(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 August 2007 (09.08.2007)

PCT

(10) International Publication Number
WO 2007/088478 A1

(51) International Patent Classification:
C07D 413/14 (2006.01) *A61K 31/422* (2006.01)
C07D 413/04 (2006.01) *A61P 31/04* (2006.01)

(21) International Application Number:
PCT/IB2007/000259

(22) International Filing Date: 22 January 2007 (22.01.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/764,114 1 February 2006 (01.02.2006) 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, GT, 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, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

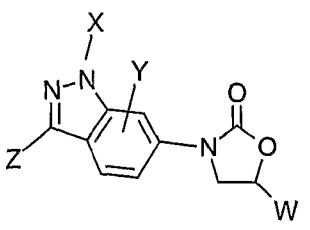
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, 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.

WO 2007/088478 A1

(54) Title: INDAZOLE OXAZOLIDINONES AS ANTIBACTERIAL AGENTS



(I)

(57) Abstract: The present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof wherein: W is $C(=O)NHR^1$, $C(=S)NHR^1$, or CH_2het; Y is H, or CF; R^1 is H, C_{1-6}alkyl, or OC_{1-6}alkyl; X is H, C_{1-6}alkyl, or C_{3-7}cycloalkyl; Z is H, halo, C_{1-6}alkyl, OC_{1-6}alkyl, or SC_{1-6}alkyl; het is a five-(5) or six-(6) membered heterocyclic ring having 1-4 heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen within the ring. The compounds are useful as antibacterial agents.

INDAZOLE OXAZOLIDINONES AS ANTIBACTERIAL AGENTS

FIELD OF INVENTION

The present invention relates to novel derivatives of indazole oxazolidinones, pharmaceutical compositions thereof, methods for their use, and methods for preparing the isoxazol oxazolidinone derivatives. These compounds have potent activities against gram-positive bacteria.

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 result, structurally novel antibacterials with a new mode of action have become increasingly important in the treatment of bacterial infections.

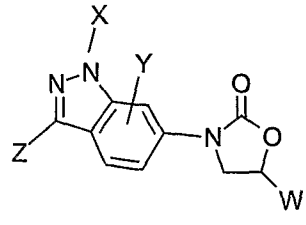
Among newer antibacterial agents, oxazolidinone compounds are the most recent synthetic class of antimicrobials. This invention provides novel indazole oxazolidinone derivatives, which are active against a number of human and veterinary pathogens, including multiple resistant strains of bacteria.

INFORMATION DISCLOSURE

U.S. Patent 5,182,403; U.S. Patent 6,239,152 discloses; U.S. Patent 5,164,510; WO 1996/38444; and WO 2004/074282 disclose oxazolidinones as antibacterial agents.

SUMMARY OF THE INVENTION

The present invention provides a compound of formula I



I

or a pharmaceutically acceptable salt thereof wherein:

W is $C(=O)NHR^1$, $C(=S)NHR^1$, or CH_2het;

Y is H, or CF;

R^1 is (a) H,

(b) C_{1-6}alkyl, or

(c) OC_{1-6}alkyl;

X is (a) H,

(b) C_{1-6}alkyl, or

(c) C_{3-7}cycloalkyl;

Z is

(a) H,

(b) halo,

(c) C_{1-6}alkyl,

(d) OC_{1-6}alkyl, or

(e) SC_{1-6}alkyl;

het is a five-(5) or six-(6) membered heterocyclic ring having 1-4 heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen within the ring, wherein each carbon atom I het is optionally substituted with C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, halo, OR^2, CN, NO_2, NR^2R^2, oxo, CF_3, OCF_3, $C(=O)C_{1-4}$alkyl, $OC(=O)C_{1-4}$alkyl, or $C(=O)OR^2$; at each occurrence, C_{1-6}alkyl is optionally substituted with aryl, het, halo, CN, OR^2, NO_2, N_3, NR^2R^2, or C_{1-4}alkyl; and R^2 is H or C_{1-4}alkyl.

In another aspect, the present invention also provides:

a pharmaceutical composition which comprises a pharmaceutically acceptable carrier and an effective amount of a compound of formula I,

a method for treating gram-positive 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 to prepare a medicament for treating gram-positive 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

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_{1-7} alkyl refers to alkyl of one to seven carbon atoms, inclusive.

