# AN OXINDOLE OXAZOLIDINONE AS ANTIBACTERIAL AGENT

## FIELD OF INVENTION

The present invention relates to an oxindol oxazolidinone derivative, to its use as an antibacterial agent, to pharmaceutical compositions containing this compound, and to methods for its preparation.

## BACKGROUND OF THE INVENTION

Antibacterial resistance is a global, clinical, and public health problem that has 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 a result, structurally novel antibacterials with a 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 an oxindole oxazolidinone derivative as an inhibitor of bacterial protein synthesis for the treatment of serious infections caused by a number of human and veterinary pathogens, including multiple resistant strains of bacteria.

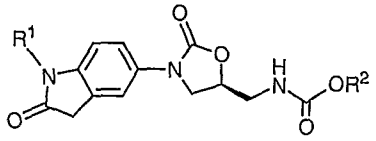
## INFORMATION DISCLOSURE

WO 2003072553 discloses N-aryl-2-oxazolidinone-5-carboxamides having antibacterial activity useful for treating microbial infections. WO 200281470 discloses oxazolidinone compounds useful for treating bacterial infections. WO 200073301 discloses bicyclic oxazolidinone derivatives useful as antimicrobial agents. WO 200032599 discloses oxazolidinone derivatives useful for treatment of microbial infections. WO 200029396 discloses 3-phenyl-5-aminomethyl-oxazolidinone derivatives useful as antibacterial agents. WO 9937630 discloses oxazolidinone derivatives including combinatorial libraries. DE 19604223 discloses new substituted oxazolidinone compounds useful as antibacterial agents. DE 19649095 discloses 5-(acyl-aminomethyl)-3-hetero-aryl-oxazolidinone compounds useful as antibacterial agents. EP 694543 discloses hetero-aryl substd. oxazolidinone derivatives useful as antibacterial agents. EP 693491 discloses 3-hetero-aryl-2-oxazolidinone derivatives useful as antibacterial agents. EP 609905 discloses indaxolyl, benzimidazolyl, and benzofrizxolyl oxazolidinone derivatives useful as antibacterial agents. US 5164510 discloses 5-Indolinylioxazolidin-2-one(s) useful as antibacterial agents. WO 04/074282 discloses

indolone oxazolidinones and derivatives thereof. US provisional patent application 60/599822 discloses oxazolidinones containing oxindoles as antibacterial agents.

## SUMMARY OF THE INVENTION

The present invention provides a compound of formula I



I

or a pharmaceutically acceptable salt thereof wherein $R^1$ is $C_{1-4}$alkyl, optionally substituted with a fluoro atom, or $R^1$ is a cyclopropyl or cyclopropylmethyl; and $R^2$ is methyl or ethyl.

In another aspect, the present invention also provides:

pharmaceutical compositions which comprise a pharmaceutically acceptable carrier and a compound of formula I,

methods for treating microbial infections in a mammal by administering to a mammal 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 to prepare a medicament for treating microbial infections.

## DETAILED DESCRIPTION OF THE INVENTION

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, $C_{1-6}$ alkyl refers to alkyl of one to seven carbon atoms, inclusive.

The term alkyl refers 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 "$C_{3-5}$cycloalkyl" refers to a cyclic saturated monovalent hydrocarbon group of three to five carbon atoms, e.g., cyclopropyl, and the like.

The term "pharmaceutically acceptable carrier" means a carrier that is useful in 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.

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 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.

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.

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".

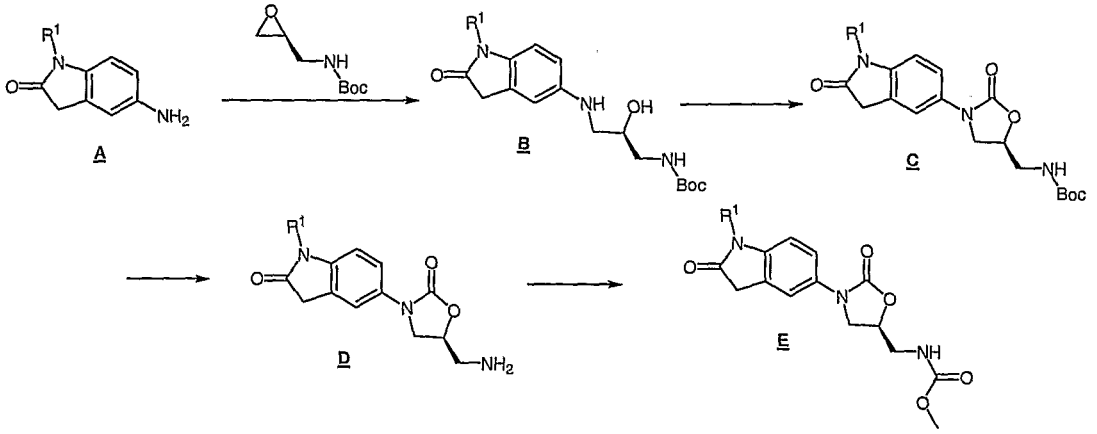
It will be appreciated by those skilled in the art that the compound of the invention having a chiral center and may be isolated in optically active and racemic forms. It may also exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, tautomeric, or stereoisomeric form, or mixture thereof, of a compound of the invention, which possesses the useful properties described herein, it being well known 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.

The compound of the present invention is 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).

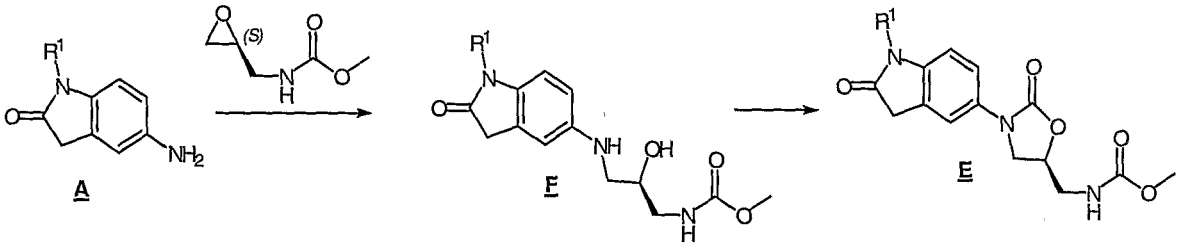
Schemes I and II describe the preparation of the compound of the present invention. The starting materials are prepared by procedures described in these schemes or by procedures known to one of ordinary skill in the art.

Scheme I



According to Scheme I, the N-substituted –5-amino-1,3-dihydroindol-2-one (**A**) is reacted with an appropriated substituted (S)-oxiranylmethyl-carbamic acid tert-butyl ester ad a Lewis acid such as lithium trifluoromethanesulfonate in a suitable solvent such as acetonitrile at a suitable temperature. (S)-oxiranylmethyl-carbamic acid tert-butyl ester can be conveniently prepared following methods described in WO 02/32857 and WO02/85849. The amino alcohol (**B**) can then be ring closed using 1,1-carbonylimidazole in solvents such as acetonitrile or tetrahydrofuran at an appropriate temperature or using phosgene in a solvent such as methylene chloride or toluene at an appropriate temperature. Boc group in (**C**) can be deprotected under acid conditions (using acids such as trilfuoroacetic acid or hydrochloric acid) in a suitable solvent such as methylene, chloride, or dioxane. The amine in (**D**) further could be converted to its methyl (or alkyl) carbamate by treating with methyl (or $C_{1-4}$ alkyl) chloroformate or dimethyl carbonate in the presence of suitable bases such as triethylamine or pyridine to compound (**E**).

Scheme II



In an alternate Scheme (Scheme II) compound (**A**) may be reacted with (S)-oxiranylmethyl-carbamic acid methyl ester (WO 99/52855; US 6417403) as described in EP 99/00097. The amino alcohol (**F**) can then be ring closed to give oxazolidinones (**E**) using

1,1-carbonylimidazole in solvents such as acetonitrile or tetrahydrofuran at an appropriate temperature or using phosgene in a solvent such as methylene chloride or toluene at an appropriate temperature.

