

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
4 January 2007 (04.01.2007)

PCT

(10) International Publication Number
WO 2007/000644 A1

(51) International Patent Classification:

C07D 413/10 (2006.01) A61P 31/04 (2006.01)
C07D 413/14 (2006.01) A61K 31/4178 (2006.01)

(21) International Application Number:

PCT/IB2006/001730

(22) International Filing Date: 20 June 2006 (20.06.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/694,862 29 June 2005 (29.06.2005) US

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

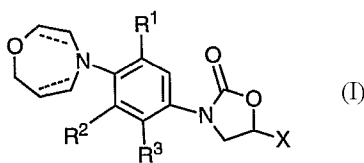
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HOMOMORPHOLINE OXAZOLIDINONES AS ANTIBACTERIAL AGENTS



(57) Abstract: The present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof wherein X is -C(=O)NHR⁴, or CH₂-het; R¹, R², R³ are independently H or F; R⁴ is H, C₁₋₆ alkyl, or OC₁₋₆alkyl; het is a five (5)-membered heterocyclic ring having 1, 2 or 3 heteroatoms selected from the group consisting of non-peroxide oxygen, sulfur, and nitrogen within the ring. The compounds of the present are useful as antibacterial agents.

HOMOMORPHOLINE OXAZOLIDINONES AS ANTIBACTERIAL AGENTS

FIELD OF INVENTION

The present invention relates to a new class of oxazolidinone derivatives, to
5 their use as antibacterial agents, to pharmaceutical compositions containing these
compounds and to methods for their preparation.

BACKGROUND OF THE INVENTION

Antibacterial resistance is a global clinical and public health problem that has
10 emerged with alarming rapidity in recent years and undoubtedly will increase in the
near future. Resistance is a problem in the community as well as in health care
settings, where transmission of bacteria is greatly amplified. Because multiple drug
resistance is a growing problem, physicians are now confronted with infections for
which there is no effective therapy. As result, structurally novel antibacterials with a
15 new mode of action have become increasingly important in the treatment of bacterial
infections.

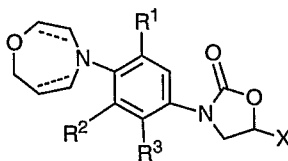
Among newer antibacterial agents, oxazolidinone compounds are the most
recent synthetic class of antimicrobials. This invention provides a new class of
oxazolidinone derivatives containing a homomorphline ring, which are active against
20 a number of human and veterinary pathogens, including multiple resistant strains of
bacteria.

INFORMATION DISCLOSURE

WO 9323384, WO 9507271, WO 20028084, WO 2003072553, WO
2003072576, WO 2003072575, WO 200142229, WO 200264575, WO 9615130, WO
25 200216960, WO 200027830, WO 200146185, WO 200281469, WO 200281470, WO
2001080841, WO 2003084534, WO 2003093247, WO 200202095, WO 200230395,
WO 200272066, WO 2003063862, WO 2003072141, WO 2003072081, WO
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WO 9924428, WO 2004014392, WO 2004002967, WO 2004009587, WO
30 2004018439, US Patent Application Publication No. US 2004/0044052, US Patent
No. 5547950, US Patent No. 5700799, DE 10034627 disclose oxazolidinone
compounds having antibacterial activity useful for treating microbial infections.

SUMMARY OF THE INVENTION

The present invention provides a compound of formula I



I

or a pharmaceutically acceptable salt thereof wherein:

X is $-\text{C}(=\text{O})\text{NHR}^4$, or $\text{CH}_2\text{-het}$;

$\text{R}^1, \text{R}^2, \text{R}^3$ are independently H or F;

10 R^4 is H, C_{1-6} alkyl, or OC_{1-6} alkyl;

het is a five (5)-membered heterocyclic ring having 1, 2 or 3 heteroatoms selected from the group consisting of non-peroxide oxygen, sulfur, and nitrogen within the ring wherein het is optionally substituted with 1-3 halo, C_{1-4} alkyl, ethylene, ethynyl, CN, N_3 , $\text{O}(\text{C}=\text{O})\text{C}_{1-4}$ alkyl, NH_2 , $\text{NHC}(=\text{O})\text{C}_{1-4}$ alkyl, or $\text{C}(=\text{O})\text{C}_{1-4}$ alkyl; each dotted line

15 "... is independently a single bond or absent; and

at each occurrence, C_{1-6} alkyl is optionally substituted by 1-3 halo, OH, OC_{1-4} alkyl, CN, N_3 , $\text{O}(\text{C}=\text{O})\text{C}_{1-4}$ alkyl, NH_2 , $\text{NHC}(=\text{O})\text{C}_{1-4}$ alkyl, or $\text{C}(=\text{O})\text{C}_{1-4}$ alkyl. .

In another aspect, the present invention also provides:

a pharmaceutical composition which comprises a pharmaceutically acceptable
20 carrier and a compound of formula I,

a method for treating microbial infections in a mammal by administering to the subject in need a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof, and

a use of a compound of formula I or a pharmaceutically acceptable salt thereof
25 to prepare a medicament for treating microbial infections.

The invention may also provide novel intermediates and novel processes that are useful for preparing compounds of formula I.

DETAILED DESCRIPTION OF THE INVENTION

30 Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, C₁₋₆ alkyl refers to alkyl of
5 one to six carbon atoms, inclusive.

The term alkyl, or alkenyl, etc. refer to both straight and branched groups, but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to.

The term "halo" refers to fluoro (F), chloro (Cl), bromo (Br), or iodo (I).

10 The term "het" is a five (5)-membered heterocyclic ring having 1, 2 or 3 heteroatoms selected from the group consisting of non-peroxide oxygen, sulfur, and nitrogen within the ring. Examples of het including, but not limiting, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, 1,2,3-oxadiazole, 1,2,4—oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole; and also in an alternative
15 embodiment, isothiazole, 1,2,5-thiadiazole, 1,2,4-thiadiazole or 1,2,3-thiadiazole.

The term "a pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound.

The term "pharmaceutically acceptable carrier" means a carrier that is useful in
20 preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier" as used in the specification and claims includes both one and more than one such carrier.

25 The term "mammal" refers to human or warm-blooded animals including livestock and companion animals. Livestock refers to animals suitable for human meat consumption. Examples include pigs, cattle, chickens, fish, turkeys, rabbits, etc. Companion animals refer to animals kept as pets such as dogs, cats, etc.

The term "optional" or "optionally" means that the subsequently described
30 event or circumstance may, but need not, occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

The term "treating" or "treatment" of a disease includes: (1) preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a mammal

that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease; (2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms; or (3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

5 The term "therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

10 The term "leaving group" has the meaning conventionally associated with it in synthetic organic chemistry i.e., an atom or group capable of being displaced by a nucleophile and includes halogen, alkylsulfonyloxy, ester, or amino such as chloro, bromo, iodo, mesyloxy, tosyloxy, trifluorosulfonyloxy, methoxy, N,O-dimethylhydroxyl-amino, and the like.

15 Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers".

 It will be appreciated by those skilled in the art that compounds of the
20 invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, tautomeric, or stereoisomeric form, or mixture thereof, of a compound of the invention, which possesses the useful properties described herein, it being well known
25 in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine antiviral activity using the standard tests described herein, or using other similar tests which are well known in the art.

30 The compounds of the present invention are generally named according to the IUPAC or CAS nomenclature system.

Abbreviations which are well known to one of ordinary skill in the art may be used (e.g. "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "h" for an hour or hours and "rt" for room temperature).

Specific and preferred values listed below for radicals, substituents, and
5 ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

Specifically, alkyl denotes both straight and branched groups; but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to.

10 Specifically, alkyl is methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, and their isomeric forms thereof.

Specifically, halo is fluoro (F), or chloro (Cl).

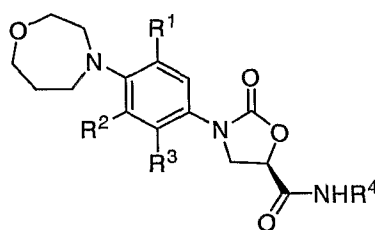
Specifically, R^1 , R^2 and R^3 are independently H or F.

Specifically, R^4 is H, $-CH_3$, or $-CH_2CH_3$.

15 Specifically, R^4 is $-OCH_3$, or $-OCH_2CH_3$.

Specifically, het is triazol.

