents, either fluoro, chloro, bromo, iodo, or combinations thereof.

The term "alkoxy" and "aryloxy" are defined as -OR, wherein R is alkyl or aryl, respectively.

The term "hydroxy" is defined as -OH.

"Biologically active compounds" or "bioactive compounds" refers to present quinolone derivatives that exhibit biological activity. For instance, a biologically active compound can inhibit the interaction between an enzyme or receptor and its respective substrate(s) or endogenous ligand(s), or inhibit cell growth of a microorganism, by about at least 15% at a solution concentration of 10^{-3} molar or lower (i.e. has inhibitory activity). For example, a biologically active compound can inhibit such processes at solution concentrations of 10^{-4} M or lower, preferably 10^{-5} M or lower, and more preferably 10^{-6} M or lower.

The compounds of the present invention are effective antimicrobial agents against a number of human and veterinary pathogens, including Gram-positive, Gram-negative and anaerobic bacteria, and in treating microbial infections in mammals. The present compounds also can be used as cytotoxic anticancer compounds.

It is also preferred that compounds of formula (I) are optically pure enantiomers having the S-configuration at the five-position carbon of the oxazolidinone ring.

Preferred compounds of the present invention are those of Examples 1 to 3.

The substituted quinolone derivatives of the present invention can be prepared by the following general synthetic schemes.

Scheme 1 illustrates one general method of synthesizing the 7-oxazolidinone-, isoxazoline-, and isoxazolinone-substituted quinolone compounds (B) of the present invention. Scheme 2 illustrates specific examples of synthesizing oxazolidinone-substituted quinolone compounds (3 and 6) of the present invention.
In Scheme 1, an appropriately substituted quinolone, preferably containing a leaving group (LG) at the 7-position (compound A), such as a fluoro, chloro, or triflate derivative, is used as a starting material. Specific examples of such compounds are illustrated by compounds (1), (4), and (5). Compounds (1), (4), and (5) are readily available from a number of commercial sources or, alternatively, are known in the chemical literature or can be readily prepared by one skilled in the art. 7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-3-carboxylic acid (1) is commercially available from Acros Organics, and its synthesis is described in German Patents DE 3142854, DE 3248505, and DE 3248507. 1-Cyclopropyl-6,7-difluoro-4-oxo-3-quinolinecarboxylic acid is commercially available from Louston International, and its synthesis is described in German patent DE3248507. 9,10-Difluoro-3-methyl-7-oxo-2,3-dihydro-7H-[1,4]oxazino[2,3,4-λ]quinoline-6-carboxylic acid is commercially available from Maybridge Chemical Company and its synthesis is described in Japanese patents JP 57088182 and JP 58072589 and EP 47005. 9-Chloro-10-fluoro-3-methyl-7-oxo-2,3-dihydro-7H-[1,4]oxazino[2,3,4-λ]quinoline-6-carboxylic acid is commercially available from Zhejiang Hengdian Imp. & Exp. Co., Ltd. and its synthesis is described in Chem. Pharm. Bull., 32, 4907-13 (1984) and EP 206283.

In one embodiment, the appropriately substituted quinolone (1), (4), or (5) is treated with an oxazolidinone substituted with a sufficiently nucleophilic linking group, L, such that the subsequent nucleophilic substitution reaction provides, in a one-pot reaction sequence, the respective crude oxazolidinone-substituted quinolone (I).

The L group on the oxazolidinone can be introduced by standard synthetic methods from commercially available reagents as described hereafter. For example, when quinolone (1), (4), or (5) is treated with 5-(S)-aminomethyl-3-(3-fluoro-4-piperazinophenyl)oxazolidine-2-one in N-methylpyrrolidine-2-one (NMP) and N-methylmorpholine (NMM), the respective crude oxazolidinone-substituted quinolone (3) or (6) is formed in moderate to high yield. Compounds (3) and (6) then can be purified following chromatographic techniques well known in the art.

Alternatively, Scheme 3 outlines a representative procedure for preparing compounds where a carbon-carbon bond connects the quinolone fragment to a phenyloxazolidinone subunit. Quinolone triflates 7a,b, (Kiely et. al. J.
Heterocyclic Chem. 1991, 28, 1581-1585), is reacted with boronic acid 8 in the presence of 1,2-dimethoxyethane, aqueous dibasic potassium phosphate and a suitable palladium catalyst, such as bis(triphenylphosphine)palladium bichloride or tetrakis(triphenylphosphine)palladium, and at a suitable temperature, preferably at reflux, to generate the respective coupled products 9a, b. It will be apparent to one skilled in the art that compounds 9a, b are both antimicrobial compounds and synthetic intermediates. For example, the tert-butoxycarbonyl (BOC) moiety of 9a, b can be removed with, for example, trifluoroacetic acid to give an amino intermediate which can be further elaborated, for example, acetylated, employing conditions described below. Additionally, the ester moiety of 10 or a subsequent acylated derivative can be hydrolyzed under acidic or basic conditions to give the corresponding carboxylic acid 11. Furthermore, when R1 = Bn hydrogenolysis in the presence of a suitable catalyst such as palladium on carbon also affords the corresponding carboxylic acid 11.

[0028] The compounds of the present invention contain at least one chiral centre. It is apparent to one skilled in the art that when one chiral centre is present, the compound can exist as one of two possible optical isomers ((R) and (S) enantiomers) or a racemic mixture of both. Both individual (R) and (S) enantiomers, as well as mixtures thereof, are within the scope of the invention. In the event a second chiral center is present in the oxazolidinone-substituted quinolones (I) of the invention, the resultant diastereomers, in racemic and enantiomerically enriched forms, also are within the scope of the compounds (I) of the invention.

[0029] The preferred compounds of the present invention are optically pure enantiomers having the (S)-configuration at C5 of the oxazolidinone ring, because, for example, S-ofloxacin exhibits a 10 to 100-fold greater potency than R-ofloxacin. However, the racemic mixture also is useful, but a greater amount of the racemic material may be required to produce the same effect as the pure S-enantiomer.