N-Substituted –5-amino-1,3-dihydroindol-2-one (A) intermediates may be prepared using any of the synthetic procedures described in *J.A. Joule, Science of Synthesis, 2001, 10.13, 361 – 653pp.*

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

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. 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 unexceptedly weak MAO inhibitory activity, which indicates it possess the capacity to minimize or eliminate potential drug-drug interactions since strong inhibition of monoamine 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 and Monoamine Oxidase Inhibition Activities

The *in vitro* antibacterial activity of the compound 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.

Following procedure may assess monoamine oxidase inhibition activity of the compound of the present invention:

MAO-A and B inhibition were analyzed by measuring the inhibition of conversion of an MAO substrate, 1-methyl-4-(1-methyl-2-pyrryl)-1,2,3,6-tetrahydropyridine, to its dihydropyridinium metabolite ($\lambda$=421 nm). The substrate concentration was equal to the $K_m$ (64 μM for MAO-A and 43 μM for MAO-B). The MAO-A concentration was 0.01 mg/mL, and the MAO-B concentration was 0.008 mg/mL. Each inhibitor was tested at seven concentrations. Percent inhibition at each concentration was established relative to the uninhibited control rate, and the $IC_{50}$ and $K_i$ values were calculated. A low Ki value indicates that the tested inhibitor possesses a tight binding ability to MAO enzyme, thus, it is a strong MAO inhibitor.

Results of the antibacterial and monoamine oixidase inhibition activities testing for Example 2 are shown in Table 1. The antibacterial activities are shown in Table 2.

Table 1

| Parameters | Compound No. 1 |
|---|---|

| Parameters | Compound No. 1 |
|---|---|
| *S. aureus* (LORSA) $MIC_{90}$ (μg/mL) | 4 |
| *S. pneumoniae* (LRSA) $MIC_{90}$(μg/mL) | 2 |
| *E.faecalis* (VREF) $MIC_{90}$ (μg/mL) | 4 |
| *E. faecium* (VREF) $MIC_{90}$ (μg/mL) | 4 |
| MAO - A $K_i$ (μM) | 880 |
| MAO - B $K_i$ (μM) | 57.4 |

Table 2
Results of *in vitro* antibacterial activity $MIC_{90}$ (μg/mL)

| Example No. | *S. aureus* UC-76 SA-1 | *S. pneumoniae* SV1 SP-3 | *E.faecalis* MGH-2 EF 1-1 |
|---|---|---|---|
| 2 | 4 | 1 | 2 |
| 3 | 4 | 2 | 2 |
| 4 | 8 | 4 | 8 |
| 5 | 8 | 4 | 4 |
| 6 | 4 | 4 | 4 |
| 7 | 8 | 4 | 8 |
| 8 | 4 | 4 | 4 |

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, intravetricular injections or infusions techniques.

Topical administrations include the treatment of infectious areas or organs readily accessibly by local application, for example, eyes, ears including 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 applications.

The preferred routes of administration are oral and parenteral.

Composition/Formulation

Pharmaceutical compositions of the present invention may be manufactured by 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 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. 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. 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 pharmaceutically 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 a mixture 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 monosterate, polysorbate 60, cetyl esters wax, ceteary 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 sparing 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 know in the art may be used to determine the desired dosage amount.

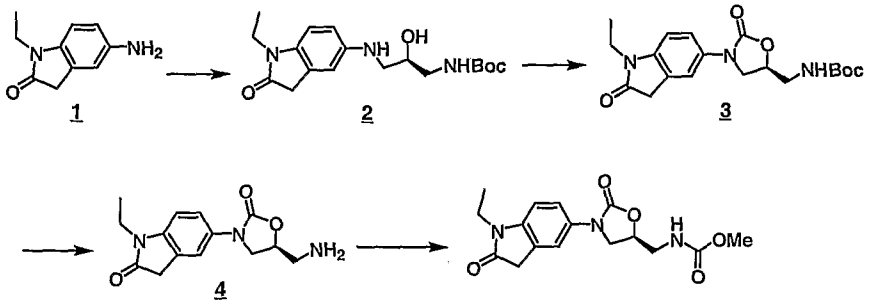
The compound of this invention can be prepared in accordance with one or more of the methods discussed below. All of the starting materials are either commercially available or can be prepared by procedures that would be well known to one of ordinary skill in organic chemistry. Also, in the discussion 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 |
| BOC | = | *tert*-butoxycarbonyl |

| | | | |
|---|---|---|---|
| | bd | = | broad doublet |
| | bs | = | broad singlet |
| | bt | = | broad triplet |
| | CDI | = | carbodiimidazole |
| | d | = | doublet |
| | dd | = | doublet of doublets |
| | dq | = | doublet of quartets |
| | dt | = | doublet of triplets |
| | dm | = | doublet of multiplets |
| | DMF | = | dimethylformamide |
| | DMAP | = | dimethylaminopyridine |
| | DIEA | = | diisopropylethylamine |
| | DMSO | = | dimethyl sulfoxide |
| | eq. | = | equivalents |
| | g | = | grams |
| | h | = | hours |
| | HPLC | = | high pressure liquid chromatography |
| | HATU | = | N-[(dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-yl-methylene]-N-methylmethanaminium hexafluorophosphate N-oxide |
| | LG | = | leaving group |
| | m | = | multiplet |
| | M | = | molar |
| | M% | = | mole percent |
| | max | = | maximum |
| | meq | = | milliequivalent |
| | mg | = | milligram |
| | mL | = | milliliter |
| | mm | = | millimeter |
| | mmol | = | millimol |
| | q | = | quartet |
| | s | = | singlet |
| | t or tr | = | triplet |
| | TBS | = | tributylsilyl |
| | TFA | = | trifluoroacetic acid |
| | THF | = | tetrahydrofuran |
| | TLC | = | thin layer chromatography |
| | p-TLC | = | preparative thin layer chromatography |
| | µL | = | microliter |
| | N | = | normality |
| | MeOH | = | methanol |
| | DCM | = | dichloromethane |
| | HCl | = | hydrochloric acid |
| | ACN | = | acetonitrile |
| | MS | = | mass spectrometry |
| | rt | = | room temperature |
| | EtOAc | = | ethyl acetate |
| | EtO | = | ethoxy |
| | Ac | = | acetate |
| | NMP | = | 1-methyl-2-pyrrolidinone |
| | µL | = | microliter |
| | J | = | coupling constant |
| | NMR | = | Nuclear magnetic resonance |
| | MHz | = | megahertz |

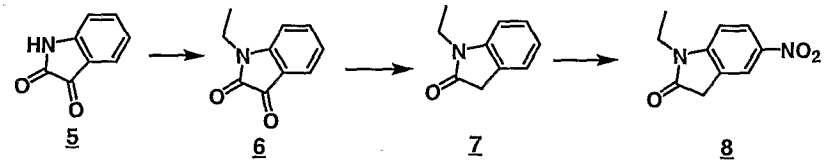
| | | |
|---|---|---|
| Hz | = | hertz |
| m/z | = | mass to charge ratio |
| min | = | minutes |
| Boc | = | *tert*-butoxycarbonyl |
| CBZ | = | benzyloxycarbonyl |
| DCC | = | 1,3-dicyclohexylcarbodiimide |
| PyBop | = | benzotriazole-1-yl-oxy-trispyrrolidinophosphonium hexafluorophosphate |

**Example 1** Preparation of (5*S*)-[3-(1-ethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid methyl ester




Step 1 Preparation of 1-ethyl-5-nitro-1,3-dihydro-indol-2-one (8)

Method A




Step 1a: Preparation of 1-ethyl-1*H*-indole-2,3-dione (**6**)

1*H*-Indole-2,3-dione (**5**, 5.00 g, 0.034 mol), iodoethane (5.44 ml, 0.068 mol) and potassium carbonate (9.28 g, 0.068 mol) in DMF (50 ml) are stirred at room temperature for 72 hours. The reaction mixture is diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$) and evaporated to give product as a solid (5.95 g, 100%); HPLC r.t. 3.96 min; MS for $C_{10}H_9NO_2$ m/z 176.1 $(M+H)^+$.