Specifically the present invention provides a compound of formula Ia

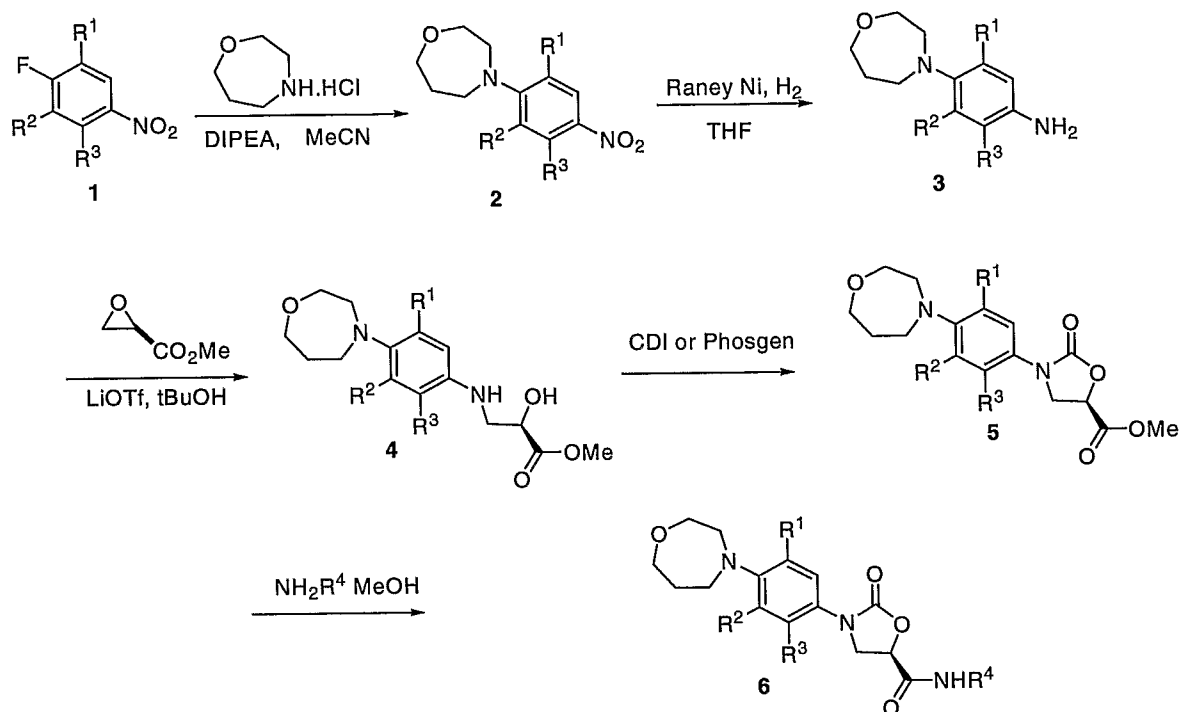


20

Ia.

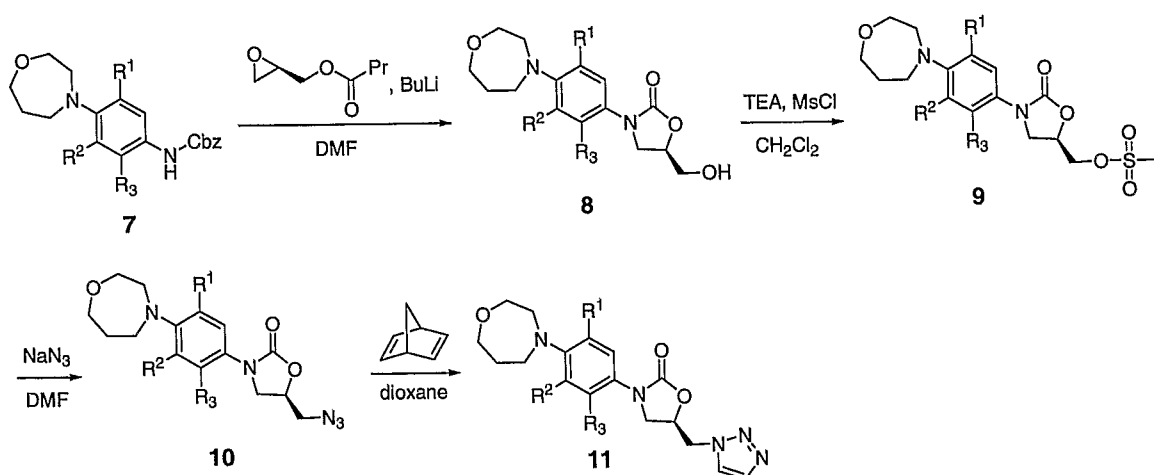
Schemes I and II describe the preparation of compounds of the present invention. The starting materials are prepared by procedures described in these schemes or by procedures known to one of ordinary skill in the art.

Scheme I



According to Scheme I, the appropriately substituted 4-fluoronitrobenzene (1) is converted to the corresponding anilines (2) via aromatic nucleophilic displacement by treating with the corresponding amine in the presence of a base. The nitro compound (2) is reduced to its corresponding amino compound (3) via chemical (using metal like Fe and ammonium chloride) or catalytic reduction (catalyst like Raney nickel in the presence of hydrogen). Amine (3) is reacted with an appropriately protected (R)-methyl glycidate and a Lewis acid such as lithium triflate as described in US Patent Application Publication No. US2004/0044052. The amino alcohol (4) can then be ring closed to give aryl oxazolidinone (5) using methods known to one skilled in the art. For instance, treatment of structure 4 with 1,1'-carbonyldiimidazole in solvent such as acetonitrile or tetrahydrofuran at an appropriate temperature, typically in the range of 20 °C to 60 °C or with phosgene in a solvent such as toluene or methylene chloride, or mixture thereof, in the presence of a base such as triethylamine at an appropriate temperature, typically in a range from -10 °C to 25 °C affords the oxazolidinone (5). Subsequent treatment of oxazolidinone ester (5) with ammonia or optionally substituted amines (RNH₂) in a suitable solvent such as methanol or acetonitrile affords amides (6). Similarly, treatment of ester (5) with O-alkylhydroxylamines or hydrazines gives the hydroxamate (R = O-alkyl) or hydrazide (R = NH₂) respectively.

Scheme II



- 5 According to Scheme II, the appropriately substituted 4-morpholinyl-aniline (3) is converted to its benzyl carbamate (7) by treating it with benzyl chloroformate in the presence of a base like triethylamine or sodium bicarbonate. Benzyl carbamate (7) on treatment with the corresponding epoxide in the presence of a lithium base (e.g.; n-butyllithium) afforded the corresponding oxazolidinone (8). The alcohol (8) is
- 10 converted to its mesylate (9) by treating with methanesulfonyl chloride in the presence of base. Subsequent treatment of mesylate with sodium azide affords the corresponding azide (10). The compound 10 is converted to the product 11 by heating with 2,5-norbornadiene (J. Med. Chem. 2004, 48, 499-506). Other substituted triazoles are synthesized as shown in J. Med. Chem. 2004, 48, 499-506.

15

Medical and Veterinary Uses

- It is known that as a chemical compound class, oxazolidinones generically inhibit monoamine oxidase (MAO), the enzyme responsible for preventing acute blood pressure elevation by the endogenous and dietary amine, tyramine.
- 20 Accordingly, there is a demand to discover oxazolidinone antibiotics, which possess minimum MAO inhibitory activity to lower risk of potential drug-drug interactions. It has been discovered that, the compound of the present invention has unexpectedly weak MAO inhibitory activity, which indicates it possesses the capacity to minimize or eliminate potential drug-drug interactions since strong inhibition of monoamine
- 25 oxidase can result in altered clearance rates for other compounds normally metabolized by it, including several pharmaceuticals.

The compound of the present invention may be used for the treatment of infectious, Gram-positive bacterial infections caused by a variety of bacterial organisms, including those that require long-term therapy (>28 days).

Examples of the bacterial organisms include gram-positive bacteria such as multiple resistant staphylococci, for example *S. aureus* and *S. epidermidis*; multiple resistant streptococci, for example *S. pneumoniae* and *S. pyogenes*; and multiple resistant Enterococci, for example *E. faecalis*; gram negative aerobic bacteria such as Haemophilus, for example *H. influenzae* and Moraxella, for example *M. catarrhalis*; as well as anaerobic organisms such as bacteroides and clostridia species, and acid-fast organisms such as Mycobacteria, for example *M. tuberculosis*; and/or *Mycobacterium avium*. Other examples include Escherichia, for example *E. coli*. intercellular microbes, for example Chlamydia and Rickettsiae.