The term alkyl, alkenyl or alkynyl 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 "C_{3-7}cycloalkyl" refers to a cyclic saturated monovalent hydrocarbon group of three to seven carbon atoms, e.g., cyclopropyl, cyclohexyl, and the like.

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

The term "het" is a five- (5) or six- (6) membered heterocyclic ring having 1-4 heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen within the ring. An examples of het includes, but are not limited to, pyrrole, imidazole, pyrazole, 1,2,3-triazole, 1,3,4-triazole, oxazole, thiazole, isoxazole, isothiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,2,3-thiadiazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, dihydroindole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, isoxazolinone, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, thiadiazole, tetrazole, thiazolidine, thiophene, benzo[b]thiophene, morpholine, thiomorpholine, (also referred to as thiamorpholine,), piperidine, pyrrolidine, tetrahydrofuran, or the like. Another example of het includes, but are not limited to, pyridine, thiophene, furan, pyrazole, pyrimidine, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazinyl, 4-oxo-2-imidazolyl, 2-imidazolyl, 4-imidazolyl, 3-isoxaz-olyl, 4-is-oxaz-olyl, 5-isoxaz-olyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 4-oxo-2-oxazolyl, 5-oxazolyl, 1,2,3-oxathiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazole, 4-isothiazole, 5-isothiazole, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 3-isopyrrolyl, 4-isopyrrolyl, 5-isopyrrolyl, 1,2,3,-oxathiazole-1-oxide, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 5-oxo-1,2,4-oxadiazol-3-yl, 1,2,4-thiadiazol-3-yl, 1,2,5-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 3-oxo-1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-oxo-1,3,4-thiadiazol-5-yl, 1,2,3-triazole-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, tetrazole-1-yl, 1,2,3,4-tetrazol-5-yl, 5-oxazolyl, 3-isothiazolyl, 4-isothiazolyl and 5-isothiazolyl, 1,3,4,-oxadiazole, 4-oxo-2-thiazolinyl, or 5-methyl-1,3,4-thiadiazol-2-yl, thiazoledione, 1,2,3,4-thiatriazole, or 1,2,4-dithiazolone.

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.

The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formulas, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

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.

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 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 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 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 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. Specifically, alkyl is methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, and their isomeric forms thereof. Specifically, cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and their isomeric forms thereof. Specifically, halo is fluoro (F), chloro (Cl).

Specifically Y is H.

Specifically W is $C(=O)NHR^1$.

Specifically, R^1 is C_{1-4}alkyl, optionally substituted with one, two or three fluoro (F), or chloro (Cl).

Specifically, R^1 is H, CH_3, or CH_2CH_3.

Specifically, W is CH_2het.

Specifically, W is 1,2,3-triazole-1-yl methyl.

Specifically, V is an oxygen atom (O).

Specifically, X is H.

Specifically, X is methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, or sec-butyl.

Specifically, R^2 is H, or C_{1-4}alkyl.

Examples of the present invention include:

(1) (*R*)-3-(1-Isopropyl-1*H*-indazol-5-yl)-2-oxooxazolidine-5-carboxamide,

(2) (*R*)-3-(1-Isopropyl-1*H*-indazol-5-yl)-*N*-methyl-2-oxooxazolidine-5-carboxamide,

(3) (*R*)-3-(1-Methyl-1*H*-indazol-5-yl)-2-oxooxazolidine-5-carboxamide,

(4) (*R*)-*N*-Methyl-3-(1-methyl-1*H*-indazol-5-yl)-2-oxooxazolidine-5-carboxamide,

(5) (*R*)-3-(1-Ethyl-1*H*-indazol-5-yl)-2-oxooxazolidine-5-carboxamide,

(6) (*R*)-3-(1-Ethyl-1*H*-indazol-5-yl)-*N*-methyl-2-oxooxazolidine-5-carboxamide,

(7) (5*R*)-3-(1-*sec*-Butyl-1*H*-indazol-5-yl)-2-oxooxazolidine-5-carboxamide,

(8) (5*R*)-3-(1-*sec*-Butyl-1*H*-indazol-5-yl)-*N*-methyl-2-oxooxazolidine-5-carboxamide,

(9) (*R*)-5-((1H-1,2,3-Triazol-1-yl)methyl)-3-(1-methyl-1*H*-indazol-5-yl)oxazolidin-2-one,