[0030] If desired, the mixture of enantiomers is resolved by means known to those skilled in the art. Optically pure material can be obtained by resolution of the racemic mixture by HPLC using a chiral phase, such as a Chiralpack AD column as described in Examples 4 and 6 for compounds 15 and 17 and shown in Scheme 2. Alternatively, resolution of the racemic mixture can be accomplished by selective crystallization of a salt form using methods known to those skilled in the art. See for example, "Optical Remixture Procedures for Chemical Compounds, Vol 1; Amines and Related Compounds," Paul Newman, Optical Remixture Information Center, Manhattan College, Riverdale, N.Y., 10471, 1978. For example, treatment of the R,S-aminomethyl mixture (25) with an appropriate optically active acid, such as (+)-tartaric acid, or alternatively with (-)-tartaric acid, yields a mixture of diastereomeric salts, which can be separated by fractional crystallization to give a salt containing one enantiomer of the racemic mixture. Other suitable optically active acids include (-)-dibenzoyl-tartaric acid, (+)-camphoric acid, (+)- and (-)-malic acid, and (+)-camphor-10-sulfonic acid. By reacting the diastereomeric salt with a base, the optically pure free amino compound (25) is obtained.

[0031] A compound of formula (I), or a prodrug or a physiologically acceptable salt or solvate thereof, can be administered as the neat compound or as a pharmaceutical composition containing either entity.

[0032] The pharmaceutical compositions of the present invention can be prepared by admixing a compound of formula
(I) with a solid or liquid pharmaceutically acceptable carrier, and, optionally, with pharmaceutically acceptable adjuvants and excipients employing standard and conventional techniques. Solid form compositions include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be at least one substance which also can function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Inert solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, cellulosic materials, a low melting wax, cocoa butter, and the like. Liquid form compositions include solutions, suspensions, and emulsions. For example, compounds of the present invention can be dissolved in water, water-propylene glycol, or water-polyethylene glycol, optionally containing suitable conventional coloring agents, flavoring agents, stabilizers and thickening agents. The oxazolidinone-, isoxazoline-, and isoxazolinone-substituted quinolones (I) can be used alone, or in conjunction with other antibacterial agents and/or non-antibacterial agents, as known to those skilled in the art.

[0033] Pharmaceutically acceptable refers to those properties and/or substances which are acceptable from a pharmacological or toxicological point of view and from a physical or chemical point of view regarding composition, formulation, stability, patient acceptance, and bioavailability. Pharmaceutically acceptable hydrate means hydrates useful for administering the compounds of this invention, and suitable hydrates include the compounds complexed with at least one water molecule.

[0034] Pharmaceutically acceptable salts means salts useful for administering compounds of the present invention. Suitable salts include acid addition salts when a basic group is present, such as occurs with the preferred piperazinyl group. Acid addition salts include those made from mineral acids, for example, hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, and the like, organic sulfonic acids, e.g., methanesulfonic, 2-hydroxyethyl sulfonates, organic carboxylic acids, e.g., amino and carbohydrate acids, e.g., gluconic, galacturonic, acetates, propionates, lactates, maleates, malates, succinates, tartrates, citric acid, fumarates, and the like. These salts can be in a hydrated form.

[0035] Pharmaceutically acceptable prodrugs means prodrugs useful for administering the compounds of this invention. Suitable prodrugs include acid derivatives, for example, amides, esters, for example, methyl esters, ethyl esters, and the like. It also is appreciated by those skilled in the art that the appropriate nitrogen oxides of the nitrogens of the oxazolidinone-substituted quinolones (I) are included within the scope of the invention. These prodrugs also can be in a hydrated form.

[0036] Compounds and pharmaceutical compositions suitable for use in the present invention include those wherein the active ingredient is administered in an effective amount to achieve its intended purpose. More specifically, a "therapeutically effective amount" means an amount effective to prevent development of, or to alleviate the existing symptoms of, the subject being treated. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0037] A "therapeutically effective dose" refers to that amount of the compound that results in achieving the desired effect. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose lethal to 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, which is expressed as the ratio between LD50 and ED50. Compounds which exhibit high therapeutic indices are preferred. The data obtained from such data can be used in formulating a dosage range for use in humans. The dosage of such compounds preferably lies within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed, and the route of administration utilized.

[0038] Humans and other mammals, for example, cattle, horses, sheep, hogs, dogs, and cats, can be treated with the oxazolidinone-substituted quinolones (I) of the present invention. The quinolones (I) of the present invention can be administered in a manner and in dosage forms similar to those of the known anti-bacterial agents described above. In therapeutic use for treating, or combating, bacterial infections in humans and warm-blooded animals, the compounds of formula (I), or pharmaceutical compositions thereof, are administered by conventional techniques, such as orally in solid and liquid dosage forms and/or, parenterally (IV, IM, SQ), at a unit dosage form to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which is antibacterially effective or appropriate.

[0039] Generally, the amount of compound (I) in a pharmaceutical composition is about 0.5% to about 90% by weight. An antibacterially effective dosage of compound (I) is about 0.1 to about 100 mg/kg of body weight/day, more preferably about 3 to about 50 mg/kg of body weight/day. The quantity of the oxazolidinone substituted quinolone compounds of formula (I) in the pharmaceutical composition, the exact unit dosage form thereof to be administered, the frequency of administration, and the route of administration will vary, and can be adjusted widely depending upon a number of factors known to those skilled in the art including the particular mode of administration, the particular compound being used, the potency of the particular compound, the desired concentration, the age, weight, sex, and general physical condition and requirements of the patient, the nature and severity of the bacterial infection being treated, and the like, as is well known to the physician treating infectious diseases. 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 the initial dosage can be smaller than the optimum and the daily dosage can be progressively increased during the course of treatment depending on the particular situation. The usual pharmaceutical dosage forms appropriate for parenteral (mixture, suspension in oil) and oral (tablet, capsule, syrup, suspension, etc) administration are known to those skilled in the art.

[0040] Compounds of the present invention can be administered by any suitable route, for example by oral, topical, buccal, inhalation, sublingual, rectal, vaginal, transurethral, nasal, topical, percutaneous, i.e., transdermal, or parenteral (including intravenous, intramuscular, subcutaneous, and intracoronary) administration. Parenteral administration can be accomplished using a needle and syringe, or using a high pressure technique, like POWDERJECT™.