Examples of infections that may be treated with the compound of the present invention include central nervous system infections, external ear infections, infections of the middle ear, such as acute otitis media, infections of the cranial sinuses, eye infections, infections of the oral cavity, such as infections of the teeth, gums and mucosa, upper respiratory tract infections, lower respiratory tract infections, genitourinary infections, gastrointestinal infections, gynecological infections, septicemia, bone and joint infections, skin and skin structure infections, bacterial endocarditis, burns, antibacterial prophylaxis of surgery, and antibacterial prophylaxis in immunosuppressed patients, such as patients receiving cancer chemotherapy, or organ transplant patients. Specifically, infectious diseases that may be treated with the compound of the present invention are gram-positive infections such as osteomyelitis, endocarditis and diabetic foot.

Antibacterial activity

The *in vitro* antibacterial activity of the compounds of the present invention may be assessed by following procedures recommended in (1) National Committee for Clinical Laboratory Standards (Jan. 2003), *Methods for dilution antimicrobial tests for bacteria that grow aerobically*, Approved Standard (6th ed), M7-A6, NCCLS, Wayne, PA; (2) National Committee for Clinical Laboratory Standards (Mar. 2001), *Methods for antimicrobial susceptibility testing of anaerobic bacteria*, Approved Standard (5th ed), M11-A4, NCCLS, Wayne, PA; (3) National Committee for Clinical

Laboratory Standards (Jan.2003), *MIC testing supplemental tables*, M100-S13 (for use with M7-A6), NCCLS, Wayne, PA; and (4) Murray PR, Baron EJ, Jorgensen JH, et al. *Manual of Clinical Microbiology* (8th ed) Washington, DC: American Society for Microbiology Press, 2003. The antibacterial activity can be presented in the form of MIC value. The MIC value is the lowest concentration of drug, which prevented macroscopically visible growth under the conditions of the test.

Table 1
(Minimum Inhibitory concentrations $\mu\text{g/mL}$)

Example	<i>S. aureus</i> (UC-76)	<i>S. pyogenes</i> (C203)	<i>S. pneumoniae</i> (SV-1)
1	8	8	16
5	4	4	8
6	4	4	8
9	4	1	2
11	4	2	2

Pharmaceutical Salts

The compound of formula I may be used in its native form or as a salt. In cases where forming a stable nontoxic acid or base salt is desired, administration of the compound as a pharmaceutically acceptable salt may be appropriate. Examples of pharmaceutically acceptable salts of the present invention include inorganic salts such as hydrochloride, hydrobromide, sulfate, nitrate, bicarbonate, carbonate salts, and organic salts such as tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, etoglutarate, and glycerophosphate.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example, reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

Routes of Administration

In therapeutic use for treating, or combating, bacterial infections in a mammal (i.e. human and animals), a compound of the present invention or its pharmaceutical compositions can be administered orally, parenterally, topically, rectally, transmucosally, or intestinally.

Parenteral administrations include indirect injections to generate a systemic effect or direct injections to the afflicted area. Examples of parenteral administrations

are subcutaneous, intravenous, intramuscular, intradermal, intrathecal, intraocular, intranasal, intraventricular injections or infusions techniques.

Topical administrations include the treatment of infectious areas or organs readily accessibly by local application, such as, for example, eyes, ears including
5 external and middle ear infections, vaginal, open wound, skins including the surface skin and the underneath dermal structures, or other lower intestinal tract. It also includes transdermal delivery to generate a systemic effect.

The rectal administration includes the form of suppositories.

The transmucosal administration includes nasal aerosol or inhalation
10 applications.

The preferred routes of administration are oral and parenteral.

Composition/Formulation

Pharmaceutical compositions of the present invention may be manufactured by
15 processes well known in the art, *e.g.*, by means of conventional mixing, dissolving, granulation, dragee-making, levigating, emulsifying, encapsulating, entrapping, lyophilizing processes or spray drying.

Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically
20 acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active compound into preparations, which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For oral administration, the compound can be formulated by combining the active compound with pharmaceutically acceptable carriers well known in the art.
25 Such carriers enable the compound of the invention to be formulated as tablets, pills, lozenges, dragees, capsules, liquids, solutions, emulsions, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient. A carrier can be at least one substance which may also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent.
30 Examples of such carriers or excipients include, but are not limited to, magnesium carbonate, magnesium stearate, talc, sugar, lactose, sucrose, pectin, dextrin, mannitol, sorbitol, starches, gelatin, cellulosic materials, low melting wax, cocoa butter or

powder, polymers such as polyethylene glycols and other pharmaceutical acceptable materials.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical compositions, which can be used orally, include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with a filler such as lactose, a binder such as starch, and/or a lubricant such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compound may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, liquid polyethylene glycols, cremophor, capmul, medium or long chain mono-, di- or triglycerides. Stabilizers may be added in these formulations, also.

Liquid form compositions include solutions, suspensions and emulsions. For example, there may be provided solutions of the compound of this invention dissolved in water and water-propylene glycol and water-polyethylene glycol systems, optionally containing suitable conventional coloring agents, flavoring agents, stabilizers and thickening agents.

The compound may also be formulated for parenteral administration, *e.g.*, by injections, bolus injection or continuous infusion. Formulations for parenteral administration may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating materials such as suspending, stabilizing and/or dispersing agents.

For injection, the compound of the invention may be formulated in aqueous solution, preferably in physiologically compatible buffers or physiological saline buffer. Suitable buffering agents include trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine.

Parenteral administrations also include aqueous solutions of a water soluble form, such as, without limitation, a salt, of the active compound. Additionally, suspensions of the active compound may be prepared in a lipophilic vehicle. Suitable lipophilic vehicles include fatty oils such as sesame oil, synthetic fatty acid esters such as ethyl oleate and triglycerides, or materials such as liposomes. Aqueous injection suspensions may contain substances, which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers and/or agents that increase the solubility of the compound to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile, pyrogen-free water, before use. For suppository administration, the compound may also be formulated by mixing the agent with a suitable non-irritating excipient, which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and other glycerides.

For administration by inhalation, compound of the present invention can be conveniently delivered through an aerosol spray in the form of solution, dry powder, or suspensions. The aerosol may use a pressurized pack or a nebulizer and a suitable propellant. In the case of a pressurized aerosol, the dosage unit may be controlled by providing a valve to deliver a metered amount. Capsules and cartridges of, for example, gelatin for use in an inhaler may be formulated containing a power base such as lactose or starch.

For topical applications, the pharmaceutical composition may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion such as suspensions, emulsion, or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan

monostearate, polysorbate 60, cetyl esters wax, cetearly alcohol, 2-octyldodecanol, benzyl alcohol and water.

For ophthalmic and otitis uses, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as a benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

In addition to the formulations described previously, the compound may also be formulated as depot preparations. Such long acting formulations may be in the form of implants. A compound of this invention may be formulated for this route of administration with suitable polymers, hydrophobic materials, or as a sparingly soluble derivative such as, without limitation, a sparingly soluble salt.

Additionally, the compound may be delivered using a sustained-release system. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compound for 24 hours or for up to several days.

Dosage

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an amount sufficient to achieve the intended purpose, *i.e.*, the treatment or prevent of infectious diseases. More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated.

The quantity of active component, that is the compound of this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the manner of administration, the potency of the particular compound and the desired concentration. Determination of a therapeutically effective amount is well within the capability of those skilled in the art. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

Generally, a therapeutically effective amount of dosage of active component will be in the range of about 0.1 to about 400 mg/kg of body weight/day, more preferably about 1.0 to about 50 mg/kg of body weight/day. It is to be understood that the dosages may vary depending upon the requirements of each subject and the severity of the bacterial infection being treated. In average, the effective amount of active component is about 200 mg to 800 mg and preferable 600 mg per day.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired plasma concentration. On the other hand, the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g., two to four times per day.

In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration and other procedures known in the art may be used to determine the desired dosage amount.