(10) (*R*)-1-((3-(1-Methyl-1*H*-indazol-5-yl)-2-oxooxazolidin-5-yl)methyl)-1*H*-1,2,3-triazole-4-carbonitrile,

(11) (*R*)-1-((3-(1-Isopropyl-1*H*-indazol-5-yl)-2-oxooxazolidin-5-yl)methyl)-1*H*-1,2,3-triazole-4-carbonitrile,

(12) (5*R*)-5-((1*H*-1,2,3-Triazol-1-yl)methyl)-3-(1-sec-butyl-1*H*-indazol-5-yl)oxazolidin-2-one,

(13) (*R*)-3-(1-Isopropyl-1H-indazol-5-yl)-5-((4-methyl-1*H*-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one,

(14) (*R*)-3-(1-Isopropyl-1H-indazol-5-yl)-5-((4-fluoro-1*H*-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one,

(15) (*R*)-3-(1-Isopropyl-1*H*-indazol-5-yl)-5-((1*H*-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one,

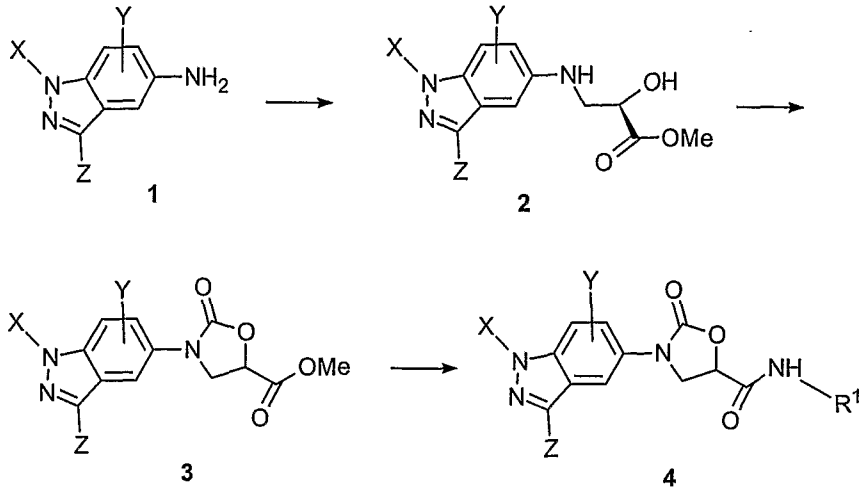
(16) (*R*)-5-((1*H*-1,2,3-Triazol-1-yl)methyl)-3-((*S*)-1-sec-butyl-1*H*-indazol-5-yl)oxazolidin-2-one,

(17) (*R*)-5-((1*H*-1,2,3-Triazol-1-yl)methyl)-3-((*R*)-1-sec-butyl-1*H*-indazol-5-yl)oxazolidin-2-one, or

(18) (*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-3-((*S*)-1-*sec*-butyl-7-fluoro-1*H*-indazol-5-yl)oxazolidin-2-one.

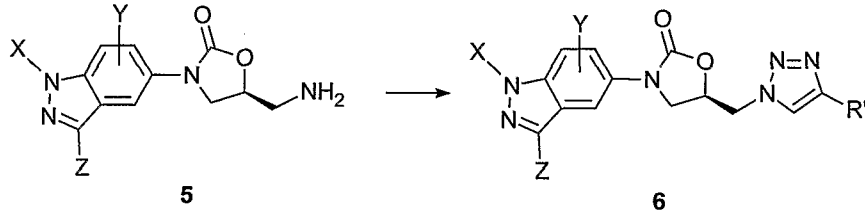
Compounds of this invention can be prepared in accordance with one or more of the Schemes discussed below. All of the starting materials are either commercially available or can be prepared by procedures that would be well known to one of ordinary skill in organic chemistry. The variables used in the Schemes are as defined below, or as in the summary of the invention or claims.