[0041] If the compounds or pharmaceutical compositions of the present invention are administered parenterally, i.e., by injection, for example, by intravenous injection or by other parenteral routes of administration, it generally is as a soluble salt (acid addition salt or base salt) of the compound according to formula (I) in a pharmaceutically acceptable amount dissolved in a pharmaceutically acceptable liquid carrier such as, for example, water-for-injection; and a buffer to provide a suitable buffered isotonic solution, for example, having a pH of about 3.5 to about 6. Suitable buffering agents include, for example, trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine, and L(+)-arginine. A compound of formula (I) generally is dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 to about 400 mg/ml of solution. The resulting liquid pharmaceutical composition is administered so as to obtain the above-mentioned antibacterially effective amount of dosage.

[0042] Suitable buffering agents include, for example, trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine, and L(+)-arginine. A compound of formula (I) generally is dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 to about 400 mg/ml of solution. The resulting liquid pharmaceutical composition is administered so as to obtain the above-mentioned antibacterially effective amount of dosage.

[0043] For human use, a compound of the formula (I) can be administered alone, but generally is administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. Pharmaceutical compositions for use in accordance with the present invention can be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries that facilitate processing of compounds of formula (I) into preparations which can be used pharmaceutically.

[0044] These pharmaceutical compositions can be manufactured in a conventional manner, e.g., by conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Proper formulation is dependent upon the route of administration chosen. When a therapeutically effective amount of a compound of the present invention is administered orally, the composition typically is in the form of a tablet, capsule, powder, solution, or elixir. When administered in tablet form, the composition can additionally contain a solid carrier, such as a gelatin or an adjuvant. The tablet, capsule, and powder contain about 5 to about 95% compound of the present invention, and preferably from about 25 to about 90% compound of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, or oils of animal or plant origin can be added. The liquid form of the composition can further contain physiological saline solution, dextrose or other saccharide solutions, or glycols. When administered in liquid form, the composition contains about 0.5 to about 90% by weight of a compound of the present invention, and preferably about 1 to about 50% of a compound of the present invention.

[0045] When a therapeutically effective amount of a compound of the present invention is administered by intravenous, cutaneous, or subcutaneous injection, the composition is in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred composition for intravenous, cutaneous, or subcutaneous injection typically contains, in addition to a compound of the present invention, and isotonic vehicle.

[0046] For oral administration, the compounds can be formulated readily by combining a compound of formula (I) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the present compounds to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by adding a compound of formula (I) with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers and cellulose preparations. If desired, disintegrating agents can be added.

[0047] For administration by inhalation, compounds of the present invention can be delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant. In the case of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin, for use in an inhaler or insufflatot can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0048] The compounds can be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, e.g., in ampules or in multidose containers, with an added preservative. The compositions can take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing, and/or dispersing agents.

[0049] Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils or synthetic fatty acid esters. Aqueous injection
Compounds of the present invention also can be formulated in rectal compositions, such as suppositories or retention enemas, e.g., containing conventional suppository bases. In addition to the formulations described previously, the compounds also can be formulated as a depot preparation. Such long-acting formulations can be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For topical administration, the present compounds can be applied in neat form, e.g., when the compound is a liquid. However, it is desirable to administer the compounds to the skin as compositions in combination with a dermatologically acceptable carrier, which can be a solid, semi-solid, or a liquid. Useful solid carriers include, but are not limited to, finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina, and the like. Useful liquid carriers include; but are not limited to, water, alcohols, glycols, and water-alcohol/glycol blends in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of a surfactant. Adjuvants, such as fragrances and additional antimicrobial agents, can be added to optimize the properties for a given use. The resultant liquid compositions can be applied topically by absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

For veterinary use, a compound of formula (I) or a nontoxic sale thereof, is administered as a suitably acceptable formulation in accordance with normal veterinary practice. The veterinarian can readily determine the dosing regimen and route of administration that is most appropriate for a particular animal.

General Methods and Definitions

Reagents were purchased from commercial sources and used without further purification. All temperatures are in degrees Centigrade. When solvent pairs are used, the ratios of solvents used are volume/volume (v/v). When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v). Reactions with moisture-sensitive reagents were performed under a nitrogen atmosphere. Concentration of solutions was performed by reduced pressure rotary evaporation. Brine refers to an aqueous saturated sodium chloride mixture. High performance liquid chromatography (HPLC) analysis and purification were performed using Beckman System Gold®; detection at 220 nm. Analytical HPLC was performed on a YMC 5 micron C18 (4.6 mm × 50 mm) reverse phase (RP) column (gradient from 100% of the aq. 0.1 % trifluoroacetic acid (TFA) to 100% of 0.1% TFA in acetonitrile (MeCN) over 6 min, flow rate 2.0 mL/min). Preparative thin-layer chromatography (TLC) were performed using EM silica gel (SG) 60 F254 plates (20 x 20 cm, thickness 2 mm). NMR refers to nuclear magnetic resonance spectroscopy. 1H NMR refers to proton nuclear magnetic resonance spectroscopy with chemical shifts reported in ppm downfield from tetramethylsilane. Mass-spectra (MS) refers to mass spectrometry expressed as m/e or mass/charge unit and was obtained using electron impact (EI) technique. [M+H]+ refers to the positive ion of a parent plus a hydrogen atom. Retention time (Rt) is in minutes and refers to x. IR refers to infrared spectroscopy. FTIR refers to Fourier Transform IR.

In the following examples, the following abbreviations are used: millimole (mmol), milliliter (mL), potassium carbonate (K2CO3), ethyl acetate (EtOAc), DMSO (dimethyl sulfoxide), magnesium sulfate (MgSO4), sodium bicarbonate (NaHCO3), and ethyl alcohol (EtOH).

EXAMLES

The following examples describe how to prepare the various compounds and/or perform the various processes of the invention, and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will recognize appropriate variations from the procedures both as to reagents and as to reaction conditions and techniques.

General Procedure for the Synthesis of Quinolone-7-yl Linked Quinolone-Oxazolidinones and Related Analogs.