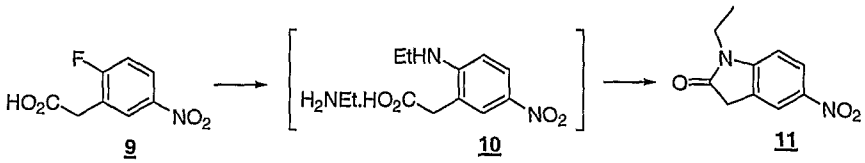
Step 1b: Preparation of 1-ethyl-1,3-dihydro-indol-2-one (**7**)

1-Ethyl-1*H*-indole-2,3-dione (**6**, 5.60 g, 31.9 mmol) is heated with neat hydrazine hydrate (20 ml) at 130 °C for 1 hour. The reaction mixture is cooled, diluted with ice water, and extracted with ethyl acetate. The organic layer is washed with brine, dried ($Na_2SO_4$) and evaporated to give product as a solid (4.85 g, 94%); HPLC r.t. 4.12 min; MS for $C_{10}H_{11}NO$ m/z 162.1 $(M+H)^+$.

Step 1c: 1-ethyl-5-nitro-1,3-dihydro-indol-2-one (8)

1-Ethyl-1,3-dihydro-indol-2-one (7, 4.00 g, 24.8 mmol) is added to a stirred solution of sodium nitrate (2.10 g, 24.8 mmol) in trifluoroacetic acid (100 ml). The reaction mixture is stirred at room temperature for 30 minutes and then poured on ice. The resulting precipitate is filtered, washed with water, and dried under vacuum to give product as a solid (3.7 g, 72%); HPLC r.t. 4.29 min; MS for $C_{10}H_{10}N_2O_3$ m/z 207.2 $(M+H)^+$.

Method B




9 10 11

Step 1a: (2-Ethylamino-5-nitro-phenyl)-acetate ethylamine salt (10)

A pressure reaction vessel was charged with 2-fluoro-5-nitrophenyl acetic acid (9) (25g, 126 mmol) and ethylamine (125 ml). The contents were sealed and stirred at 60 °C for 14h. The resulting reaction was concentrated in vacuo to afford the desired salt (42.35 g, 157 mmol, quant). $^1$H NMR (400 MHz, CDCl3): δ 1.27 (t, 3 H), 1.32 (t, 3 H), 2.96 (q, 4 H), 3.45 (s, 2 H), 6.63 (d, 1 H), 8.01-8.04 (m, 2 H). MS-APCI (m/z$^+$): 225 (M-45+1).

Step 1b: 1-Ethyl-5-nitro-1,3-dihydro-indol-2-one (11):

To the suspension of (2-ethylamino-5-nitro-phenyl)-acetate ethylamine salt (9) (6.762g, 25.11 mmol) in water (120 ml) hydrochloric acid solution (6 M, 15 ml) was added. Upon the addition of hydrochloric acid solution precipitate appeared in the reaction. The mixture was stirred at rmt for 18h. The resulting precipitate was filtered and washed with water to afford the desired product (5.34g, 25.90 mmol, quant.). $^1$H NMR (400 MHz, CDCl3): δ 1.29 (t, 3 H), 3.61 (q, 2 H), 3.82 (s, 2 H), 6.91 (d, 1 H), 8.15 (dd, 1 H), 8.27 (dd, 1 H).

Step 2: Preparation of 5-amino-1-ethyl-1,3-dihydro-indol-2-one (1)




11 1

Method A

Iron powder (3.89 g, 69.8 mmol) is added portionwise to a mixture of 1-ethyl-5-nitro-1, 3-dihydro-indol-2-one (8, 3.60 g, 17.5 mmol) and ammonium chloride (9.24 g, 175 mmol) in ethanol (150 ml) and water (75 ml) at 90 °C. The reaction mixture is stirred vigorously and heated for 30 minutes, cooled to room temperature and diluted with dichloromethane (300 ml). The mixture is filtered through celite, the organic layer separated and washed with

water and brine, dried over sodium sulfate and evaporated to give product as a solid (2.74 g, 89%); HPLC r.t. 1.86 min; MS for $C_{10}H_{12}N_2O$ m/z 177.1 $(M+H)^+$.

Method B

1-Ethyl-5-nitro-1,3-dihydro-indol-2-one (**11**) (5.30 g, 25.70 mmol) was dissolved in THF (100 ml) and placed in Parr shaker with Raney Nickel at 50 psi with a supply of $H_2$ for 16 h. The resulting solution was filtered and concentrated to afford the desired product as a solid (5.78, 32.8 mmol, quant.). $^1$H NMR (400 MHz, CDCl3): δ1.24 (t, 3 H), 3.44 (q, 2 H), 3.72 (s, 2 H), 6.58-6.60 (m, 2 H), 6.67-6.69 (m, 1 H). MS-APCI ($m/z^+$): 177 (M+1).

Step 3: Preparation of (5*R*)-[3-(1-ethyl-2-oxo-2,3-dihydro-1*H*-indol-5-ylamino)-2-hydroxy-propyl]-carbamic acid tert-butyl ester (**2**)

5-Amino-1-ethyl-1,3-dihydro-indol-2-one (**1**, 0.91g, 5.16 mmol), (*S*)-oxiranylmethyl-carbamic acid tert-butyl ester (0.893g, 5.16 mmol) and lithium trifluoromethanesulfonate (0.798 g, 5.16 mmol) in acetonitrile (10 ml) are heated at 70 °C for 2 hours. The reaction mixture is diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$) and evaporated. Final purification by flash chromatography (30%Acetone / DCM) gives pure product as a solid. (0.90 g, 50%); HPLC R.T. 3.39 min; MS for $C_{18}H_{27}N_3O_4$ m/z 350.4 $(M+H)^+$.

Step 4: Preparation of (5*S*)-[3-(1-ethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid *tert*-butyl ester (**3**)

Method A

Phosgene (20% solution in toluene, 0.140 ml, 1.43 mmol) is added to (5*R*)-[3-(1-ethyl-2-oxo-2,3-dihydro-1*H*-indol-5-ylamino)-2-hydroxy-propyl]-carbamic acid tert-butyl ester (**2**, 0.05 g, 0.143 mmol) and diisopropylethylamine (0.245 ml, 1.43 mmol) in dichloromethane (2 ml) at 0 °C. The reaction is allowed to warm to room temperature and stirred for 2 hours. The mixture is diluted with dichloromethane, washed with water and brine, dried ($Na_2SO_4$) and evaporated. The residue is purified by PTLC (5%MeOH / DCM) to give product as a solid (0.04g, 75%); HPLC r.t. 4.48 min; MS for $C_{19}H_{25}N_3O_5$ m/z 376.3 $(M+H)^+$.

Method B

[3-(1-Ethyl-2-oxo-2,3-dihydro-1H-indol-5(*R*)-ylamino)-2-hydroxy-propyl]-carbamic acid tert-butyl ester (**2**, 10 g, 28.6 mmol), 1,1'-carbonyldiimidazole (5.8 g, 35.8 mmol) and 125 mL of $CH_3CN$ were stirred at 55 °C for 18 h. After cooling to RT, 100 mL of 10% aq citric acid and 200 mL of $CH_2Cl_2$ were added and the phases were separated. The organic

layer was washed with 10% aq citric acid, water, brine, dried over $Na_2SO_4$ and conc *in vacuo* to give the title compound which was used without further purification or alternatively, was purified by column chromatography. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.55 (m, 1H), 7.25 (dd, *J*=8.4, 2.4 Hz, 1H), 6.79 (d, *J*=8.4 Hz, 1 H), 4.98 (m, 1H), 4.73 (m, 1H), 4.00 (t, *J*=8.8 Hz, 1H), 3.82 (dd, *J*=8.8, 7.2 Hz, 1H), 3.73 (q, *J*=7.2 Hz, 2H), 3.50 (m, 2H), 3.50 (s, 2H), 1.39 (s, 9H), 1.23 (t, *J*=7.2 Hz, 3H). MS-APCI (*m/z*+): 276, 376.