SCHEME I



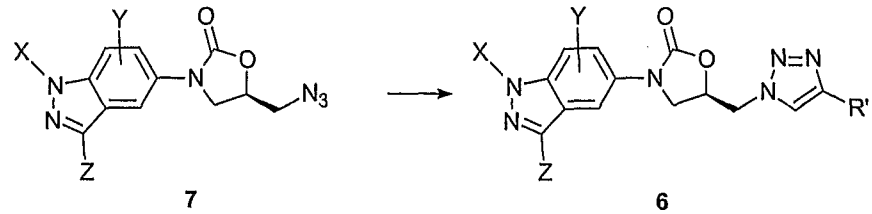
The compounds of the present invention may be prepared according to Scheme I. The substituted 5-amino-indazole (**1**) is reacted with an alkyl (2*R*)-epoxypropanoate and a Lewis acid such as lithium triflate as described in US Patent 6,919,329. The resulting amino alcohol (**2**) can then be ring closed to give the aryl oxazolidinones (**3**) **following conditions as described in Scheme 3**?. Subsequent treatment of oxazolidinone ester (**3**) with ammonia or optionally substituted amines (R^1NH_2) in a suitable solvent such as methanol or acetonitrile affords amides (**4**) (R^1 is H or optionally substituted alkyl). Similarly treatment of ester (**3**) with *O*-alkylhydoxylamines or hydrazines provides the hydroxamate ($R^1$is Oalkyl).

SCHEME II



Triazole indazole oxazolidinones (**6**) are most conveniently prepared, as shown in Scheme II, by reacting amine (**5**) with 2,2-dichloroacetaldehyde-*p*-tosylhydrazone (R' = H) or α,α-dichloroacetone tosylhydrazone (R' = Me) according to the methods of Ichikawa (*Chem. Pharm. Bull.*, **2000**, *48*, 1947-1953) and Sakai (*Bull. Chem. Soc. Jpn.*, **1986**, *59*, 179-184). The starting material (**5**) can be prepared according to the procedure described in US patent No. 5,182,403.

SCHEME III



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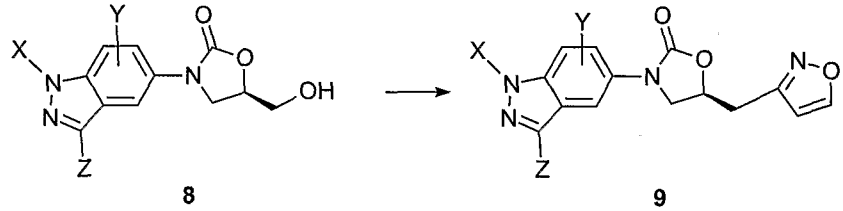
Alternatively, triazole indazole oxazolidinones can be prepared according to Scheme III following the sequence of chemical transformations described by Brickner (*J. Med. Chem.*, **1996**, *39*, 673-679). Cycloaddition of the intermediate azido compound (can be prepared according to the procedure described in US patent No. 5,182,403) with norbornadiene in a suitable solvent, such as dioxane at reaction temperatures in the range of about 50 °C to about 100°C affords the 1,2,3-triazolyl derivative (R' = H). A variety of other substituted triazoles (R' = Me, Cl, F, $-CH_2OH$, $-NO_2$, -CN, $-C{\equiv}CH$, $-NH_2$, etc.) may be prepared via cycloaddition and subsequent chemical group modification by known methods when necessary.

SCHEME IV



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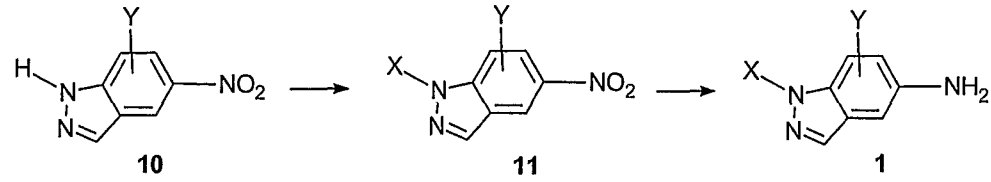
In Scheme IV, hydroxymethyl indazole derivatives (can be prepared according to the proceduer described by Brickner, *J. Med. Chem.*, **1996**, *39*, 673-679) can be further converted to heteroaryl amine analogs using chemistry described by Perova et al. in Zh. Org. Khim. 1994, vol. 30, pp.1660-1663 and the methods described in PCT publication WO 9964417. In these procedures the hydroxymethyl indazole (**8**) is coupled with an appropriate amino-isoxazole or hydroxy-isoxazole, for example 3-(2,2,2-trichloroethoxycarbonyl-amino)isoxazole (may be prepared as described in PCT publication WO 0021960) or 3-hydroxyisoxazole (may be prepared as described in US Patent 3,687,968). These reactions can be performed with a suitable coupling reagent, such as diisopropylazo-dicarboxylate (DIAD). The coupling reaction is typically conducted in a polar aprotic solvent, such as dimethylformamide, acetonitrile, tetrahydrofuran, or mixtures thereof, in the presence of organic base, such as triphenylphosphine. The process is typically carried out at about 0 to about 50 °C. When coupling to an amino-isoxazole, the resulting carbamic acid intermediate can then be reduced to the heteroaryl amine (**9**).