A mixture of an appropriate nucleophile linked oxazolidinone, or an oxazolidinone precursor such as an amino alcohol, (1-2 mmol) with an appropriate 7-substituted quinolone (preferably, 7-fluoro, 7-chloro, or 7-triflate derivative) (1 mmol) in N-methylpyrrolidine-2-one (NMP) (2 mL), N-methylmorpholine (NMM) (0.4 mL) and (optionally, DMSO, as an additional co-solvent, is stirred at 110-130 °C for 24 - 96 h (preferably, 24-48 h (hours) and 96 h for reactions with 7-fluoro and 7-chloroquinolones, respectively). The mixture is cooled to room temperature (r.t.), and a majority of the solvent removed under vacuum. The residue is triturated with water (7 mL), precipitated, filtered, washed with excess water,
THF (ca. 4 x 15 mL), ether, and dried under vacuum. Optionally, the resulting intermediate amino alcohol derivative is purified by crystallization from an appropriate solvent (e.g., MeOH) or by silica gel column chromatography (eluent: dichloromethane-MeOH). The amino alcohol (1 mmol) is dissolved in a aprotic organic solvent (e.g., tetrahydrofuran (THF) or NMP) (2-5 mL), and carbonyldiimidazole (1.1 mmol) is added. Optionally, an organic base is added (e.g., imidazole) (1.1 mmol). The mixture is stirred at 20 - 40 °C for 1 - 3 h. The solvent is removed under vacuum, and the crude product is purified by crystallization from an appropriate solvent (e.g., MeOH) or by silica gel column chromatography (eluent: dichloromethane-MeOH). Optionally, the carboxylic functionality is esterified under standard alcohol coupling conditions (e.g., polyethyleneglycol with diethyl cyanophosphate, 4-dimethylaminopyridine in NMP at 20-40 °C for 4-8 h) to provide an ester prodrug derivative.

EXAMPLE 1

[0057]

Preparation of 7-[4-[(5-(S)-Acetamidometbyloxazolidine-2-one-3-yl)-2-fluorophenyl]piperazine-1-yl]-3-carboxy-cyclopropyl-6-fluoro-1,4-dihydroquinoline-4-one (Compound 3).

[0058] Compound 3 was prepared from 5-(S)-aminomethyl-3-(3-fluoro-4-piperazinophenyl)oxazolidine-2-one (0.372 g, 1.1 mmol) and 3-carboxy-1-cyclopropyl-7-chloro-6-fluoro-1,4-dihydroquinoline-4-one (0.282 g, 1 mmol) according to the General Procedure for the Synthesis of Quinolone-7-yl Linked Oxazolidinones. The reaction was performed at 120 °C for 96 h. Yield 0.36 g (62%). MS (m/z): 582 [M+H]+. R_t 4.6 min.

EXAMPLE 2

[0059]

Preparation of 10-[4-[(5-(S)-Acetamidometbyloxazolidine-2-one-3-yl)-2-fluorophenyl]piperazine -1-yl]-6-carboxy-9-fluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine (Compound 6).

[0060] Compound 6 was prepared from 5-(S)-aminomethyl-3-(3-fluoro-4-piperazinophenyl)oxazolidine-2-one (0.372 g, 1.1 mmol) and 9,10-difluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid (0.281 g, 1 mmol) according to the General Procedure for the Synthesis of Quinolone-7-yl Linked Oxazolidinones. The reaction was performed at 110 °C for 24 h. Yield 0.444 g (74%). MS (m/z): 598 [M+H]+. R_t 4.5 min. The separation of enantiomers by chiral HPLC provides the preferred (S)-configuration isomer.

EXAMPLE 3

[0061]
Preparation of 7-(4-[(5S)-5-[(Acetylamino)methyl]2-oxo-1,3-oxazolidin-3-yl]-2-fluorophenyl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid (Compound 11).

Benzyl-1-cyclopropyl-6-fluoro-4-oxo-7-[[[trifluoromethyl]sulfonyl]oxy]-1,4-dihydro-3-quinolinecarboxylate (Compound 7a).

[0062] A slurry of 1-cyclopropyl-6-fluoro-4-oxo-7-hydroxy-1,4-dihydro-3-quinolinecarboxylate (1.51 g, 5.75 moles), prepared as described in Kiel, J.S.; Laborde, E.; Lesheshki, L.E.; Busch, R.A. J. Heterocyclic Chem. 1991, 28, 1581-1585, in dry pyridine (15 mL) was cooled to 0°C and treated via syringe with trifluoromethanesulfonic anhydride (2.5 mL, 14.86 moles). The resulting homogeneous, amber-colored solution was warmed slowly to room temperature and stirred for 24 hours. Benzyl alcohol (20 mL, 193.3 moles) was added, and the reaction stirred at room temperature for 2 hours. After pouring the solution into 100 mL of water, the aqueous phase was extracted (3X) with CH$_2$Cl$_2$. The combined organic layers were dried (Na$_2$SO$_4$), filtered and evaporated. The crude product was chromatographed on a Biogate 40 g column. The column was conditioned and loaded with CH$_2$Cl$_2$ and eluted with 850 mL of CH$_2$Cl$_2$ and 800 mL of 5% MeOH/CH$_2$Cl$_2$. Fractions 7-13 (A) and fractions 27-28 (B) (~45 mL cuts) were combined and evaporated, but neither was pure. Impure fraction A contained benzyl alcohol, which was removed in a nitrogen stream. The resulting solids were triturated with EtOAc, filtered and dried (House vacuum, 55°C, 1 hour) to yield Compound 7a as a white solid (36A) that weighed 99.0 mg (3.5%). Another 67 mg of 7a was obtained from the filtrate. Impure fraction B was combined and evaporated and eluted with 850 mL of CH$_2$Cl$_2$ and 800 mL of 5% MeOH/CH$_2$Cl$_2$. Fractions 7-13 (A) and fractions 27-28 (B) (~45 mL cuts) were combined and evaporated, but neither was pure. Impure fraction A contained benzyl alcohol, which was removed in a nitrogen stream. The resulting solids were triturated with EtOAc, filtered and dried (House vacuum, 55°C, 1 hour) to yield Compound 7a as an off-white solid that weighed 285 mg (10%). Another 235 mg of Compound 7a was obtained in the mother liquors. ES-MS of these products did not provide useful information.

Preparation of tert-Butyl [(5S)-3-(4-borono-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl] methylcarbamate (Compound 8)

2-Methylpropyl (4-bromo-3-fluorophenyl)carbamate.