The compounds of this invention can be prepared in accordance with the methods discussed below. All of the starting materials are either commercially available or can be prepared by procedures that would be well known to one of ordinary skill in organic chemistry. Also, in the discussion the preparations below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

	bm	=	broad multiplet
	bd	=	broad doublet
	bs	=	broad singlet
30	bt	=	broad triplet
	CDI	=	1,1 <i>O</i> -carbodiimidazole
	d	=	doublet
	dd	=	doublet of doublets
	dq	=	doublet of quartets
35	dt	=	doublet of triplets
	dm	=	doublet of multiplets
	DMF	=	dimethylformamide

	DMAP	=	dimethylaminopyridine
	DIEA	=	diisopropylethylamine
	DMSO	=	dimethyl sulfoxide
	eq.	=	equivalents
5	g	=	grams
	h	=	hour or hours
	HPLC	=	high pressure liquid chromatography
	HATU	=	N-[(dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-yl-methylene]-N-methylmethanaminium
10			hexafluorophosphate N-oxide
	LG	=	leaving group
	m	=	multiplet
	M	=	molar
	M%	=	mole percent
15	max	=	maximum
	meq	=	milliequivalent
	mg	=	milligram
	mL	=	milliliter
	mm	=	millimeter
20	mmol	=	millimol
	q	=	quartet
	s	=	singlet
	t or tr	=	triplet
	TBS	=	tributylsilyl
25	TFA	=	trifluoroacetic acid
	THF	=	tetrahydrofuran
	TLC	=	thin layer chromatography
	p-TLC	=	preparative thin layer chromatography
	μL	=	microliter
30	N	=	normality
	MeOH	=	methanol
	DCM	=	dichloromethane
	HCl	=	hydrochloric acid
	ACN	=	acetonitrile
35	MS	=	mass spectrometry
	rt	=	room temperature
	EtOAc	=	ethyl acetate
	EtO	=	ethoxy
	Ac	=	acetate
40	NMP	=	1-methyl-2-pyrrolidinone
	μL	=	microliter
	J	=	coupling constant
	NMR	=	Nuclear magnetic resonance
	MHz	=	megahertz
45	Hz	=	hertz
	m/z	=	mass to charge ratio
	min	=	minutes
	Boc	=	<i>tert</i> -butoxycarbonyl
	CBZ	=	benzyloxycarbonyl
50	DCC	=	1,3-dicyclohexylcarbodiimide

PyBop = benzotriazole-1-yl-oxy-trispyrrolidinophosphonium
hexafluorophosphate

General Methods

General Method I

5

Step 1: The appropriate fluoronitrobenzene (1) is dissolved in NMP and cooled to 0 °C. To the solution Hünig's base and homomorpholine hydrochloride salt is added. The reaction is stirred at the appropriate temperature for about 18 h. Water is added and stirred for about 1 h resulting in the formation of a solid. The solid is collected via filtration, then rinsed with water and dried under vacuum to afford the desired nitro compound (2).

10

Step 2: The appropriate nitrobenzene (2) is dissolved in THF and placed in Parr shaker with Raney Nickel at 50 psi with a supply of H₂ for about 16 h. The resulting solution is filtered and concentrated to afford the desired aniline compound (3).

15

Step 3: The appropriate aniline (3) is dissolved in *tert*-butanol. To the solution oxirane-2-carboxylic acid methyl ester and lithium triflate is added. The reaction is heated at about 70 °C for about 16 h. To the reaction water and dichloromethane is added. The phase is separated and aqueous layer is extracted with dichloromethane.

20

The combined organic layer is washed with brine and then with water, dried over Na₂SO₄ and concentrated *in vacuo*. The resulting oil is re-dissolved in dichloromethane. To the solution CDI is added and the reaction is stirred at rmt for about 16 h. The reaction is quenched with the addition of 10% citric acid and dichloromethane. The phase is separated and aqueous layer is extracted with dichloromethane. The combined organic layer is washed with brine and then with water, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by silica gel chromatography afforded the desired methyl ester compound (5).

25

Step 4: The appropriate methyl ester (5) is placed in a round bottom flask and the appropriate amine as a solution in methanol is added. The reaction is stirred at rmt for 5 h and then concentrated to afford the desired final product of the present invention.

30

The invention may also provide novel intermediates and novel processes that are useful for preparing compounds of formula I.

General Method II

Step 1: The appropriate benzyl carbamate (7) is dissolved in THF then cooled to -78 °C. To the reaction, butyl lithium is added and stirred at -78 °C for 1h followed by the addition of glycidyl butyrate. The resulting solution is stirred at -78 °C for 1 h
5 then warmed to rmt and stirred at rmt for 18 h. The reaction is diluted with the addition of dichloromethane followed by water. Layers are separated and aqueous layer is extracted with dichloromethane. Combined organic layer is washed with brine and water, dried over NaSO₄ and concentrated. Purification by silica gel chromatography afforded the desired product (8).

10

Step 2: The appropriate alcohol (8) is dissolved in dichloromethane then cooled to 0 °C. To the solution mesyl chloride is added followed by triethylamine. The reaction is stirred at 0 °C for 2 h then diluted with dichloromethane and water. Layers are separated and aqueous layer is extracted with dichloromethane. Combined organic
15 layer is washed with brine and water, dried over NaSO₄ and concentrated to afford the desired product (9).

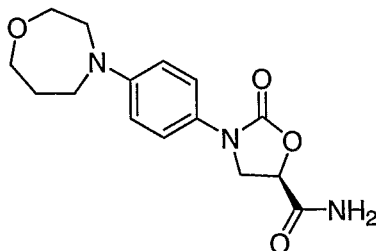
Step 3: The mesylate (9) dried under vacuum overnight is dissolved in DMF then sodium azide is added. The reaction is stirred at 75 °C for 18 h. The resulting
20 solution is cooled to rmt and diluted with water and EtOAc. Layers are separated and aqueous layer is extracted with EtOAc. Combined organic layer is washed with brine and water, dried over NaSO₄ and concentrated to afford the desired product (10).

Step 4: To the solution of the appropriate azide (10) in dioxane 2,5-norboadiene is added. The resulting solution is refluxed for 4 h. The reaction is cooled to rmt and diluted with dichloromethane and water. Layers are separated and aqueous layer is extracted with dichloromethane. Combined organic layer is washed with brine and water, dried over NaSO₄ and concentrated. Purification by silica gel chromatography afforded the desired product (11).

30

EXAMPLES

Example 1 Preparation of 3-(4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid amide



Step 1: Preparation of 4-(4-nitro-phenyl)-[1,4]oxazepane

Following Step 1 of above general method, 2-fluoro nitrobenzene (500.0 mg, 3.54 mmol) in NMP (1.7 ml) with hünig's base (1.3 ml, 7.7 mmol) and homomorpholine hydrochloric salt (507.0 mg, 3.68 mmol) afforded the title compound as a solid.

^1H NMR (400 MHz, CDCl_3): δ 2.05 (quint, 2 H), 3.70-3.74 (m, 6 H), 3.87 (t, 2 H), 6.67 (d, 2 H), 8.13 (d, 2 H). MS-APCI (m/z^+): 223 (M+1).

Step 2: Preparation of 4-[1,4]oxazepan-4-yl-phenylamine

Following Step 2 of above general method, 4-(4-nitro-phenyl)-[1,4]oxazepane (720.3 mg, 2.79 mmol) in THF (50 ml) with Raney Nickel (400.0 mg) afforded the title compound as oil.

^1H NMR (400 MHz, CDCl_3): δ 2.03 (quint, 2 H), 3.50-3.53 (m, 4 H), 3.70 (t, 2 H), 3.82 (dd, 2 H), 6.62-6.67 (m, 4 H). MS-APCI (m/z^+): 193 (M+1).

Step 3: Preparation of 3-(4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid methyl ester

Following Step 3 of above general method, 4-[1,4]oxazepan-4-yl-phenylamine (620.0 mg, 3.22 mmol) is reacted with oxirane-2-carboxylic acid methyl ester (311 \square l, 3.55 mmol) and lithium triflate (580.0 mg, 3.50 mmol) in *tert*-butanol (8.3 ml) and later with CDI (784.0 mg, 4.84 mmol) in dichloromethane (3 ml) to afford the title compound as a solid.

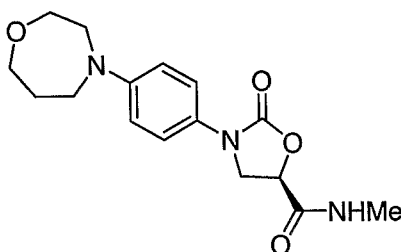
^1H NMR (400 MHz, CDCl_3): δ 2.01 (quint, 2 H), 3.57-3.62 (m, 4 H), 3.66 (t, 2 H), 3.81 (t, 2 H), 3.86 (s, 3 H), 4.07 (dd, 1 H), 4.23 (t, 1 H), 5.03 (dt, 1H), 6.69 (d, 2 H), 7.28 (d, 2 H). MS-APCI (m/z^+): 321 (M+1).

Step 4: Preparation of 3-(4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid amide:

Following Step 4 of above general method, 3-(4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid methyl ester (72.4 mg, 0.23 mmol) is reacted with ammonia in methanol (2M, 1.1 ml, 2.3 mmol) to afford the title compound as a solid.

5 ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.82 (quint, 2 H), 3.47-3.50 (m, 6 H), 3.64 (t, 2 H), 3.85 (dd, 1 H), 4.14 (t, 1 H), 4.90 (dd, 1 H), 6.69 (d, 2 H), 7.25 (d, 2 H), 7.51 (s, 1 H), 7.74 (s, 1 H). MS-APCI (m/z^+): 306 ($M+2$).