SCHEME V



In Scheme V, the requisite 1-alkyl-5-nitro-1H-indazole (**1**) starting material is most conveniently prepared via alkylation of an appropriately known substituted 5-nitro-1H-indazole (**10**) with an alkylating agent such as an alkyl halide or tosylate in the presence of an inorganic or organic base such as potassium hydroxide, sodium hydride, lithium bis(trimethylsilylamide), 1,8-diazabicyclo[5.4.0]undec-7-ene, or sodium methoxide in a suitable solvent such as methanol, dimethylformamide or dimethyl sulfoxide leading to a mixture of 1-alkyl-1H- and 2-alkyl-2H-indazoles which are readily separated by chromatography or selective crystallization. The ratio of 1-alkyl-1H- and 2-alkyl-2H-indazole products is influenced by a variety of factors including the choice of alkylating agent, the acidity or basicity of the reaction media, protic or aprotic solvents, as well as steric and electronic effects. 5-Nitro-1H-indazole precursors may be prepared by diazotization of suitably substituted 2-methylanilines in protic solvents followed by a spontaneous cyclization as described by Porter (*Org. Synth., Coll. Vol. III*, **1955**, 660)

Medical and Veterinary Uses

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 lists the *in vitro* antibacterial activity of the present invention.

Table 1

Results of *in vitro* antibacterial activity MIC_s (μg/mL)

Example No.	*S. aureus* UC-76 SA-1	*S. pneumoniae* SV1 SP-3	*E.faecalis* MGH-2 EF 1-1
1	4	4	4
2	4	4	4
3	8	16	16
4	8	8	16
5	4	4	4
6	4	4	4
7	4	4	4
8	4	4	4
9	8	4	8
10	16	8	16
11	4	4	4
12	8	2	8
13	8	4	8
14	16	16	32
15	2	2	4
16	4	2	4
17	8	8	16
18	2	2	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, such as, 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 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 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.

EXAMPLES

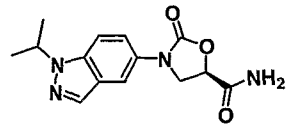
The compounds of this invention can be prepared in accordance with the examples discussed below. All of the starting materials are either commercially available or can be prepared by procedures that would be well known to one of ordinary skill in organic chemistry. Also, in the discussion the preparations 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
CDI	=	1,1*O*-carbodiimidazole
d	=	doublet
dd	=	doublet of doublets
dq	=	doublet of quartets
dt	=	doublet of triplets
DMF	=	dimethylformamide
DMAP	=	dimethylaminopyridine
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
5	mm	=	millimeter
	mmol	=	millimol
	q	=	quartet
	s	=	singlet
	t or tr	=	triplet
10	TBS	=	tributylsilyl
	TFA	=	trifluoroacetic acid
	THF	=	tetrahydrofuran
	TLC	=	thin layer chromatography
	p-TLC	=	preparative thin layer chromatography
15	µL	=	microliter
	N	=	normality
	MeOH	=	methanol
	DCM	=	dichloromethane
	HCl	=	hydrochloric acid
20	ACN	=	acetonitrile
	MS	=	mass spectrometry
	rt	=	room temperature
	EtOAc	=	ethyl acetate
	EtO	=	ethoxy
25	Ac	=	acetate
	NMP	=	1-methyl-2-pyrrolidinone
	µL	=	microliter
	J	=	coupling constant
	NMR	=	Nuclear magnetic resonance
30	MHz	=	megahertz
	Hz	=	hertz
	m/z	=	mass to charge ratio
	min	=	minutes
	Boc	=	*tert*-butoxycarbonyl
35	CBZ	=	benzyloxycarbonyl
	DCC	=	1,3-dicyclohexylcarbodiimide
	PyBop	=	benzotriazole-1-yl-oxy-trispyrrolidinophosphonium hexafluorophosphate