[0063] To a solution of 500 g (4.50 mol) of 3-fluoroaniline and 2 L of CH$_2$Cl$_2$ in a 12 L round bottom flask was added a solution of 473 g (3.42 mol, 0.76 equiv.) of K$_2$CO$_3$ in 2 L of water. Isobutylchloroformate (663 g, 4.86 mol, 1.08 equiv.) was added with stirring via an addition funnel over 3 h so as to allow the isotherm to warm and maintain the mixture at gentle reflux. Gas evolves vigorously near the end of the addition. The organic phase was sampled for GC analysis 1 h after completion of the addition; less than 0.5% 3-fluoroaniline remained. The mixture was quenched by addition of 987 g (3.45 mol, 0.77 equiv.) of 1,3-dibromo-5,5-dimethylhydantoin and 2.5 L of water. The mixture was allowed to isotherm to 39°C and held at that temperature by gentle heating for 2 hours. The reaction was judged complete by HPLC analysis of the organic layer. The mixture was cooled to 32°C by addition of 500 g of ice, and the solids not soluble in either liquid layer (mostly hydantoins and partially brominated hydantoins) were removed by filtration. The filtrate layers were separated, extracting the aqueous layer with 500 mL of CH$_2$Cl$_2$. The combined organic layers were added with rapid stirring to a solution of 410 g of Na$_2$SO$_4$ in 3 L of water. The layers were separated, extracting the aqueous layer with 3400 mL of CH$_2$Cl$_2$. The combined organics were distilled on a rotovap and replaced with heptane, maintaining a constant volume, the resulting thick slurry was cooled to 4°C over 2.5 h. The solids were collected by filtration, washed with heptane (2 x 750 mL) and air dried, affording 1097 g (84%) of 2-Methylpropyl (4-bromo-3-fluorophenyl)carbamate as a white crystalline solid.
**EP 1 349 853 B1**

(5R)-3-(4-bromo-3-fluorophenyl)-5-(hydroxymethyl)-1,3-oxazolidin-2-one.

[0064] To a solution of 1056 g (3.64 mol) of 2-Methylpropyl (4-bromo-3-fluorophenyl)carbamate in 6.65 L of THF cooled to -15 °C in a 22 L round bottom flask was added a solution of 428 g (4.55 mol, 1.25 equiv.) of lithium t-amylate over 10 min via an addition funnel, maintaining -15 °C to -12 °C. In a separate 5 L flask, a solution of 438 g (4.37 mol, 1.20 equiv.) of (S)-3-chloro-1,2-propanediol in 1.75 L of THF was cooled to -25 °C and treated with a 20% t-BuOK solution in THF (2645 mL, 4.29 mol, 1.18 equiv.) over 25 min, resulting in a thick but stirrable slurry. This was allowed to warm to 10 °C over 75 min and then poured into the 22 L flask containing the carbamate solution. The resulting slurry was allowed to warm from 7.5 °C to 7 °C over 1.5 h, monitoring reaction progress by HPLC. Upon completion (2.5% each of remaining 2-Methylpropyl (4-bromo-3-fluorophenyl)carbamate and the over addition product), a quench solution composed of 1.05 L of AcOH and 3.5 L of water was added. The layers were separated. The aqueous layer was back-extracted with 1 L of THF, and the combined organic layers were washed with brine. The volatile were removed, giving white solids wet with acetic acid. This material was slurried in 1.6 L of EtOAc. Hexane (4L) was added over 1 h. The resulting slurry was cooled to 2 °C over 1 h and filtered, giving 916 g (87%) of (5R)-3-(4-bromo-3-fluorophenyl)-5-(hydroxymethyl)-1,3-oxazolidin-2-one as coarse white crystals: TLC Rf = 0.008 (50% EtOAc/hexane); HPLC rt = 2.55 min; mp 114-121 °C; [α]D = +22 * 2° c = 1, MeOH); 1H NMR (DMSO-D6) δ 7.49 (m, 2H), 7.15 (d, 1H, J = 8.5 Hz), 5.30 (br s, 1H), 4.54 (m, 1H), 3.89 (t, 1H, J = 8.6 Hz), 3.67 (m, 1H), 3.50 (dd, 1H, J = 3.0, 11.8 Hz), 3.39 (dd, 1H, 3.8, 11.8 Hz); 13C NMR (DMSO-D6) δ 158.1 (s, JCF = 241 Hz), 154.2 (S), 139.7 (S, JCF = 10 Hz), 133.3 (D), 114.9 (D), 105.9 (D, JCF = 29 Hz), 100.9 (s, JCF = 21 Hz), 73.3 (D), 61.5 (t), 45.9 (t); Anal. calcd for C15H13BrFNO3S: C, 41.40; H, 3.13; N, 4.83; Br, 26.97.

(5R)-3-(4-bromo-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl 3-nitrobenzene sulfonate.

[0065] To a slurry of 907 g (3.13 mol) of (5R)-3-(4-bromo-3-fluorophenyl)-5-(hydroxymethyl)-1,3-oxazolidin-2-one in 4.5 L of CH2Cl2 in a 22 L round bottom flask was added 654 mL (4.69 mol, 1.50 equiv.) of triethylamine. The mixture was cooled to 0 °C, and a solution of 832 g (34.75 mol, 1.20 equiv) of m-nitrobenzenesulfonyl chloride in 2 L of CH2Cl2 was added. The resulting slurry was heated to 30 °C, and a solution of 438g (4.37 mol, 1.20 equiv.) of (S)-3-chloro-1,2-propanediol in 8.5 L of CH2Cl2 was added. After 10 min via an addition funnel, maintaining -15° to -12° C. In a separate 5 L flask, a solution of 438g (4.37 mol, 1.20 equiv.) of (S)-3-chloro-1,2-propanediol in 3L of EtOAc was heated to 70 °C to dissolve. Upon cooling to room temperature, 5-yl methylcarbamate. This was suspended in 3L of EtOAc and heated to 70 °C to dissolve. Upon cooling to room temperature, 3L of hexane was added over 1 h. The resulting slurry was allowed to warm from 7.5 °C to 7 °C over 1.5 h, monitoring reaction progress by HPLC. Upon completion (2.5% each of remaining 2-Methylpropyl (4-bromo-3-fluorophenyl)carbamate and the over addition product), a quench solution composed of 1.05 L of AcOH and 3.5 L of water was added. The layers were separated. The aqueous layer was back-extracted with 1 L of THF, and the combined organic layers were washed with brine. The volatile were removed, giving white solids wet with acetic acid. This material was slurried in 1.6 L of EtOAc. Hexane (4L) was added over 1 h. The resulting slurry was cooled to 2 °C over 1 h and filtered, giving 916 g (87%) of (5R)-3-(4-bromo-3-fluorophenyl)-5-(hydroxymethyl)-1,3-oxazolidin-2-one as coarse white crystals: TLC Rf = 0.008 (50% EtOAc/hexane); HPLC rt = 2.55 min; mp 114-121 °C; [α]D = +22 ° 2° c = 1, MeOH); 1H NMR (DMSO-D6) δ 7.49 (m, 2H), 7.15 (d, 1H, J = 8.5 Hz), 5.30 (br s, 1H), 4.54 (m, 1H), 3.89 (t, 1H, J = 8.6 Hz), 3.67 (m, 1H), 3.50 (dd, 1H, J = 3.0, 11.8 Hz), 3.39 (dd, 1H, 3.8, 11.8 Hz); 13C NMR (DMSO-D6) δ 158.1 (s, JCF = 241 Hz), 154.2 (S), 139.7 (S, JCF = 10 Hz), 133.3 (D), 114.9 (D), 105.9 (D, JCF = 29 Hz), 100.9 (s, JCF = 21 Hz), 73.3 (D), 61.5 (t), 45.9 (t); Anal. calcd for C15H13BrFNO3S: C, 41.40; H, 3.13; N, 4.83; Br, 26.97.