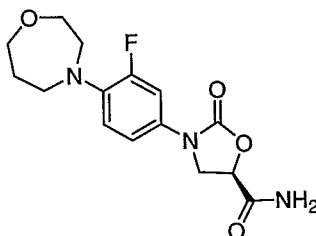
10 Example 2 Preparation of 3-(4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid methylamide



15 Following Step 4 of above general method, 3-(4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid methyl ester (70.2 mg, 0.22 mmol) is reacted with methyl amine in methanol (2M, 1.1 ml, 2.2 mmol) to afford the title compound as a solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.88 (quint, 2 H), 2.66 (d, 3 H), 3.53-3.57 (m, 6 H), 3.70 (t, 2 H), 3.92 (dd, 1 H), 4.20 (t, 1 H), 5.00 (dd, 1 H), 6.75 (d, 2 H), 7.31 (d, 2 H), 8.33 (q, 1 H). MS-APCI (m/z^+): 320 ($M+1$).

20

Example 3 Preparation of 3-(3-Fluoro-4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid amide



25

Step 1: Preparation of 4-(2-fluoro-4-nitrophenyl)-[1.4]oxazepane

Following Step 1 of above general method, 3,4-difluoronitrobenzene (6.60 g, 41.49 mmol, 4.59 mL) in NMP (40 mL) is cooled to at about -20 °C (ice/salt water bath). Added Hunig's base (11.53 g, 89.19 mmol, 15.54 mL) followed by addition of homomorpholine HCl (5.99 g, 43.60 mmol) portion wise over approx. 30 min. After the addition is completed, the reaction solution is stirred for about 45 min. at 0 °C and the reaction is diluted with H₂O (175 mL) to provide a yellow precipitate. The solid is collected by filtration; the solids are washed with H₂O (3x) and dried under house high vacuum on buchner funnel over night to afford the title compound.

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.00-2.06 (m, 2 H) 3.62-3.68 (m, 4 H) 3.74-3.77 (m, 2 H) 3.3.82-3.85 (m, 2 H) 6.74 (t, *J*=9.1 Hz, 1 H) 7.83-7.92 (m, 2 H).

Step 2: Preparation of 3-fluoro-4-[1.4]oxazepan-4-yl-phenylamine

Following Step 2 of above general method, 4-(2-Fluoro-4-nitrophenyl)-[1.4]oxazepane (9.15 g, 38.10 mmol) is dissolved in tetrahydrofuran (200 mL) in a Parr shaker and placed in a H₂ atmosphere at 50 psi in the presence of Raney Ni for 15 hrs. The solution is then filtered and the solvent removed in vacuo to afford the title compound.

MS-APCI (*m/z*⁺): 211.

Step 3: Preparation of 3-(3-fluoro-4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid methyl ester

Following Step 3 of above general method, 3-fluoro-4-[1.4]oxazepan-4-yl-phenylamine (1.00 g, 4.76 mmol) is dissolved in t-butanol (15mL), methyl glycidate (0.483 g, 5.71 mmol, 0.500 mL) is added, heated to approx 40 °C in oil bath then added lithium triflate (0.890 g, 5.71 mmol) then raised temperature to 70 °C and stirred under N₂ at 70 °C overnight. Heat is then removed and H₂O added, extracted (2x) with dichloromethane, organics combined, washed with brine, dried over sodium sulfate, filtered, conc. The isolated residue is then dissolved in dichloromethane (40 mL), 1-hydroxybenzotriazole (0.354 g, 2.60 mmol) added and stirred under N₂ at room temperature for 10 minutes. Carbonyldiimidazole (0.0.50 g, 3.08 mmol) is added and the reaction mixture heated at 35 ° in an oil bath overnight. Heating is then removed and additional dichloromethane added, washed organic phase with saturated ammonium chloride solution and then with brine, dried over sodium sulfate, filtered

and solvent removed in vacuo. The isolated residue is subjected to silica gel flash chromatography, eluting with 20% MeOH in dichloromethane/dichloromethane gradient (0-10% of 20% MeOH in dichloromethane over 1 hr) to afford the title compound.

5 ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.00-2.03 (m, 2 H) 3.38-3.41 (m, 4 H) 3.78-3.83 (m, 7 H) 4.04 (dd, $J=9.2, 5.5$ Hz, 1 H) 4.20 (t, $J=9.4$ Hz, 1 H) 5.01 (dd, $J=9.6, 5.3$ Hz, 1 H) 6.87 (br s, 1 H) 7.00-7.03 (m, 1 H) 7.30-7.33 (m, 1 H).

Step 4: Preparation of 3-(3-fluoro-4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid amide

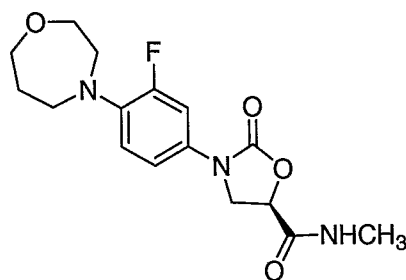
10 Following Step 4 of above general method, 3-(3-Fluoro-4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid methyl ester (0.50 g, 1.48 mmol) is dissolved in 7 mL of MeOH. Cooled in an ice bath and 2N NH_3/MeOH (4.43mL, 8.87 mmol) is added, ice bath removed and stirred for 2 1/2 hours at room temperature after which the solvent is removed in vacuo. MeOH added and cooled in ice bath.

15 Resulting solids are filtered off and washed with cold MeOH, then with diethyl ether to afford the title compound.

^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.00-2.03 (m, 2 H) 3.38-3.40 (m, 4 H) 3.78-3.83 (m, 4 H) 4.14 (dd, $J=9.4, 5.9$ Hz, 1 H) 4.21 (t, $J=9.6$ Hz, 1 H) 4.93 (dd, $J=9.8, 5.9$ Hz, 1 H) 5.72 (s, 1 H) 6.59 (s, 1 H) 6.88 (br s, 1 H) 6.98-7.01 (m, 1 H)

20 7.33 (dd, $J=14.8, 2.5$ Hz, 1 H)

Example 4 Preparation of 3-(3-fluoro-4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid methylamide



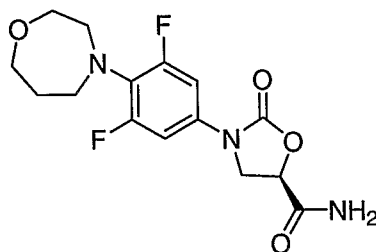
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Following Step 4 of above general method, 3-(3-fluoro-4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid methyl ester (0.40 g, 1.07 mmol) (0.32 g, 0.95 mmol) is dissolved in 4 mL of MeOH and cooled in an ice bath and 2N

NH₃/MeOH (2.84 mL, 5.67 mmol) is added, ice bath removed and stirred for about 1/2 hours at room temperature after which the solvent is removed in vacuo. MeOH added and cooled in ice bath. Resulting solids are filtered off and washed with cold MeOH, then with diethyl ether to afford the title compound.

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.00-2.03 (m, 2 H) 2.86 (d, *J*=5.1 Hz, 3 H) 3.38-3.40 (m, 4 H) 3.78-3.83 (m, 4 H) 4.14 (dd, *J*=9.4, 5.7 Hz, 1 H) 4.20 (t, *J*=9.6 Hz, 1 H) 4.91 (dd, *J*=9.8, 5.5 Hz, 1 H) 6.71 (m, 1 H) 6.88 (br s, 1 H) 6.97-7.00 (m, 1 H) 7.33 (dd, *J*=14.8, 2.3 Hz, 1 H).

Example 5 Preparation of 3-(3,5-difluoro-4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid amide



Step 1: Preparation of 4-(2,6-difluoro-4-nitro-phenyl)-[1,4]oxazepane

Following Step 1 of above general method, 3,4,5-trifluoro nitrobenzene (5.03 g, 28.42 mmol) in MeCN (15 ml) with hünig's base (10.3 ml, 58.97 mmol) and homomorpholine hydrochloric salt (4.06 g, 29.5 mmol) afforded the title compound as a solid

¹H NMR (400 MHz, CDCl₃): δ 2.02 (quint, 2 H), 3.53-3.58 (m, 4 H), 3.80-3.85 (m, 4 H), 7.73 (ddd, 2 H). MS-APCI (*m/z*⁺): 259 (M+1).

Step 2: Preparation of 3,5-difluoro-4-[1,4]oxazepan-4-yl-phenylamine

Following Step 2 of above general method, 4-(2,6-difluoro-4-nitro-phenyl)-[1,4]oxazepane (624.3 mg, 2.42 mmol) in THF (50 ml) with Raney Nickel (300.0 mg) afforded the title compound as oil.