Step 5: Preparation of (5*R*)-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-1-ethyl-1,3-dihydro-indole-2-one (**4**)

Method A

(5*S*)-[3-(1-Ethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid *tert*-butyl ester (**3**, 0.25 g, 0.665 mmol) is treated with 50% TFA/DCM (4 ml) for 30 minutes at room temperature. The reaction is evaporated and the product isolated as the TFA salt (0.257 g, 99%); HPLC r.t. 2.68 min; MS for $C_{14}H_{17}N_3O_3$ m/z 276.2 $(M+H)^+$.

Method B

A solution of 4 M HCl in dioxane (100 mL) was added dropwise to a solution of 3-(1-Ethyl-2-oxo-2,3-dihydro-1*H*-indol-5(*S*)-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid *tert*-butyl ester (**3**, 4.44 g, 11.8 mmol), 25 mL of THF, and 0.1 mL of anisole. The resultant mixture was stirred overnight at RT. Ether was added dropwise, resulting in the formation of a solid. Under reduced pressure, the mixture was concentrated to approx. one-third of its original volume. The solid was collected via filtration, rinsed with ether, and dried under vacuum to give the title compound, which was used without further purification. $^1$H NMR (400 MHz, DMSO): δ 8.31 (br s, 3H), 7.54 (m, 1H), 7.33 (dd, *J*=8.4, 2.4 Hz, 1H), 7.06 (d, *J*=8.4 Hz, 1H), 4.92 (m, 1H), 4.17 (t, *J*=9.2 Hz, 1H), 3.85 (dd, *J*=9.2, 6.8 Hz, 1H), 3.69 (q, *J*=7.2 Hz, 2H), 3.58 (s, 2H), 3.24 (m, 2H), 1.14 (t, *J*=7.2 Hz, 3H). MS-APCI (*m/z*+): 276, 317 ($M+CH_3CN$).

Step 6: Preparation of (5*S*)-[3-(1-ethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid methyl ester

Method A

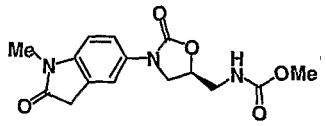
Methyl chloroformate (0.026 ml, 0.33 mmol) is added dropwise to (5*R*)-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-1-ethyl-1,3-dihydro-indole-2-one (**4**, 0.065 g, 0.167 mmol) and diisopropylethylamine (0.114 ml, 0.668 mmol) in dichloromethane (3 ml) at 0°C. The reaction is stirred at 0 °C for 30 minutes and then allowed to warm at room temperature. The reaction mixture is diluted with dichloromethane, washed with water, citric acid and

brine, dried ($Na_2SO_4$) and evaporated. The residue is purified by PTLC (5% MeOH/DCM) to give product as a solid (0.04g, 72 %); HPLC r.t. 3.597 min.

Method B

5-(5(*S*)-Aminomethyl-2-oxo-oxazolidin-3-yl)-1-ethyl-1,3-dihydro-indol-2-one hydrochloride (4, 3.7 g, 11.8 mmol), 50 mL of THF, 25 mL of water, sodium bicarbonate (3.0 g, 35.5 mmol) and methyl chloroformate (1.4 mL, 17.7 mmol) were stirred at RT for 2 h. The reaction mixture was diluted with 100 mL of $CH_2Cl_2$ and the phases were separated. The organic layer was washed with 3x100 mL of water, brine, dried over $Na_2SO_4$, and conc *in vacuo* to give the title compound, which was recrystallized from isopropanol. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.55 (m, 1H), 7.26 (dd, *J*=8.4, 2.4 Hz, 1H), 6.79 (d, *J*=8.4 Hz, 1 H), 5.11 (m, 1H), 4.75 (m, 1H), 4.03 (t, *J*=8.8 Hz, 1H), 3.82-3.49 (m, 10H), 1.24 (t, *J*=7.2 Hz, 3H). $^1$H NMR (400 MHz, DMSO): δ7.53 (m, 2H), 7.32 (dd, *J*=8.4, 2.4 Hz, 1H), 7.04 (d, *J*=8.4 Hz, 1H), 4.68 (m, 1H), 4.09 (t, *J*=9.2 Hz, 1H), 3.75 (dd, *J*=9.2, 6.4 Hz, 1H), 3.68 (q, *J*=7.0 Hz, 2H), 3.57 (s, 2H), 3.54 (s, 3H), 3.33 (m, 2H), 1.13 (t, *J*=7.0 Hz, 3H). MS-APCI (*m/z*+): 276, 334.

**Example 2** Preparation of (*S*)-[3-(1-methyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid methyl ester




Step 1: Preparation of 1-methyl-1,3-dihydro-indol-2-one

1-Methyl-1*H*-indole-2,3-dione (5.00 g, 31.0 mmol) is heated with neat hydrazine hydrate (30 ml) at 130 °C for 1.5 hours. The reaction mixture is cooled, diluted with ice water, and extracted with ethyl acetate. The extract is washed with brine, dried over sodium sulfate, and evaporated to give the title compound as a yellowish brown solid. HPLC r.t. 3.69 min; MS for $C_9H_9NO$ m/z 148.1$(M+H)^+$.

Step 2: Preparation of 1-methyl-5-nitro-1,3-dihydro-indol-2-one

1-Methyl-1,3-dihydro-indol-2-one (Step 1, 2.10 g, 14.3 mmol) is added in portions to 70% nitric acid (10 ml) at –10 °C. After the addition is complete, the reaction is allowed to warm to room temperature and then stirred for 5 hours. The mixture is diluted with ice water and the resulting precipitate filtered, washed with water, and dried under a vacuum to give the title compound as a brown solid. HPLC r.t. 3.97 min; MS for $C_9H_8N_2O_3$ m/z 193.9$(M+H)^+$.

Step 3: Preparation of 5-amino-1-methyl-1,3-dihydro-indol-2-one

Iron powder (2.09 g, 37.46 mmol) is added in small portion to a mixture of 1-methyl-5-nitro-1, 3-dihydro-indol-2-one (Step 2, 1.8 g, 9.36 mmol) and ammonium chloride (4.96 g, 93.6 mmol) in ethanol (100 ml) and water (50 ml) at 90°C. The reaction mixture is stirred vigorously and heated for 30min, cooled to room temperature, and diluted with dichloromethane (200 ml). The mixture is filtered through celite, the organic layer separated and washed with water and brine, dried over sodium sulfate, and evaporated to give the title compound as a dark brown solid. HPLC r.t. 1.06 min; MS for $C_9H_{10}N_2O$ m/z 163.2$(M+H)^+$.

Step 4: Preparation of (*R*)-[2-hydroxy-3-(1-methyl-2-oxo-2,3-dihydro-1*H*-indol-5-ylamino)-propyl]-carbamic acid *tert*-butyl ester

5-Amino-1-methyl-1,3-dihydro-indol-2-one (1.20 g, 7.40 mmol), (*S*)-oxiranylmethyl-carbamic acid tert-butyl ester (1.28 g, 7.40 mmol) and lithium trifluoromethanesulfonate (1.14 g, 7.398 mmol) in acetonitrile (10 ml) are heated at 70 °C for 1 hour. The reaction mixture is diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$) and evaporated. The residue is purified by flash column chromatography (70% EtOAc/Hexane) to give the title compound as a light brown solid. HPLC r.t. 3.20 min; MS for $C_{17}H_{25}N_3O_4$ m/z 336.4$(M+H)^+$.

Step 5: Preparation of (*S*)-[3-(1-methyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid *tert*-butyl ester

(*R*)-[2-Hydroxy-3 -(1-methyl-2-oxo-2,3-dihydro-1*H*-indol-5-ylamino)-propyl]-carbamic acid tert.butyl ester (Step 1, 0.10 g, 0.298 mmol) and 1,1-carbonyldiimidazole (0.053 g, 0.327 mmol) in acetonitrile (3 ml) is stirred and heated at 60 °C for 2 hours. The reaction mixture is diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$) and evaporated. The residue was purified by PTLC (10% MeOH/DCM) to give the title compound as a light brown solid. HPLC r.t. 4.24 min; MS for $C_{18}H_{23}N_3O_5$ m/z 362.3$(M+H)^+$.