40 EXAMPLES

Example 1 Preparation of (R)-3-(1-isopropyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxamide



Step 1: Preparation of 1-isopropyl-5-nitro-1H-indazole

45 1,8-Diazabicyclo[5.4.0]undec-7-ene (4.58 mL, 0.0307 mol) is added to 5-nitroindazole (4.00 g, 0.0245 mol) in DMF (50 mL) at room temperature and then stirred for 30 minutes. 2-Iodopropane (3.06 mL, 0.0307 mol) is added dropwise and the mixture

allowed to react overnight at room temperature. The solvent is removed *in vacuo* and the residue diluted with ethyl acetate, washed with water and brine, the organic layer dried (Mg_2SO_4) and evaporated. The residue is purified by flash column chromatography (20% EtOAc/Hexanes) to give the title compound (2.45 g, 57%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 5.27 min; MS for $C_{10}H_{11}N_3O_2$ m/z 206.2$(M+H)^+$.

Step 2: Preparation of 1-isopropyl-1H-indazol-5-amine

Iron powder (2.45 g, 0.0439 mol) is added portionwise to a solution of 1-isopropyl-5-nitro-1H-indazole (2.25 g, 0.0110 mol) and ammonium chloride (5.86 g, 0.110 mol) in ethanol (100 mL) and water (45 mL) at 80 °C. The mixture is vigorously stirred and heated for 45 minutes, diluted with dichloromethane (250 ml) and filtered. The organic layer is separated, dried (Mg_2SO_4) and evaporated to afford the title compound (1.92 g, 99%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 2.69 min; MS for $C_{10}H_{13}N_3$ m/z 176.2$(M+H)^+$.

Step 3: Preparation of (R)-methyl 2-hydroxy-3-(1-isopropyl-1H-indazol-5-ylamino)propanoate

(R)-Methyl oxirane-2-carboxylate (0.875 mL, 0.00999 mol), 1-isopropyl-1H-indazol-5-amine (1.75 g, 0.00999 mol) and lithium trifluoromethanesulfonate (1.56 g, 0.00999 mol) in acetonitrile (20 mL) are stirred and heated at 55 °C overnight. The reaction is diluted with ethyl acetate, washed with water and brine, the organic layer dried (Mg_2SO_4) and evaporated. The residue is purified by flash chromatography (50% EtOAc/Hexanes) to give the title compound (1.07 g, 39%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 3.04 min; MS for $C_{14}H_{19}N_3O_3$ m/z 278.3$(M+H)^+$.

Step 4: Preparation of (R)-methyl 3-(1-isopropyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxylate

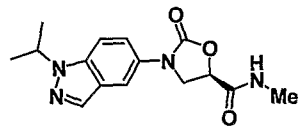
1,1'Carbonyldiimidazole (0.906 g, 0.00559 mol) and (R)-methyl 2-hydroxy-3-(1-isopropyl-1H-indazol-5-ylamino)propanoate (1.03 g 0.00373 mol) in acetonitrile (10 mL) are heated at 45°C for 1 h. The reaction is diluted with ethyl acetate, washed with water and brine, the organic layer dried (Mg_2SO_4) and evaporated to give the title compound (1.09 g, 97%) suitable for use in the next step; HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm

column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 4.50 min; MS for $C_{15}H_{17}N_3O_4$ m/z 304.3$(M+H)^+$.

Step 5: Preparation of (R)-3-(1-isopropyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxamide

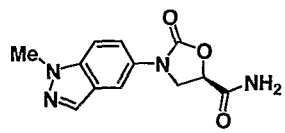
Ammonia (2M solution in methanol, 2mL) is added to solid (R)-methyl 3-(1-isopropyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxylate (0.589 g, 0.00194 mol) and the mixture stirred at room temperature for 1h. The solvent is then removed *in vacuo*, the residue triturated with a minimum amount of methanol, and filtered to afford the title compound (0.149 g, 27%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 3.69 min; ^{1}H NMR (300 MHz, DMSO-d_6) 8.04 (s, 1H), 7.72 (d, 2H), 7.78-7.62 (m, 3H), 5.05-4.92 (m, 2H), 4.33 (t, J = 8.9Hz, 1H), 4.03(dd, J = 6.0, 8.8 Hz 1H), 1.46 (d, J = 6.6Hz, 6H); MS for $C_{14}H_{16}N_4O_3$ m/z 289.3$(M+H)^+$.