Tert-Butyl (5S)-3-(4-bromo-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl carbamate.

[0066] In three portions, the sulfonate (5R)-3-(4-bromo-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl 3-nitrobenzene sulfonate (1400 g, 2.95 mol) was suspended in 15 mL/kg of a solvent mixture of 29% aqueous NH4OH, MeCN, and MeOH in a 5:2:5:1 ratio in an autoclave. The system was sealed and heated to 80 °C for 3-4 h with stirring. Upon cooling, the mixtures were extracted three times each with CH2Cl2; the combined extracts were concentrated, giving the crude amine as solid. The solids were suspended in 8.5 L of CH2Cl2. Di-t-butyl dicarbonate (985 g, 4.42 mol, 1.5 equiv.) was added as a solid over 15 min. With vigorous gas evolution. The mixture was stirred at room temperature overnight, after which the reaction was complete by TLC. Water (3L) was added, and stirring was continued for 30 min. The mixture was filtered, washing the solids that collected with additional CH2Cl2. The layers in the filtrate were separated. The organic layer was concentrated to a white solid, crude tert-butyl (5S)-3-(4-bromo-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl carbamate. This was suspended in 3L of EtOAc and heated to 70 °C to dissolve. Upon cooling to room temperature, 3L of hexane was added over 1 h. The resulting slurry was cooled to 0 °C. The solids were collected by filtration and washed with hexane to obtain 763 g of tert-butyl (5S)-3-(4-bromo-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl carbamate. A second crop was obtained by concentrating the mother liquor to 1.2 L and cooling to 0 °C, yielding an additional 50 g (total 813 g, 71 %); TLC Rf = 0.31 (50% EtOAc/hexane); HPLC rt = 5.02 min; mp 145-146 °C; [α]D = +30.0° C = 1, MeOH); 1H NMR (CDCl3) δ 7.50 (m, 2H), 7.12 (d, 1H, 8.5 Hz), 5.04 (br s, 1H), 4.77 (m, 1H), 4.01 (t, 1H).
10 Benzyl-[(5S)-3-(4-borono-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl] methylcarbamate (Compound 8).

**[0067]** To a solution of 2.00g (5.14 mmol) of tert-Butyl [(5S)-3-(4-bromo-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl] methylcarbamate in 40 mL of THF was added 1.94 mL (1.49 g, 12.8 mmol, 2.50 equiv.) of N,N,N',N'-tetramethylethene-amine. The solution was cooled to -50°C, and 4.86 mL (4.54 mmol, 1.06 equiv.) of 1.12 M ethyl magnesium bromide in THF solution was added by syringe. After 5 min., 4.06 mL (10.8 mmol, 2.10 equiv.) of 2.66 M tert-butyl lithium in hexane solution was added dropwise by syringe with vigorous stirring, keeping the temperature below 45°C. A thick slurry resulted, which was stirred for an additional 15 min. Trimethylborate (1.17 mL, 1.07 g, 10.3 mmol, 2.00 equiv.) was added by syringe. The mixture was allowed to warm to 20°C over 90 min. It was then poured into 25 mL of 4M hydrochloric acid and stirred for 15 min. The layers were separated, and the aqueous layer was extracted with 20 mL of CH₂Cl₂ to complete the removal of boronic acid. The combined organic extracts were dried (MgSO₄), filtered, and concentrated to give crude Compound 8 as an oil.

**Benzy1-7-[(5S)-[(tert-butoxycarbonyl)amino]methyl]2-oxo-1,3-oxazolidin-3-yl]2-fluorophenyl]1-cyclopropyl-6-flouro-4-oxo-1,4-dihydro-3-quinoilinecarboxylate (Compound 9a).**

**[0068]** A mixture of Compound 7a (369 mg, 0.76 moles) and Compound 8 (298 mg, 0.84 moles) in 1.2 dimethoxythane (8 mL) was degassed and flushed with nitrogen several times. Dichlorobis(triphenyolphosphine)palladium(II) (56.3 mg, 0.08 moles) and 2M K₂HPO₄ (0.77 mL, 1.54 moles) was added. The mixture was degassed and flushed with nitrogen several times and then heated at 90°C for 22 hours. After cooling to room temperature, the reaction was concentrated under reduced pressure, and the residue was chromatographed on a Biotage 40 gram column. The column was conditioned with 3:3 CH₂Cl₂/EtOAc/heptane, loaded with CH₂Cl₂ and eluted with 900 mL of 3:3:4 CH₂Cl₂/EtOAc/heptane and 500 mL of EtOAc. Fractions 23-49 (~20 mL cuts) were combined, evaporated and dried (house vacuum, r.t., 1 hour) to yield 257.1 mg (52%) of Compound 9a as a tan, amorphous solid. MS (ESI+) for C₁₅H₁₃BrN₃O₅: 500.2 (M+H).