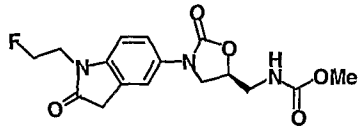
Step 6: Preparation of (*R*)-(5-aminomethyl-2-oxo -oxazolidin-3-yl)-1-methyl-1,3-dihydro-indole-2-one

(*S*)-[3-(1-Methyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid *tert*-butyl ester (Step 2, 0.20 g, 0.553 mmol) is treated with 50% TFA/DCM (3 ml) for 30 minutes at room temperature. The reaction is evaporated to give the title compound as the TFA salt. HPLC r.t. 2.46 min; MS for $C_{13}H_{15}N_3O_3$ m/z 262.2$(M+H)^+$.

Step 7: Preaparation of (*S*)-[3-(1-methyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid methyl ester

Methyl chloroformate (0.0256 ml, 0.332 mmol) is added to (*R*)-(5-aminomethyl-2-oxo -oxazolidin-3-yl)-1-methyl-1,3-dihydro-indole-2-one (Preparation 1, 0.062 g, 0.166 mmol) and diisopropylethylamine (0.172 ml, 0.996 mmol) in dichloromethane (5 ml) at 0 °C. The reaction is stirred at 0 °C for 30 minutes and then allowed to warm at room temperature. The reaction mixture is diluted with dichloromethane, washed with water, citric acid and brine, dried ($Na_2SO_4$) and evaporated to give the title compound as an off white solid. HPLC r.t. 3.351 min; $^1$H NMR (300 MHz, $CDCl_3$) 7.59 (s, 1H), 7.27 (dd, $J$ = 2.1, 8.4 Hz, 1H), 6.79 (d, $J$ = 8.7 Hz, 1H), 5.16 (m, 1H), 4.73-4.81 (m, 1H), 4.05 (t, $J$ = 8.7 Hz, 1H), 3.82 (dd, $J$ = 6.3, 9 Hz, 1H), 3.69 (s, 3H), 3.56-3.64 (m, 2H), 3.54 (s, 2H), 3.21 (s, 3H); MS for $C_{15}H_{17}N_3O_5$ m/z 320 $(M+H)^+$.

**Example 3** Preparation of (*S*)-{3-[1-(2-fluoro-ethyl)-2-oxo-2,3-dihydro-1*H*-indol-5-yl]-2-oxo-oxazolidin-5-ylmethyl}-carbamic acid methyl ester




Step 1: Preparation of (*R*)-{3-[1-(2-fluoro-ethyl)-2-oxo-2,3-dihydro-1*H*-indol-5-ylamino]-2-hydroxy-propyl}-carbamic acid *tert*-butyl ester

5-Amino-1- (2-fluoro-ethyl)-1,3-dihydro-indol-2-one (1.00 g, 5.15 mmol), (*S*)-oxiranylmethyl-carbamic acid tert-butyl ester (0.894 g, 5.15 mmol) and lithium trifluoromethanesulfonate (0.793 g, 5.15 mmol) in acetonitrile (10 ml) are heated at 90 °C for 1 hour. The reaction mixture is diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$) and evaporated. Final purification by flash chromatography (70% ethyl acetate/hexane) gives the title compound as a light yellow-brown solid. HPLC r.t. 3.28 min; MS for C18H26FN3O4 m/z 368.3 $(M+H)^+$.

Step 2: Preparation of (*S*)-{3-[1-(2-fluoro-ethyl)-2-oxo-2,3-dihydro-1*H*-indol-5-yl]-2-oxo-oxazolidin-5-ylmethyl}-carbamic acid *tert*-butyl ester

Phosgene (20% solution in toluene, 0.532 ml, 5.44 mmol) is added to (*R*)-{3-[1-(2-fluoro-ethyl)-2-oxo-2,3-dihydro-1*H*-indol-5-ylamino]-2-hydroxy-propyl}-carbamic acid *tert*-butyl ester (Step 1, 0.20 g, 0.544 mmol) and triethylamine (0.378 ml, 2.72 mmol) in dichloromethane (5 ml) at 0 °C and stirred for 30 minutes. The mixture is diluted with dichloromethane, washed with water and brine, dried ($Na_2SO_4$) and evaporated to give the title compound as a light brown solid. HPLC r.t. 4.37 min; MS for C19H24FN3O5 m/z 394.1 $(M+H)^+$.

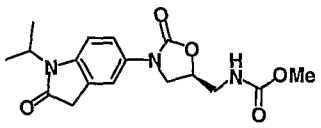
Step 3: Preparation of (R)-5-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-1-(2-fluoro-ethyl)-1,3-dihydro-indol-2-one

(*S*)-{3-[1-(2-Fluoro-ethyl)-2-oxo-2,3-dihydro-1*H*-indol-5-yl]-2-oxo-oxazolidin-5-ylmethyl}-carbamic acid *tert*-butyl ester (Step 2, 0.110 g, 0.280 mmol) is treated with 50% TFA/DCM (3 ml) for 15 minutes at room temperature. The reaction is evaporated and the title compound isolated as the TFA salt. HPLC r.t. 2.61 min; MS for C14H16FN3O3 m/z 294.0 $(M+H)^+$.

Step 4: Preparation of (*S*)-{3-[1-(2-fluoro-ethyl)-2-oxo-2,3-dihydro-1*H*-indol-5-yl]-2-oxo-oxazolidin-5-ylmethyl}-carbamic acid methyl ester

Methyl chloroformate (0.033 ml, 0.42 mmol) is added dropwise to (*R*)-5-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-1-(2-fluoro-ethyl)-1,3-dihydro-indol-2-one (0.114 g, 0.279 mmol) and diisopropylethylamine (0.194 ml, 1.12 mmol) in dichloromethane (4 ml) at 0°C. The reaction is stirred at 0 °C for 30 minutes and then allowed to warm at room temperature. The reaction mixture is diluted with dichloromethane, washed with water and brine, dried ($Na_2SO_4$) and evaporated. The residue is purified by PTLC (10% MeOH/DCM) to give the title compound as an off-white solid. HPLC r.t. 3.45 min; $^1H$ NMR (300 MHz, $CDCl_3$) 7.63 (m, 1H), 7.24 (m, 1H), 6.92 (d, $J$ = 8.1 Hz, 1H), 5.13 (t, 1H), 4.75 (m, 1H), 4.74 (t, $J$ = 4.8 Hz, 1H), 4.59 (t, $J$ = 5.1 Hz, 1H), 4.06 (t, $J$ = 5.1 Hz, 1H), 4.05 (t, $J$ = 9 Hz, 1H), 3.97 (t, $J$ = 5.1 Hz, 1H), 3.81 (dd, $J$ = 6.6, 9 Hz, 1H), 3.69 (s, 3H), 3.58 (s, 2H), 3.50-3.64 (m, 2H); MS for $C_{16}H_{18}FN_3O_5$ m/z 352.1 $(M+H)^+$.

**Example 4** Preparation of (*S*)-[3-(1-isopropyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid methyl ester




Step 1: Preparation of 1-isopropyl-1*H*-indole-2,3-dione

1*H*-Indole-2, 3-dione (5.0 g, 0.034 mol), iodopropane (6.83 ml, 0.068 mol) and potassium carbonate (9.28 g, 0.068 mol) in DMF (30 ml) are stirred at room temperature for 72 hours. The reaction mixture is diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$) and evaporated to give the title compound as an orange solid. HPLC r.t. 4.38 min; MS for $C_{11}H_{11}NO_2$ m/z 190.1 $(M+H)^+$.