Example 2 Preparatio of (R)-3-(1-isopropyl-1H-indazol-5-yl)-N-methyl-2-oxooxazolidine-5-carboxamide



Methylamine (2M solution in methanol, 2mL) is added to solid (R)-methyl 3-(1-isopropyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxylate (0.502 g, 0.00166 mol) and the mixture stirred for 1 hour at room temperature. The solvent is then removed *in vacuo*, the residue triturated with a minimum amount of methanol, and filtered to afford the title compound (0.113 g, 23%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 3.85 min; ^{1}H NMR (300 MHz, DMSO-d_6) 8.37 (d, J = 4.7 Hz, 1H), 8.04 (s, 1H), 8.04-7.66 (m, 3H), 5.06 (dd, J = 6.0, 9.6Hz, 1H), 4.97 (m, 1H), 4.33 (t, J = 9.3Hz, 1H), 4.05 (dd, J = 6.1, 9.1Hz, 1H), 2.66 (d, J = 4.4Hz, 3H), 1.46 (d, J = 6.6Hz, 6H); MS for $C_{15}H_{18}N_4O_3$ m/z 303.3$(M+H)^+$.

Example 3 (R)-3-(1-methyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxamide



Step 1: Preparation of 1-methyl-5-nitro-1H-indazole

Sodium hydride (5.40 g, 0.135 mol) is added portionwise to a solution of 5-nitroindazole (20.0 g, 0.122 mol) in DMF (250 mL) at room temperature. The reaction is

stirred for 30 minutes, iodomethane (8.40 mL, 0.135 mol) added dropwise, and the mixture allowed to react overnight at room temperature. The solvent is then removed *in vacuo* and the residue diluted with ethyl acetate, washed with water and brine, the organic layer dried (Mg_2SO_4) and evaporated. The residue is purified by flash chromatography (20% EtOAc/Hexanes) to give the title compound (12.0 g, 55%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 4.29 min; MS for $C_8H_7N_3O_2$ m/z 178.2$(M+H)^+$.

Step 2: Preparation of 1-methyl-1H-indazol-5-amine

Iron powder (5.04 g, 0.0903 mol) is added portionwise to a solution of 1-methyl-5-nitro-1H-indazole (4.00 g, 0.0226 mol) and ammonium chloride (12.1 g, 0.225 mol) in ethanol (225 mL) and water (100 mL) at 80°C. The mixture is stirred and heated for 1h, diluted with dichloromethane (500 mL) and filtered. The organic layer is separated, dried (Mg_2SO_4) and evaporated to afford the title compound (3.29 g, 99%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 1.06 min; MS for $C_{10}H_{13}N_3$ m/z 147.2$(M+H)^+$.

Step 3: Preparation of (R)-methyl 2-hydroxy-3-(1-methyl-1H-indazol-5-ylamino)propanoate

(R)-Methyl oxirane-2-carboxylate (0.988 mL, 0.0113 mol), 1-methyl-1H-indazol-5-amine (2.00 g, 0.0113 mol) and lithium trifluoromethanesulfonate (1.76 g, 0.0113 mol) in acetonitrile (25 mL) are heated at 50 °C overnight. The reaction solution is diluted with ethyl acetate, washed with water and brine, the organic layer dried (Mg_2SO_4) and evaporated. The residue is purified by flash chromatography (50% EtOAc/Hexanes) to give the title compound (0.870 g, 31%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 2.47 min; MS for $C_{12}H_{15}N_3O_3$ m/z 250.3$(M+H)^+$.

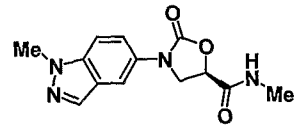
Step 4: Preparation of (R)-methyl 3-(1-methyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxylate

1,1'Carbonyldiimidazole (0.849 g, 0.00524 mol) and (R)-methyl 2-hydroxy-3-(1-methyl-1H-indazol-5-ylamino)propanoate (0.870 g 0.00349 mol) in acetonitrile (15 mL) are stirred at 55 °C for 1 h. The reaction is diluted with ethyl acetate, washed with water and brine, the organic layer dried (Mg_2SO_4) and evaporated to give the title compound (0.780 g, 81%) suitable for use in the next step; HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 5.05 min; MS for $C_{13}H_{13}N_3O_4$ m/z 276.3$(M+H)^+$.