¹H NMR (400 MHz, CDCl₃): δ 1.97 (quint, 2 H), 3.23-3.27 (m, 4 H), 3.78 (dd, 2 H), 3.91 (t, 2 H), 6.16-6.21 (m, 2 H). MS-APCI (*m/z*⁺): 229 (M+1).

Step 3: Preparation of 3-(3,5-difluoro-4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid methyl ester

Following Step 3 of above general method, 3,5-difluoro-4-[1,4]oxazepan-4-yl-phenylamine (2.0 g, 8.76 mmol) is reacted with oxirane-2-carboxylic acid methyl ester

(843 μ l, 9.64 mmol) and lithium triflate (1.6 g, 9.6 mmol) in *tert*-butanol (27 ml) and later with CDI (1.78 g, 11.0 mmol) in dichloromethane (44 ml) to afford the title compound as a solid.

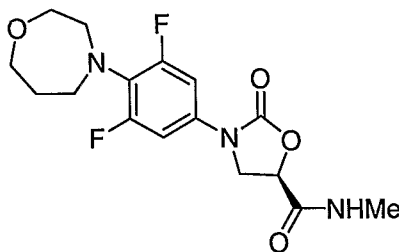
^1H NMR (400 MHz, CDCl_3): δ 2.00 (quint, 2 H), 3.32-3.37 (m, 4 H), 3.79-3.81 (m, 2 H), 3.87 (s, 3 H), 3.90 (t, 2 H), 4.07 (dd, 1 H), 4.21 (t, 1 H), 5.06 (dd, 1 H), 7.06-7.11 (m, 2 H). MS-APCI (m/z^+): 357 (M+1).

Step 4: Preparation of 3-(3,5-Difluoro-4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid amide

Following Step 4 of above general method, 3-(3,5-difluoro-4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid methyl ester (6) (151.4 mg, 0.42 mmol) is reacted with ammonia in methanol (2M, 2.1 ml, 4.2 mmol) to afford the title compound as a solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 2.00 (quint, 2 H), 3.30-3.35 (m, 4 H), 3.79 (dd, 2 H), 3.91 (t, 2 H), 4.07 (dd, 1 H), 4.30 (t, 1 H), 5.07 (dd, 1 H), 7.22-7.28 (m, 2 H). MS-APCI (m/z^+): 342 (M+1).

Example 6 Preparation of 3-(3,5-difluoro-4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid methylamide

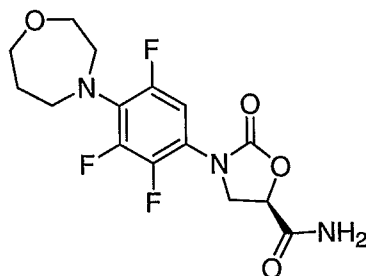


Step 1 Preparation of 3-(3,5-difluoro-4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid methylamide

Following Step 4 of above general method, 3-(3,5-difluoro-4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid methyl ester (131.7 mg, 0.37 mmol) is reacted with methylamine in methanol (2M, 1.8 ml, 3.7 mmol) to afford the title compound as a solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 2.00 (quint, 2 H), 2.91 (d, 3 H), 3.33-3.37 (m, 4 H), 3.80 (dd, 2 H), 3.91 (dd, 2 H), 4.14-4.24 (m, 2 H), 4.97 (dd, 1 H), 6.59 (q, 1 H), 7.06-7.12 (m, 2 H). MS-APCI (m/z^+): 359 (M+1).

Example 7 Preparation of 2-oxo-3-(2,3,5-trifluoro-4-[1,4]oxazepan-4-yl-phenyl)oxazolidine-5-carboxylic acid amide



5

Step 1: Preparation of 4-(2,3,6-trifluoro-4-nitrophenyl)-[1,4]oxazepane

Following Step 1 of above general method, tetrafluoronitrobenzene (6.75 g, 34.60 mmol, 8.29 mL) in NMP (33 mL) is cooled to at about -20 °C (ice/salt water bath). Added Hunig's base (9.62 g, 74.49 mmol, 12.96 mL) followed by addition of homomorpholine HCl (5.00 g, 36.30 mmol) portion wise over approx. 30 min. After the addition is completed, the reaction solution is stirred for 45 min. at 0 °C and the reaction is diluted with H₂O (175 mL) to provide a yellow precipitate. The solid is collected by filtration; the solids are washed with H₂O (3x) and dried under house high vacuum on buchner funnel over night to afford the title compound.

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.01-2.04 (m, 2 H) 3.58-3.63 (m, 4 H) 3.80-3.84 (m, 4 H) 7.60-7.65 (m, 1 H).

Step 2: Preparation of 2,3,5-trifluoro-4-[1,4]oxazepan-4-yl-phenylamine

Following Step 2 of above general method, 4-(2,3,6-Trifluoro-4-nitrophenyl)-[1,4]oxazepane (10.42g, 37.72 mmol) is dissolved in tetrahydrofuran (200 mL) in a Parr shaker and place in a H₂ atmosphere at 50 psi in the presence of Raney Ni for 16 hrs. The solution is then filtered and the solvent removed in vacuo. The isolated residue is subjected to silica gel flash chromatography, eluting with MeOH/dichloromethane gradient (0-5% MeOH over 1 hour and 20 minutes) to afford the title compound.

MS-APCI (*m/z*⁺): 247.

Step 3: Preparation of 2-oxo-3-(2,3,5-trifluoro-4-[1,4]oxazepan-4-yl-phenyl)oxazolidine-5-carboxylic acid methyl ester

Following Step 3 of above general method, 2,3,5-trifluoro-4-[1,4]oxazepan-4-yl-phenylamine (1.00 g, 4.06 mmol) is dissolved in t-butanol (15mL), methyl

glycidate (0.456 g, 4.47 mmol, 0.39 mL).was added, heated to approx 40 °C in oil bath then added lithium triflate (0.697 g, 4.47 mmol) then raised temp. to 70 °C and stirred under N₂ at 70 °C overnight. An additional .40 eq of lithium triflate and methyl glycidate added and reaction mixture again stirred at 70 °C overnight. Heat removed, allowed to cool. H₂O added, extracted (2x) with dichloromethane, organics combined, washed with brine, dried over Sodium sulfate, filtered, conc. The isolated residue is then dissolved in dichloromethane (30 mL), 1-hydroxybenzotriazole (0.574 g, 4.25 mmol) added and stirred under N₂ at room temperature for 10 minutes. Carbonyldiimidazole (0.788 g, 4.86 mmol) is added and the reaction mixture heated at 35 ° in an oil bath overnight. Heat removed, allowed to cool, diluted with additional dichloromethane, washed organic phase with saturated NH₄Cl and then with brine, dried over Sodium sulfate, filtered, conc. The isolated residue is subjected to silica gel flash chromatography, eluting with 20% MeOH in dichloromethane/dichloromethane gradient (0-10% of 20% MeOH in dichloromethane over 1 hr) to afford the title compound.

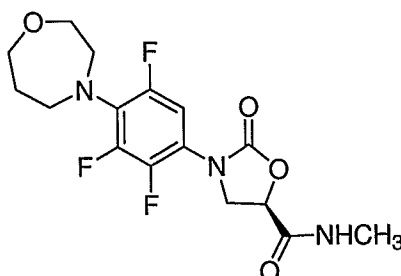
MS-APCI (*m/z*⁺): 375

Step 4: Preparation of 2-oxo-3-(2,3,5-trifluoro-4-[1,4]oxazepan-4-yl-phenyl)oxazolidine-5-carboxylic acid amide

Following Step 4 of above general method, 2-Oxo-3-(2,3,5-trifluoro-4-[1,4]oxazepan-4-yl-phenyl)-oxazolidine-5-carboxylic acid methyl ester (0.40 g, 1.07 mmol) is dissolved in 7 mL of MeOH and cooled in an ice bath and 2N NH₃/MeOH (3.21mL, 6.41 mmol) is added, ice bath removed and stirred for about 2 1/2 hours at room temperature after which the solvent is removed in vacuo. The isolated residue is subjected to silica gel flash chromatography, eluting with MeOH/dichloromethane gradient (0-10% MeOH over 1 hour and 10 minutes) to afford the title compound.