Step 2: Preparation of 1-isopropyl-1,3-dihydro-indol-2-one

1-Isopropyl-1*H*-indole-2,3-dione (3.00 g, 15.9 mmol) was heated with neat hydrazine hydrate (10 ml) at 130 °C for 1.5 hours. The reaction was cooled, diluted with ice water, and extracted with ethyl acetate. The organic layer is washed with brine, dried ($Na_2SO_4$), and evaporated to give the title compound as a light brown solid. HPLC r.t. 4.54 min; MS for $C_{11}H_{13}NO$ m/z 176.1$(M+H)^+$.

Step 3: Preparation of 1-isopropyl-5-nitro-1,3-dihydro-indol-2-one

1-Isopropyl-1,3-dihydro-indol-2-one (2.50 g, 14.3 mmol) is added to a stirred solution of sodium nitrate (1.20g, 14.26mmol) in trifluoroacetic acid (50ml) and stirred at room temperature for 5h. The reaction was diluted with ice water and resulting precipitate filtered, washed with water, and dried under vacuum to give the title compound as a brown solid. HPLC r.t. 4.71 min; MS for $C_{11}H_{12}N_2O_3$ m/z 219.0 $(M-H)^-$.

Step 4: Preparation of 5-amino-1-isopropyl-1,3-dihydro-indol-2-one

Iron powder (2.63 g, 47.2 mmol) is added in small portion to a mixture of 1-isopropyl-5-nitro-1,3-dihydro-indol-2-one (2.60 g, 11.8 mmol) and ammonium chloride (6.27 g, 118 mmol) in ethanol (80 ml) and water (40 ml) at 90 °C. The reaction mixture is stirred vigorously and heated for 45min, then cooled to room temperature and diluted with dichloromethane (250ml). The mixture is filtered through celite, the organic layer separated and washed with water and brine, dried ($Na_2SO_4$) and evaporated to give the title compound as a dark brown gummy solid. HPLC r.t. 2.51 min; MS for $C_{11}H_{14}N_2O$ m/z 191.1$(M+H)^+$.

Step 5: Preparation of (*R*)-2-hydroxy-3-(1-isopropyl-2-oxo-2,3-dihydro-1*H*-indol-5-ylamino)-propionic acid methyl ester

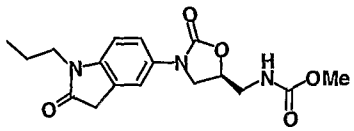
5-Amino-1-isopropyl-1,3-dihydro-indol-2-one (1.00 g, 5.25 mmol), methyl (2*R*)-glycidate (0.536 g, 5.25 mmol) and lithium trifluoromethanesulfonate (0.81 g, 5.25 mmol) in acetonitrile (10 ml) are heated at 70 °C for 3 hours. The reaction mixture is diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$) and evaporated. The residue is purified by flash chromatography (70% EtOAc/Hexane) to give the title compound as a light brown solid. HPLC r.t. 2.95 min; MS for $C_{15}H_{20}N_2O_4$ m/z 293.0$(M+H)^+$.

Step 6: Preparation of (*S*)-[3-(1-isopropyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid methyl ester

Methyl chloroformate (0.029 ml, 0.371 mmol) is added dropwise to (*R*)-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-1-isopropyl-1,3-dihydro-indole-2-one (0.075 g, 0.185 mmol) and diisopropylethylamine (0.126 ml, 0.74 mmol) in dichloromethane (3 ml) was

added at 0 °C. The reaction is stirred at 0 °C for 30 minutes and then allowed to warm to room temperature. The mixture is diluted with dichloromethane, washed with water, citric acid and brine, dried ($Na_2SO_4$) and evaporated. The residue is purified by PTLC (10% MeOH/DCM) to give the title compound as an off white solid. HPLC r.t. 3.905 min; $^1H$ NMR (300 MHz, $CDCl_3$) 7.55 (s, 1H), 7.24 (dd, $J$ = 2.4, 8.7 Hz, 1H), 6.97 (d, $J$ = 8.7 Hz, 1H), 5.12 (m, 1H), 4.76 (m, 1H), 4.61-4.71 (m, 1H), 4.05 (t, $J$ = 8.7 Hz, 1H), 3.80 (dd, $J$ = 6.6, 9 Hz, 1H), 3.68 (s, 3H), 3.54-3.62 (m, 2H), 3.51 (s, 2H), 1.46 (d, $J$ = 6.9 Hz, 6H); MS for $C_{17}H_{21}N_3O_5$ m/z 348 $(M+H)^+$.

**Example 5** Preparation of (*S*)-[2-oxo-3-(2-oxo-1-propyl-2,3-dihydro-1*H*-indol-5-yl)-oxazolidin-5-ylmethyl]-carbamic acid methyl ester




Step 1: Preparation of (*R*)-[2-hydroxy-3-(2-oxo-1-propyl-2,3-dihydro-1*H*-indol-5-ylamino)-propyl]-carbamic acid *tert*-butyl ester

5-Amino-1-propyl-1,3-dihydro-indol-2-one (0.530 g, 2.78 mmol), (*S*)-oxiranylmethyl-carbamic acid tert-butyl ester (0.483 g, 2.78 mmol) and lithium trifluoromethanesulfonate (0.428 g, 2.78 mmol) in acetonitrile (7 ml) are heated at 90 °C for 1 hour. The reaction mixture is diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$) and evaporated. Final purification by flash chromatography (70% ethyl acetate/hexane) gives pure the title compound as a light brown solid. HPLC r.t. 3.66 min; MS for C19H29N3O4 m/z 364 $(M+H)^+$.

Step 2: Preparation of (*S*)-[2-oxo-3-(2-oxo-1-propyl-2,3-dihydro-1*H*-indol-5-yl)-oxazolidin-5-ylmethyl]-carbamic acid *tert*-butyl ester

Phosgene (20% solution in toluene, 0.978 ml, 10.0 mmol) is added to (*R*)-[2-hydroxy-3-(2-oxo-1-propyl-2,3-dihydro-1*H*-indol-5-ylamino)-propyl]-carbamic acid *tert*-butyl ester (Step 1, 0.520 g, 1.43 mmol) and triethylamine (0.998 ml, 7.15 mmol) in dichloromethane (10 ml) at 0 °C and stirred for 30 minutes. The mixture is diluted with dichloromethane, washed with water and brine, dried ($Na_2SO_4$) and evaporated to give the title compound as a light brown solid. HPLC r.t. 4.88 min; MS for C20H27N3O5 m/z 390 $(M+H)^+$.

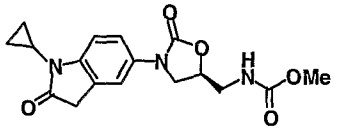
Step 3: Preparation of *R*)-5-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-1-propyl-1,3-dihydro-indol-2-one

(*S*)-[2-Oxo-3-(2-oxo-1-propyl-2,3-dihydro-1*H*-indol-5-yl)-oxazolidin-5-ylmethyl]-carbamic acid *tert*-butyl ester (Step 2, 0.220 g, 0.564 mmol) is treated with 50% TFA/DCM (4 ml) for 15 minutes at room temperature. The reaction is evaporated and the title compound isolated as the TFA salt. HPLC r.t. 3.05 min; MS for C15H19N3O3 m/z 290.2 $(M+H)^+$.

Step 4: Preparation of (*S*)-[2-oxo-3-(2-oxo-1-propyl-2,3-dihydro-1*H*-indol-5-yl)-oxazolidin-5-ylmethyl]-carbamic acid methyl ester

Methyl chloroformate (0.053 ml, 0.669 mmol) is added dropwise to (*R*)-5-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-1-propyl-1,3-dihydro-indol-2-one (0.180 g, 0.446 mmol) and diisopropylethylamine (0.326 ml, 1.78 mmol) in dichloromethane (4 ml) at 0°C. The reaction is stirred at 0 °C for 30 minutes and then allowed to warm at room temperature. The reaction mixture is diluted with dichloromethane, washed with water and brine, dried ($Na_2SO_4$) and evaporated. The residue is purified by PTLC (10% MeOH/DCM) to give the title compound as an off-white solid. HPLC r.t. 3.97 min; $^1H$ NMR (300 MHz, $CDCl_3$) 7.56 (m, 1H), 7.22-7.27 (m, 1H), 6.79 (d, $J$ = 8.4 Hz, 1H), 5.13 (t, 1H), 4.76 (m, 1H), 4.05 (t, $J$ = 8.7 Hz, 1H), 3.81 (dd, $J$ = 6.6, 9 Hz, 1H), 3.69 (s, 3H), 3.54 (s, 2H), 3.49-3.67 (m, 4H), 1.69 (m, 2H), 0.96 (t, $J$ = 7.5 Hz, 3H); MS for $C_{17}H_{21}N_3O_5$ m/z 348.3 $(M+H)^+$.