**Benzy1-7-4-[(5S)-5-[(acetylamino)methyl]2-oxo-1,3-oxazolidin-3-yl]2-fluorophenyl]1-cyclopropyl-6-flouro-4-oxo-1,4-dihydro-3-quinoilinecarboxylate (Compound 10a).**

**[0069]** A solution of Compound 9a (253 mg, 0.391 moles) in 5.2 mL of CH₂Cl₂ at 0°C was treated via syringe with trifluoroacetic acid (2.6 mL 33.7 moles). The resulting solution was stirred at 0°C for 30 minutes and at room temperature for 1.5 hours. After concentrating the reaction under reduced pressure, the residue was dried (high vacuum, r.t., 2 hours) to afford the trifluoroacetic acid salt as an amber, amorphous solid (372 mg, over theory). The above salt was dissolved in 588.2 (M+H)\(^+\). \(^1\)H NMR (CDCl₃, TMS): \(\delta 8.64 (S, 1H), 8.24 (d, J = 13 Hz, 1H), 7.98 (d, J = 7 Hz, 1H), 7.71-7.61 (m, 3H), 7.42-7.33 (m, 3H), 5.42 (s, 2H), 5.03 (m, 1H), 4.82 (m, 1H), 4.11 (m, 1H), 3.94 (m, 1H), 3.57 (m, 2H), 3.49 (m, 1H), 1.43 (s, 9H), 1.33 (m, 2H), 1.16 (m, 2H). TLC: \(R_f = 0.14 (80\%\ EtOAc/hexane)\); UV-visualized.

7-(4-[(5S)-5-[(Acetyl amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]-2-fluorophenyl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-3-quinoilinecarboxylic acid (Compound 11).

**[0070]** A solution of Compound 10a (215 mg, 0.365 moles) in absolute ethanol was treated with 30 mg of 10% Pd/C. The mixture was placed on the hydrotreater at room temperature at 40 psi H₂ for 3 hours. Since TLC analysis indicated
the presence of starting material, an additional 30 mg of catalyst was added, and the reaction was returned to the hydrogenator at 40 psi of H₂ for 16 hours. After removing the catalyst by filtration through a pad of Elite and washing the filter cake with absolute ethanol, the filtrates were combined and concentrated leaving a yellowish-black residue (160 mg). The residue was chromatographed on a Biotage δg column. The column was conditioned, loaded and eluted with 5% MeOH/CH₂Cl₂ but only mixed fractions were obtained. Fractions containing the desired product were combined and concentrated leaving a solid that was crystallized from EtOAc/heptane. TLC analysis of the solids (22 mg) revealed that crystallization did not upgrade the product. Therefore, the solids and mother liquors were dissolved in a minimal amount of MeOH/CH₂Cl₂ and loaded onto two 500µm prep TLC plates. After eluting once with 5% MeOH/CH₂Cl₂, the plates were eluted a second time with 5% MeOH/CH₂Cl₂ + 0.5% HOAc. Separation was not perfect, but a clean sample of the desired band was isolated affording 21.8 mg (12%) of Compound 11 as a gold solid. This product decomposed at 120°C. MS (ESI+) for C₂₅H₂₁F₂N₃O₆: cal'd for C₂₅H₂₁F₂N₃O₆+H, 498.1476; found, 498.1474. [H NMR (CDCl₃ + 1 drop CD₃OD, TMS): δ 8.890 (s, 1 H), 8.24 (d, J = 13 Hz, 1 H), 8.16 (d, J = 8 Hz, 1 H), 7.66 (m, 1 H), 7.38 (m, 1 H), 4.86 (m, 1 H), 4.14 (m, 1 H), 3.89 (m, 1 H), 3.70-3.61 (m, 3 H), 2.05 (s, 3 H), 1.41 (m, 2 H), 1.25 (m, 2 H). TLC: Rₜ = 0.22 (5% MeOH/CH₂Cl₂ + 1% HOAc); UV-visualized).

[0071] As shown in Table 1, the compounds of Example 1, 2 and 3 demonstrated potent antibacterial activity.

<table>
<thead>
<tr>
<th>Example No.</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E. faecalis</td>
</tr>
<tr>
<td>1</td>
<td>0.25</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

[0072] The compounds of the invention can be used for the treatment or prevention of infectious disorders caused by a variety of bacterial organisms. Examples include Gram positive and Gram negative aerobic and anaerobic bacteria, including Staphylococci, for example S. aureus; Enterococci, for example E. faecalis; Streptococci, for example S. pneumoniae; Haemophilus, for example H. influenza; Moraxella, for example M. catarrhalis; and Escherichia for example E. coli. Other examples include Mycobacteria, for example M. tuberculosis; intercellular microbes, for example Chlamydia and Rickettsiae; and Mycoplasma, for example M. pneumoniae.

Claims

1. A compound having the formula:

   ![Chemical Structure][1]

   or a pharmaceutically acceptable salt thereof;

   wherein L is a bond or -NR⁻_8(CR⁻_2)₂NR⁻_8⁻;

   R¹ is selected from H, C₁₋₄ alkyl, C₃₋₅ cycloalkyl, C₁₋₄ haloalkyl and halophenyl; and
R² is selected from H, alkyl, C₁₋₂ alkoxy, halo and haloalkoxy; or
R¹ and R² taken together form a 5- or 6-membered, optionally substituted, heteroalkyl or heteroaryl ring;
R³ is H or F;
R⁶ is selected from H, methyl, hydroxy and halo;
each R⁸ is independently H or C₁₋₄ alkyl, or the R⁸ groups are taken together to form a 4- to 9-membered, optionally substituted, heteroalkyl or heteroaryl ring;
each R⁹ is independently H or C₁₋₄ alkyl, or the R⁹ groups are taken together to form a 4- to 9-membered heterocyclic or heterobicyclic ring optionally substituted with C₁₋₂ alkyl, haloalkyl or methoximino;
R¹¹ is selected from H, C₁₋₇ alkyl, C₃₋₅ cycloalkyl, hydroxymethyl, haloalkyl, CH₂SMe, N(R¹²)₂, C₁₋₄ alkoxy and aryloxy; and
R¹² is C₁₋₄ alkyl.

2. The compound of claim 1, wherein L is a bond.

3. The compound of claim 1, wherein L is NR⁸(CR⁹)₂NR⁸.

4. The compound of claim 1, having the structural formula:

![Chemical Structure 1](image1)
or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1, having the structural formula:

![Chemical Structure 2](image2)
or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1, having the structural formula:

![Chemical Structure 3](image3)
or a pharmaceutically acceptable salt thereof.