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.95-2.00 (m, 2 H) 3.37-3.42 (m, 4 H) 3.76-3.78 (m, 2 H) 3.84-3.87 (m, 2 H) 4.14 (dd, *J*=9.4, 5.9 Hz, 1 H) 4.24 (t, *J*=9.5 Hz, 1 H) 4.98 (dd, *J*=9.6, 5.9 Hz, 1 H) 5.07 (br s, 1 H) 6.55 (br s, 1 H) 6.96 (ddd, *J*=12.3, 6.8, 2.3 Hz, 1 H).

Example 8 Preparation of 2-oxo-3-(2,3,5-trifluoro-4-[1,4]oxazepan-4-yl-phenyl)oxazolidine-5-carboxylic acid methylamide

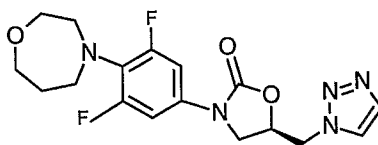


5 Following Step 1 of above general method, 2-oxo-3-(2,3,5-trifluoro-4-[1,4]oxazepan-4-yl-phenyl)-oxazolidine-5-carboxylic acid methyl ester (0.40 g, 1.07 mmol) is dissolved in 10 mL of MeOH and then cooled in an ice bath and 2N CH₃NH₂/MeOH (4.00mL, 8.00 mmol) is added, ice bath removed and stirred for 2 1/2 hours at room temperature after which the solvent is removed in vacuo. The isolated
10 residue is subjected to silica gel flash chromatography, eluting with MeOH/dichloromethane gradient (0-10% MeOH over 1 hour and 10 minutes) to afford the title compound.

¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.94-2.00 (m, *J*=5.9, 5.9, 5.9, 5.9 Hz, 2 H) 2.90 (d, *J*=4.9 Hz, 3 H) 3.38 (dd, *J*=9.1, 5.2 Hz, 3 H) 3.38 (s, 1 H) 3.75-
15 3.78 (m, 2 H) 3.84-3.86 (m, 2 H) 4.12 (dd, *J*=9.2, 5.9 Hz, 1 H) 4.24 (t, *J*=9.1 Hz, 1 H) 4.96 (dd, *J*=9.7, 5.8 Hz, 1 H) 6.58 (br d, 1H), 6.960 (ddd, *J*=12.3, 7.0, 2.3 Hz, 1 H).

Example 9 Preparation of 3-(3,5-Difluoro-4-[1,4]oxazepan-4-yl-phenyl)-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one

20



Step 1: Preparation of 5-hydroxymethyl-3-(4-[1,4]oxazepan-4-yl-phenyl)-oxazolidin-2-one:

Using General Procedure (4-[1,4]oxazepan-4-yl-phenyl)-carbamic acid benzyl
25 ester (**11**) (1.49 g, 4.56 mmol) with glycidyl butyrate (669 μl, 4.79 mmol) and butyl lithium (2.5 M in THF, 1.9 ml, 4.78 mmol) in THF (21 ml) afforded the title compound as a solid.

¹H NMR (400 MHz, CDCl₃): δ 2.00-2.04 (m, 2 H), 3.59-3.63 (m, 4 H), 3.69 (t, 2 H), 3.77 (ddd, 1 H), 3.80-3.87 (m, 2 H), 3.89-4.02 (m, 3 H), 4.72 (dt, 1 H), 6.73 (br s, 2 H), 7.36 (d, 2 H). MS-APCI (m/z⁺): 293 (M+1).

- 5 Step 2: Preparation of 3-(3,5-difluoro-4-[1,4]oxazepan-4-yl-phenyl)-5-hydroxymethyl-oxazolidin-2-one

Using General Procedure (3,5-difluoro-4-[1,4]oxazepan-4-yl-phenyl)-carbamic acid benzyl ester (**12**) (2.02 g, 5.58 mmol) with glycidyl butyrate (819 μl, 5.86 mmol) and butyl lithium (2.5 M in THF, 2.4 ml, 5.86 mmol) in THF (28 ml) afforded the title
10 compound as a solid.

¹H NMR (400 MHz, CDCl₃): δ 2.06 (quint, 2 H), 3.37-3.42 (m, 4 H), 3.77 (dd, 2 H), 3.85 (dd, 2 H), 3.91 (dd, 3 H), 3.97 (dd, 1 H), 4.01 (dd, 1 H), 4.01 (dt, 1 H), 7.11-7.18 (m, 2 H). MS-APCI (m/z⁺): 329 (M+1).

- 15 Step 3: Preparation of methanesulfonic acid 3-(4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl ester

Using General Procedure 5-hydroxymethyl-3-(4-[1,4]oxazepan-4-yl-phenyl)-oxazolidin-2-one (**13**) (677.9 mg, 2.32 mmol) with mesyl chloride (252 μl, 3.25 mmol) and triethylamine (646 μl, 4.63 mmol) in dichloromethane (8 ml) afforded the
20 title compound as oil.

¹H NMR (400 MHz, CDCl₃): δ 2.08 (br s, 2 H), 3.11 (s, 3 H), 3.55-3.76 (m, 4 H), 3.70 (t, 2 H), 3.85-3.93 (m, 3 H), 4.11 (t, 1 H), 4.46 (qd, 2 H), 4.89 (dt, 1 H), 6.81 (br s, 2 H), 7.35 (d, 2 H). MS-APCI (m/z⁺): 371 (M+1).

- 25 Step 4: Preparation of methanesulfonic acid 3-(3,5-difluoro-4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl ester

Using General Procedure I 3-(3,5-difluoro-4-[1,4]oxazepan-4-yl-phenyl)-5-hydroxymethyl-oxazolidin-2-one (**14**) (816.2 mg, 2.48 mmol) with mesyl chloride (281 μl, 3.48 mmol) and triethylamine (693 μl, 4.97 mmol) in dichloromethane (10
30 ml) afforded the title compound as oil.

¹H NMR (400 MHz, CDCl₃): δ 1.99 (quint, 2 H), 3.06 (s, 3 H), 3.31-3.36 (m, 4 H), 3.78 (dd, 2 H), 3.87 (t, 3 H), 4.05 (t, 1 H), 4.42 (qd, 2 H), 4.88 (dt, 1 H), 7.05-7.10 (m, 2 H). MS-APCI (m/z⁺): 407 (M+1).

Step 5: Preparation of 5-azidomethyl-3-(3,5-difluoro-4-[1,4]oxazepan-4-yl-phenyl)-oxazolidin-2-one

Using General Procedure methanesulfonic acid 3-(3,5-difluoro-4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl ester (**16**) (1.08 g, 2.66 mmol) with sodium azide (660.0 mg, 10 mmol) in DMF (18 ml) afforded the title compound as oil.

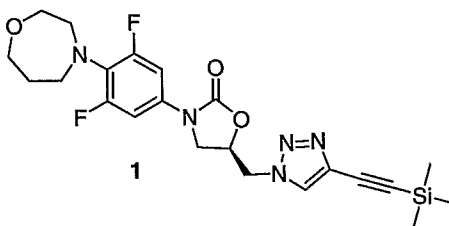
¹H NMR (400 MHz, CDCl₃): δ 2.01 (quint, 2 H), 3.33-3.38 (m, 4 H), 3.58 (dd, 1 H), 3.71 (dd, 1 H), 3.77-3.82 (m, 3 H), 3.91 (t, 2 H), 4.01 (t, 1 H), 4.79 (dt, 1 H), 7.08-7.15 (m, 2 H). MS-APCI (m/z⁺): 354 (M+1).

Step 6: Preparation of 3-(3,5-difluoro-4-[1,4]oxazepan-4-yl-phenyl)-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one

Using General Procedure L 5-azidomethyl-3-(3,5-difluoro-4-[1,4]oxazepan-4-yl-phenyl)-oxazolidin-2-one (**18**) (208.7 mg, 0.59 mmol) with 2,5-norboadiene (300 μl, 2.95 mmol) in dioxane (3.2 ml) afforded the title compound as a solid.

¹H NMR (400 MHz, CDCl₃): δ 1.96 (quint, 2 H), 3.28-3.32 (m, 4 H), 3.76 (dd, 2 H), 3.87 (dd, 3 H), 4.10 (t, 1 H), 4.77 (d, 2 H), 5.05 (dt, 1 H), 6.91-6.98 (m, 2 H), 7.72 (s, 1 H), 7.79 (s, 1 H). MS-APCI (m/z⁺): 380 (M+1).