**Example 6** Preparation of (*S*)-[3-(1-cyclopropyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid methyl ester




Step 1: Preparationof (*R*)-[3-(1-cyclopropyl-2-oxo-2,3-dihydro-1*H*-indol-5-ylamino)-2-hydroxy-propyl]-carbamic acid *tert*-butyl ester

5-Amino-1-cyclopropyl-1,3-dihydro-indol-2-one (1.30 g, 6.90 mmol), (*S*)-oxiranylmethyl-carbamic acid tert-butyl ester (1.20 g, 6.90 mmol) and lithium trifluoromethanesulfonate (1.06 g, 6.90 mmol) in acetonitrile (10 ml) are heated at 90 °C for 3 hours. The reaction mixture is diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$) and evaporated. Final purification by flash chromatography (70% ethyl acetate/hexane) gives pure the title compound as a light brown solid. HPLC r.t. 3.48 min; MS for C19H27N3O4 m/z 362.3 $(M+H)^+$.

Step 2: Preparation of (*S*)-[3-(1-cyclopropyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid *tert*-butyl ester

Phosgene (20% solution in toluene, 1.95 ml, 19.9 mmol) is added to (*R*)-[3-(1-cyclopropyl-2-oxo-2,3-dihydro-1*H*-indol-5-ylamino)-2-hydroxy-propyl]-carbamic acid *tert*-butyl ester (Step 1, 0.720 g, 1.99 mmol) and triethylamine (1.38 ml, 9.96 mmol) in dichloromethane (10 ml) at 0 °C and stirred for 30 minutes. The mixture is diluted with dichloromethane, washed with water and brine, dried ($Na_2SO_4$) and evaporated. The residue is purified by flash column chromatography (70% ethyl acetate/hexane) to give the title compound as an off-white solid. HPLC r.t. 4.63 min; MS for C20H25N3O5 m/z 388.2 $(M+H)^+$.

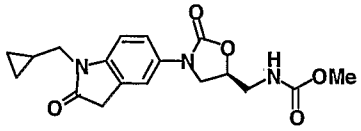
Step 3: Preparation of (*R*)-5-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-1-cyclopropyl-1,3-dihydro-indol-2-one

(*S*)-[3-(1-Cyclopropyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid *tert*-butyl ester (Step 2, 0.240 g, 0.619 mmol) is treated with 50% TFA/DCM (4 ml) for 15 minutes at room temperature. The reaction is evaporated and the title compound isolated as the TFA salt. HPLC r.t. 2.81 min; MS for C15H17N3O3 m/z 288.1 $(M+H)^+$.

Step 4: Preparation of (*S*)-[3-(1-cyclopropyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid methyl ester

Methyl chloroformate (0.043 ml, 0.559 mmol) is added dropwise to (*R*)-5-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-1-cyclopropyl-1,3-dihydro-indol-2-one (0.150 g, 0.373 mmol) and diisopropylethylamine (0.273 ml, 1.49 mmol) in dichloromethane (3 ml) at 0°C. The reaction is stirred at 0 °C for 30 minutes and then allowed to warm at room temperature. The reaction mixture is diluted with dichloromethane, washed with water and brine, dried ($Na_2SO_4$) and evaporated. The residue is purified by PTLC (10% MeOH/DCM) to give the title compound as an off-white solid. HPLC r.t. 3.67 min; $^1$H NMR (300 MHz, $CDCl_3$) 7.54 (m, 1H), 7.26 (m, 1H), 7.06 (d, $J$ = 8.4 Hz, 1H), 5.13 (t, 1H), 4.76 (m, 1H), 4.04 (t, $J$ = 8.7 Hz, 1H), 3.81 (dd, $J$ = 6.6, 9 Hz, 1H), 3.69 (s, 3H), 3.51-3.64 (m, 2H), 3.49 (s, 2H), 2.63 (m, 1H), 1.06 (m, 2H), 0.89 (m, 2H); MS for $C_{17}H_{19}N_3O_5$ m/z 346.2 $(M+H)^+$.

**Example 7** Prepartion of (*S*)-[3-(1-cyclopropylmethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid methyl ester 26, line




Step 1: Preparation of (*R*)-[3-(1-cyclopropylmethyl-2-oxo-2,3-dihydro-1*H*-indol-5-ylamino)-2-hydroxy-propyl]-carbamic acid *tert*-butyl ester

5-Amino-1-cyclopropylmethyl-1,3-dihydro-indol-2-one (0.400 g, 1.98 mmol), (*S*)-oxiranylmethyl-carbamic acid tert-butyl ester (0.344 g, 1.98 mmol) and lithium trifluoromethanesulfonate (0.304 g, 1.98 mmol) in acetonitrile (5 ml) are heated at 90 °C for 4 hours. The reaction mixture is diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$) and evaporated. Final purification by flash chromatography (70% ethyl acetate/hexane) gives the title compound as a light brown foamy solid. HPLC r.t. 3.76 min; MS for C20H29N3O4 m/z 376.3 $(M+H)^+$.

Step 2: Preparation of (*S*)-[3-(1-cyclopropylmethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid *tert*-butyl ester

Phosgene (20% solution in toluene, 0.728 ml, 7.45 mmol) is added to (*R*)-[3-(1-Cyclopropylmethyl-2-oxo-2,3-dihydro-1*H*-indol-5-ylamino)-2-hydroxy-propyl]-carbamic acid *tert*-butyl ester (Step 1, 0.280 g, 0.745 mmol) and triethylamine (0.520 ml, 3.73 mmol) in dichloromethane (5 ml) at 0 °C. The reaction is allowed to warm to room temperature and stirred for 1 hours. The mixture is diluted with dichloromethane, washed with water and brine, dried ($Na_2SO_4$) and evaporated to give the title compound suitable for use directly in the next step. HPLC r.t. 5.01 min; MS for C21H27N3O5 m/z 402 $(M+H)^+$.

Step 3: Preparation of (*R*)-5-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-1-cyclopropylmethyl-1,3-dihydro-indol-2-one

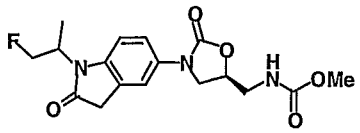
(*S*)-[3-(1-Cyclopropylmethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid *tert*-butyl ester (Step 2, 0.210 g, 0.523 mmol) is treated with 50% TFA/DCM (4 ml) for 30 minutes at room temperature. The reaction is evaporated and the title compound isolated as the TFA salt. HPLC r.t. 3.21 min; MS for C16H19N3O3 m/z 302.1 $(M+H)^+$.

Step 4: Preparation of (*S*)-[3-(1-cyclopropylmethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid methyl ester

Methyl chloroformate (0.044 ml, 0.560 mmol) is added dropwise to (*R*)-5-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-1-cyclopropylmethyl-1,3-dihydro-indol-2-one (Example 59, Step 3, 0.155 g, 0.373 mmol) and diisopropylethylamine (0.273 ml, 1.49 mmol) in dichloromethane (4 ml) at 0°C. The reaction is stirred at 0 °C for 30 minutes and then allowed to warm at room temperature. The reaction mixture is diluted with dichloromethane, washed with water and brine, dried ($Na_2SO_4$) and evaporated. The residue is purified by PTLC (5% MeOH/DCM) to give the title compound as a yellow solid. HPLC r.t. 4.10 min; $^1H$ NMR (300 MHz, $CDCl_3$) 7.57 (d, $J$ = 0.9 Hz,1H), 7.27 (m, 1H), 6.88 (d, $J$ = 8.4 Hz, 1H),

5.14 (t, 1H), 4.73-4.81 (m, 1H), 4.05 (t, $J$ = 8.7 Hz, 1H), 3.81 (dd, $J$ = 6.6, 9 Hz, 1H), 3.69 (s, 3H), 3.59 (d, $J$ = 6.6 Hz, 2H), 3.55 (s, 2H), 3.49 (m, 2H), 1.14 (m, 1H), 0.52 (m, 2H), 0.39 (m, 2H);; MS for $C_{18}H_{21}N_3O_5$ m/z 360.2 $(M+H)^+$.