7. The compound of any preceding claim, which is an optically pure enantiomer having the S-configuration at C⁵ of the oxazolidinone ring.

8. A pharmaceutical composition comprising the compound of any of claims 1 to 7 in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

9. Use of the compound of any of claims 1 to 7, for the manufacture of a medicament for treating a microbial infection in a warm-blooded animal.

Patentansprüche

1. Verbindung der Formel

oder ein pharmazeutisch verträgliches Salz davon;
worin L eine Bindung oder -NR⁸ (CR⁹)₂ NR⁸ ist;
Rⁱ ausgewählt ist aus H, C₁-C₄-Alkyl, C₃-C₅-Cycloalkyl, C₁-C₄-Halogenalkyl und Halogenphenyl; und
R² ausgewählt ist aus H, Alkyl, C₁-C₂-Alkoxy, Halogen, und Halogenalkoxy; oder
R¹ und R² zusammen genommen einen gegebenenfalls substituierten 5- oder 6-gliedrigen Heteroalkyl- oder Heteroarylring bilden;
R³ H oder F ist;
R⁶ ausgewählt ist aus H, Methyl, Hydroxy und Halogen;
jede Gruppe R⁸ unabhängig H oder C₁-C₂-Alkyl ist, oder die R⁸-Gruppen werden zusammen genommen, um einen gegebenenfalls substituierten 4- bis 9-gliedrigen Heteroalkyl- oder Heteroarylring zu bilden;
jede Gruppe R⁹ unabhängig H oder C₁-C₂-Alkyl ist, oder die R⁹-Gruppen werden zusammen genommen, um einen 4- bis 9-gliedrigen heterocyclischen oder heterobicyclischen Ring zu bilden, der gegebenenfalls substituiert ist mit C₁-C₂-Alkyl, Halogenalkyl oder Methoxyiminno;
R¹¹ ausgewählt ist aus H, C₁-C₇-Alkyl, C₃-C₅-Cycloalkyl, Hydroxymethyl, Halogenalkyl, CH₂SMe, N(R¹²)₂,
C₁⁻C₄-Alkoxy und Aryloxy; und
R¹² C₁⁻C₄-Alkyl ist.

2. Verbindung nach Anspruch 1, worin L eine Bindung ist.

3. Verbindung nach Anspruch 1, worin L NR₈ (CR₉)₂ NR₈ ist.

4. Verbindung nach Anspruch 1 mit der Strukturformel:

\[
\begin{align*}
\text{Structural formula 1}
\end{align*}
\]

oder ein pharmazeutisch verträgliches Salz davon.

5. Verbindung nach Anspruch 1, mit der Strukturformel:

\[
\begin{align*}
\text{Structural formula 2}
\end{align*}
\]

oder ein pharmazeutisch verträgliches Salz davon.

6. Verbindung nach Anspruch 1 mit der Strukturformel:

\[
\begin{align*}
\text{Structural formula 3}
\end{align*}
\]

oder ein pharmazeutisch verträgliches Salz davon.
7. Verbindung nach einem der vorstehenden Ansprüche, die ein optisch reines Enantiomer ist mit der S-Konfiguration am C₅ des Oxazolidinonrings.

8. Pharmazeutische Zusammensetzung, umfassend die Verbindung nach einem der Ansprüche 1 bis 7 im Gemisch mit einem pharmazeutisch verträglichen Adjuvanz, Verdünnungsmittel oder Trägerstoff.

9. Verwendung der Verbindung nach einem der Ansprüche 1 bis 7 zur Herstellung eines Medikaments zur Behandlung einer mikrobiellen Infektion in einem warmblütigen Tier.

Revendications

1. Composé de formule :

   ![Chemical Structure](image)

   ou sel pharmaceutiquement acceptable de celui-ci ;
   dans lequel L est une liaison ou -NR₈(CR₉)₂NR₈⁻ ;
   R¹ est sélectionné parmi H, alkyle en C₁-C₄, cycloalkyle en C₃-C₅, halogénoalkyle en C₁-C₄, et halogénophényle ; et
   R² est sélectionné parmi H, alkyle, alcoxy en C₁-C₂, halogéno et halogénoalcoxy ; ou
   R¹ et R², pris ensemble, forment un noyau hétéraalkyle ou hétéroaryle à 5 ou 6 éléments, facultativement substitué ;
   R³ représente H ou F ;
   R⁶ est sélectionné parmi H, méthyle, hydroxy et halogéno ;
   chaque R⁸ représente indépendamment H ou alkyle en C₁-C₄, ou les groupes R⁸ sont pris ensemble pour former un noyau hétéraalkyle ou hétéroaryle ayant de 4 à 9 éléments, facultativement substitué ;
   chaque R⁹ représente indépendamment H ou alkyle en C₁-C₄, ou les groupes R⁹ sont pris ensemble pour former un noyau hétérocyclique ou hétérobicyclique ayant de 4 à 9 éléments, facultativement substitué par alkyle en C₁-C₂, halogénoalkyle ou méthoximino ;
   R¹¹ est sélectionné parmi H, alkyle en C₁-C₇, cycloalkyle en C₃-C₅, hydroxyméthyle, halogénoalkyle, CH₂SMe, N
   (R¹²)₂, alcoxy en C₁-C₂ et aryloxy ; et
   R¹² représente alkyle en C₁-C₄.

2. Composé selon la revendication 1, dans lequel L est une liaison.

3. Composé selon la revendication 1, dans lequel L représente NR⁸(CR⁹)₂NR⁸⁻.

4. Composé selon la revendication 1, de formule structurelle:
5. Composé selon la revendication 1, de formule structurelle:

6. Composé selon la revendication 1, de formule structurelle :

7. Composé selon l’une quelconque des revendications précédentes, qui est un énantiomère optiquement pur de configuration S en position C5 du noyau oxazolidinone.

8. Composition pharmaceutique comprenant un composé selon l’une quelconque des revendications 1 à 7 en mélange avec un adjuvant, un diluant ou un support pharmaceutiquement acceptable.
9. Utilisation d'un composé selon l'une quelconque des revendications 1 à 7, pour la fabrication d'un médicament pour le traitement d'une infection microbienne chez un animal homéotherme.