Example 10 Preparation of 3-(3,5-Difluoro-4-[1,4]oxazepan-4-yl-phenyl)-5-(4-trimethylsilanylethynyl-[1,2,3]triazol-1-ylmethyl)-oxazolidin-2-one

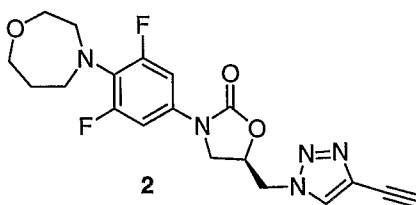


To the solution of buta-1,3-diynyl-trimethyl-silane (290 mg, 2.4 mmol) in MeCN (5 ml) 5-azidomethyl-3-(3,5-difluoro-4-[1,4]oxazepan-4-yl-phenyl)-oxazolidin-2-one (277.3 mg, 0.785 mmol) is dissolved followed by the addition of 2,6-lutidine (100.6 μl, 0.863 mmol) and copper iodide (14.9 mg, 0.0785 mmol). The reaction mixture is then stirred at rmt for 16h. Water is added to the reaction, aq layer

is extracted with dichloromethane and the combined org layer is washed with water and brine. The resulting org layer is dried over sodium sulfate and concentrated. Purification via column chromatography afforded the title compound as a solid.

¹H NMR (400 MHz, CDCl₃): δ 0.20 (s, 9 H), 1.94 (quint, 2 H), 3.25-3.30 (m, 4 H), 3.73 (dd, 2 H), 3.80 (dd, 1 H), 3.84 (dd, 1H), 4.10 (t, 1H), 4.71 (dq, 2 H), 4.99-5.05 (m, 1 H), 6.95 (d, 2 H), 7.84 (s, 1 H). MS-APCI (m/z⁺): 376 (M+1).

Example 11 Preparation of 3-(3,5-Difluoro-4-[1,4]oxazepan-4-yl-phenyl)-5-(4-ethynyl-[1,2,3]triazol-1-ylmethyl)-oxazolidin-2-one



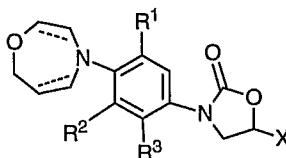
To the solution of 3-(3,5-difluoro-4-[1,4]oxazepan-4-yl-phenyl)-5-(4-trimethylsilanylethynyl-[1,2,3]triazol-1-ylmethyl)-oxazolidin-2-one (180.7 mg, 0.380 mmol) in methanol (2 ml) potassium hydroxide solution (1M, 581 μl, 0.581 mmol) is added. The solution is stirred at rmt for 4h then quenched with hydrochloric acid solution (2M, 190 μl, 0.380 mmol). The product is extracted with dichloromethane, washed with water and brine, dried over sodium sulfate and concentrated. After column chromatography the title compound is afforded as a solid.

¹H NMR (400 MHz, CDCl₃): δ 1.99 (quint, 2 H), 3.27 (s, 1 H), 3.31-3.36 (m, 4 H), 3.79 (dd, 2 H), 3.86 (dd, 1 H), 3.90 (dd, 2 H), 4.12 (t, 1 H), 4.75 (dq, 2H), 5.02-5.08 (m, 1 H), 6.99 (d, 2 H), 7.89 (s, 1 H). MS-APCI (m/z⁺): 404 (M+1).

CLAIMS

We Claim:

1. A compound of formula I



I

or a pharmaceutically acceptable salt thereof wherein:

- 10 X is $-C(=O)NHR^4$, or CH_2 -het;

R^1, R^2, R^3 are independently H or F;

R^4 is H, C_{1-6} alkyl, or OC_{1-6} alkyl;

het is a five (5)-membered heterocyclic ring having 1, 2 or 3 heteroatoms selected from the group consisting of non-peroxide oxygen, sulfur, and nitrogen within the ring

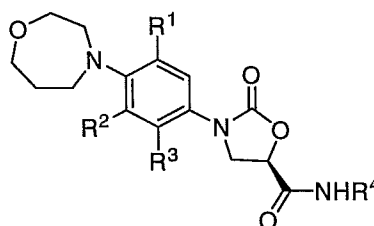
- 15 wherein het is optionally substituted with 1-3 halo, C_{1-4} alkyl, ethylene, ethynyl, CN, N_3 , $O(C=O)C_{1-4}$ alkyl, NH_2 , $NHC(=O)C_{1-4}$ alkyl, or $C(=O)C_{1-4}$ alkyl;

each dotted line “...” is independently a single bond or absent; and

at each occurrence, C_{1-6} alkyl is optionally substituted by 1-3 halo, OH, OC_{1-4} alkyl, CN, N_3 , $O(C=O)C_{1-4}$ alkyl, NH_2 , $NHC(=O)C_{1-4}$ alkyl, or $C(=O)C_{1-4}$ alkyl. .

20

2. A compound of claim 1 which is a compound of formula Ia



Ia.

25

3. A compound of claim 2 wherein R^4 is H, $-CH_3$, or $-CH_2CH_3$.

4. A compound of claim 2 wherein R^4 is $-OCH_3$, or $-OCH_2CH_3$.

5. A compound of claim 1 wherein het is triazol.
6. A compound of claim 1 which is
- (1) 3-(4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid amide,
 - 5 (2) 3-(4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid
methanamide,
 - (3) 3-(3-Fluoro-4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic
acid amide,
 - (4) 3-(3-fluoro-4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic acid
10 methanamide,
 - (5) 3-(3,5-difluoro-4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic
acid amide,
 - (6) 3-(3,5-difluoro-4-[1,4]oxazepan-4-yl-phenyl)-2-oxo-oxazolidine-5-carboxylic
acid methanamide,
 - 15 (7) 2-oxo-3-(2,3,5-trifluoro-4-[1,4]oxazepan-4-yl-phenyl)oxazolidine-5-
carboxylic acid amide,
 - (8) 2-oxo-3-(2,3,5-trifluoro-4-[1,4]oxazepan-4-yl-phenyl)oxazolidine-5-
carboxylic acid methanamide,
 - (9) 3-(3,5-difluoro-4-[1,4]oxazepan-4-yl-phenyl)-5-[1,2,3]triazol-1-ylmethyl-
20 oxazolidin-2-one, or
 - (10) 3-(3,5-Difluoro-4-[1,4]oxazepan-4-yl-phenyl)-5-(4-ethynyl-[1,2,3]triazol-1-
ylmethyl)-oxazolidin-2-one.
7. A pharmaceutical composition comprising a compound of claim 1 or a
25 pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
8. A method for treating bacteria infections comprising administering to a
mammal being treated a pharmaceutically effective amount of the compound of claim
1.
- 30 9. The method of claim 8 wherein the compound of claim 1 is administered
orally, parenterally, topically, rectally, or intranasally.

10. The method of claim 8 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.
11. The method of claim 8 wherein said compound is administered in an amount
5 of from about 1 to about 50 mg/kg of body weight/day.
12. The bacteria infection of claim 8 which is ear infections, eye infections, respiratory tract infections, skin and skin structure infections, bacterial endocarditis, osteomyelitis, endocarditis or diabetic foot.
- 10 13. The bacteria infection of claim 8 which is caused by gram-positive bacteria, gram negative bacteria, anaerobic organisms, and acid-fast organisms.
14. The bacteria infection of claim 8 which is caused by bacteria comprising
15 staphylococci, streptococci, Enterococci, Haemophilus, Moraxella, bacteroides, clostridia, Mycobacteria, or Chlamydia.
15. The bacteria of claim 14 wherein staphylococci is *S. aureus* and *S. epidermidis*; wherein streptococci is *S. pneumoniae* or *S. pyogenes*; wherein
20 Enterococci is *E. faecalis*; wherein Haemophilus is *H. influenzae*; wherein Moraxella is *M. catarrhalis*; and wherein Mycobacteria is *M. tuberculosis*; or *Mycobacterium avium*.
16. The bacteria infections of claim 8 which is caused by multi-drug resistant *S.*
25 *aureus*.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/001730

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D413/10 C07D413/14 A61P31/04 A61K31/4178

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

24 October 2006

Date of mailing of the international search report

30/10/2006

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Authorized officer

Gettins, Marc

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2006/001730

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 01/46185 A (UPJOHN CO [US]; HESTER JACKSON B JR [US]; ALEXANDER DAVID L [US]) 28 June 2001 (2001-06-28) cited in the application Claim 1 where A is ii and B is (b) -----	1-16
Y	WO 96/15130 A (UPJOHN CO [US]; BARBACHYN MICHAEL R [US]; THOMAS RICHARD C [US]; CLEEK) 23 May 1996 (1996-05-23) cited in the application Claim 1 where a is zero -----	1-16
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Y	WO 00/32599 A (UPJOHN CO [US]; HESTER JACKSON B JR [US]; NIDY ELTON GEORGE [US]; PERR) 8 June 2000 (2000-06-08) cited in the application claim 1 -----	1-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/001730

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 8-11, 16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2006/001730

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2006/001730

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