**Example 8** Preparation of (*S*)-{3-[1-(2-fluoro-1-methyl-ethyl)-2-oxo-2,3-dihydro-1*H*-indol-5-yl]-2-oxo-oxazolidin-5-ylmethyl}-carbamic acid methyl ester




Step 1: Preparation of (*R*)-{3-[1-(2-fluoro-1-methyl-ethyl)-2-oxo-2,3-dihydro-1*H*-indol-5-ylamino]-2-hydroxy-propyl}-carbamic acid *tert*-butyl ester

5-Amino-1-(2-fluoro-1-methyl-ethyl)-1,3-dihydro-indol-2-one (0.370 g, 1.77 mmol), (*S*)-oxiranylmethyl-carbamic acid tert-butyl ester (0.308 g, 1.77 mmol) and lithium trifluoromethanesulfonate (0.271 g, 1.77 mmol) in acetonitrile (5 ml) are heated at 90 °C for 3 hours. The reaction mixture is diluted with ethyl acetate, washed with water and brine, dried ($Na_2SO_4$) and evaporated. Final purification by PTLC (5% methanol/dichloromethane) gives the title compound as an off-white solid. HPLC r.t. 3.59 min; MS for C19H28FN3O4 m/z 382.3 $(M+H)^+$.

Step 2: Preparation of (*S*)-{3-[1-(2-fluoro-1-methyl-ethyl)-2-oxo-2,3-dihydro-1*H*-indol-5-yl]-2-oxo-oxazolidin-5-ylmethyl}-carbamic acid *tert*-butyl ester

Phosgene (20% solution in toluene, 0.635 ml, 6.48 mmol) is added to (*R*)-{3-[1-(2-Fluoro-1-methyl-ethyl)-2-oxo-2,3-dihydro-1*H*-indol-5-ylamino]-2-hydroxy-propyl}-carbamic acid *tert*-butyl ester (Step 1, 0.330 g, 0.865 mmol) and triethylamine (0.600 ml, 4.32 mmol) in dichloromethane (5 ml) at 0 °C. The reaction is allowed to warm to room temperature and stirred for 1 hours. The mixture is diluted with dichloromethane, washed with water and brine, dried ($Na_2SO_4$) and evaporated to give the title compound suitable for use directly in the next step. HPLC r.t. 4.78 min; MS for C20H26FN3O5 m/z 408.1 $(M+H)^+$.

Step 3: Preparation of (*R*)-5-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-1-(2-fluoro-1-methyl-ethyl)-1,3-dihydro-indol-2-one

(*S*)-{3-[1-(2-Fluoro-1-methyl-ethyl)-2-oxo-2,3-dihydro-1*H*-indol-5-yl]-2-oxo-oxazolidin-5-ylmethyl}-carbamic acid *tert*-butyl ester (Step 2, 0.250 g, 0.614 mmol) is treated with 50% TFA/DCM (4 ml) for 30 minutes at room temperature. The reaction is evaporated and the title compound isolated as the TFA salt. HPLC r.t. 2.95 min; MS for C15H18FN3O3 m/z 308.0 $(M+H)^+$.

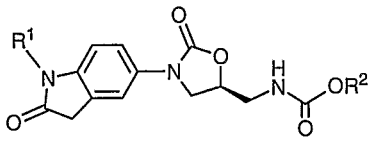
Step 4: Preparation of (*S*)-{3-[1-(2-fluoro-1-methyl-ethyl)-2-oxo-2,3-dihydro-1*H*-indol-5-yl]-2-oxo-oxazolidin-5-ylmethyl}-carbamic acid methyl ester

Methyl chloroformate (0.024 ml, 0.313 mmol) is added dropwise to (*R*)-5-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-1-(2-fluoro-1-methyl-ethyl)-1,3-dihydro-indol-2-one (Example 63, Step 3, 0.088 g, 0.208 mmol) and diisopropylethylamine (0.153 ml, 0.835 mmol) in dichloromethane (3 ml) at 0°C. The reaction is stirred at 0 °C for 30 minutes and then allowed to warm at room temperature. The reaction mixture is diluted with dichloromethane, washed with water and brine, dried ($Na_2SO_4$) and evaporated. The residue is purified by PTLC (5% MeOH/DCM) to give the title compound as a yellow solid. HPLC r.t. 3.85 min; $^1$H NMR (300 MHz, $CDCl_3$) 7.59 (m, 1H), 7.24 (m, 1H), 6.97 (d, $J$ = 8.7 Hz, 1H), 5.12 (t, 1H), 4.93 (m, 1H), 4.52-4.77 (m, 3H), 4.04 (t, $J$ = 9 Hz, 1H), 3.80 (dd, $J$ = 6.6, 9 Hz, 1H), 3.69 (m, 3H), 3.55 (s, 2H), 3.49-3.69 (m, 2H), 1.50 (d, $J$ = 7.2 Hz, 3H); MS for C17H20FN3O5 m/z 366.1 $(M+H)^+$.

CLAIMS

We Claim:

1. A compound of formula I



I

or a pharmaceutically acceptable salt thereof wherein $R^1$ is $C_{1-4}$alkyl, optionally substituted with a fluoro atom, or $R^1$ is a cyclopropyl or cyclopropylmethyl; and $R^2$ is methyl or ethyl.

2. A compound of claim 1 wherein $R^2$ is methyl.

3. A compound of claim 2 wherein $R^1$ is ethyl.

4. A compound of claim 2 wherein $R^1$ is methyl, fluoroethyl, isopropyl, propyl, cyclopropyl, cyclopropylmethyl, or 2-fluoro-1-methyl-ethyl.

5. A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

6. A method for treating bacteria infections comprising administering to a mammal being treated a pharmaceutically effective amount of the compound of claim 1.

7. The method of claim 6 wherein the compound of claim 1 is administered orally.

8. The method of claim 6 wherein the compound of claim 1 is administered parenterally, topically, rectally, or intranasally.

9. The method of claim 6 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.

10. The method of claim 6 wherein said compound is administered in an amount of from about 1 to about 50 mg/kg of body weight/day.

11. The bacteria infection of claim 6 which is ear infections, eye infections, respiratory tract infections, skin and skin structure infections, bacterial endocarditis, osteomyelitis, endocarditis or diabetic foot.

12. The bacteria infection of claim 6 which is caused by gram-positive bacteria, gram negative bacteria, anaerobic organisms, and acid-fast organisms.

13. The bacteria infection of claim 6 which is caused by bacteria comprising staphylococci, streptococci, Enterococci, Haemophilus, Moraxella, bacteroides, clostridia, Mycobacteria, or Chlamydia.

14. The bacteria of claim 13 wherein staphylococci is *S. aureus and S. epidermidis*; wherein streptococci is *S. pneumoniae* of *S. pyogenes*; wherein Enterococci is *E. faecalis*; wherein Haemophilus is *H. influenzae*; wherein Moraxella is *M. catarrhalis*; and wherein Mycobacteria is *M. tuberculosis*; or *Mycobacterium avium.*

15. The bacteria infections of claim 3 wherein infections is caused by multi-drug resistant S. aureus.

16. A compound of claim 1 which is (5*S*)-[3-(1-ethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid methyl ester.

17. The compound of claim 16 wherein said compound is substantially free of its opposite enantiomer.

18. The compound of claim 16 wherein said compound is in at least 90% enantiomeric excess.