Step 5: Preparation of (R)-N-methyl-3-(1-methyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxamide

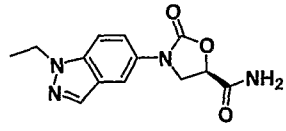
Ammonia (2M solution in methanol, 2mL) is added to solid (R)-methyl 3-(1-methyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxylate (0.432 g, 0.00157M) and stirred at room temperature for 1h. The solvent is then removed *in vacuo*, the residue triturated with a minimum amount of methanol, and filtered to afford the title compound (0.225 g, 55%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 3.03 min; ^{1}H NMR (300 MHz, DMSO-d_6) 8.02 (s, 1H), 7.79-7.64 (m, 3H), 7.72 (m, 2H), 5.05-5.0 (dd, J = 6.1, 9.6Hz, 1H), 4.34(t, J = 9.3Hz, 1H), 4.05 (dd, J = 6.0, 9.1Hz, 1H), 4.03 (s, 3H); MS for $C_{12}H_{12}N_4O_3$ m/z 261.3$(M+H)^+$.

Example 4 (R)-N-methyl-3-(1-methyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxamide



Methylamine (2M solution in methanol, 2 mL) is added to solid (R)-methyl 3-(1-methyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxylate (0.346 g, 0.00126 mol) and the mixture stirred at room temperature for 1h. The solvent is then removed *in vacuo*, the residue triturated with a minimum amount of methanol, and filtered to afford the title compound (0.179 g, 52%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 3.22 min; ^{1}H NMR (300 MHz, DMSO-d_6) 8.37 (d, J = 4.4Hz, 1H), 8.02 (s, 1H), 7.79-7.64 (m, 3H), 5.07 (dd, J = 6.1, 9.3Hz, 1H), 4.34 (t, J = 9.3Hz, 1H), 4.06 (dd, J = 6.0, 9.1Hz, 1H), 4.03 (s, 3H), 2.66 (d, J = 4.7Hz, 3H); MS for $C_{13}H_{14}N_4O_3$ m/z 275.3$(M+H)^+$.

Example 5 Preparation of (R)-3-(1-ethyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxamide



Step 1: Preparation of 1-ethyl-5-nitro-1H-indazole.

Sodium hydride (4.05 g, 0.101 mol) is added to a solution of 5-nitroindazole (15.0g, 0.0919 mol) in DMF (200 mL) at room temperature and stirred for 30 minutes. Iodoethane (8.09 mL, 0.101 mol) is added dropwise and the mixture stirred overnight. The solvent is removed *in vacuo* and the residue diluted with ethyl acetate, washed with water and brine, the

organic layer dried (Mg_2SO_4) and evaporated. The residue is purified by flash chromatography (20% EtOAc/Hexanes) to give the title compound (5.76 g, 30%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 4.73 min; MS for $C_9H_9N_3O_2$ m/z 192.2$(M+H)^+$.

Step 2: Preparation of 1-ethyl-1H-indazol-5-amine.

Iron powder (5.17 g, 0.0926 mol) is added to a solution of 1-ethyl-5-nitro-1H-indazole (4.75 g, 0.0231 mol) and ammonium chloride (12.4 g, 0.231 mol) in ethanol (175 mL) and water (75 mL) at 80 °C. The mixture is vigorously stirred and heated for 1 hour, diluted with dichloromethane (500 mL) and filtered. The organic layer is separated, dried (Mg_2SO_4) and evaporated to afford the title compound (4.06 g, 99%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 2.52 min; MS for $C_9H_{11}N_3$ m/z 162.2$(M+H)^+$.

Step 3: Preparation of (R)-methyl 3-(1-ethyl-1H-indazol-5-ylamino)-2-hydroxypropanoate.

(R)-Methyl oxirane-2-carboxylate (1.11 mL, 0.0127 mol), 1-ethyl-1H-indazol-5-amine (2.05 g, 0.0127 mol) and lithium trifluoromethanesulfonate (1.98 g, 0.0127 mol) in acetonitrile (25 mL) are stirred and heated at 50 °C overnight. The reaction is diluted with ethyl acetate, washed with water and brine, the organic layer dried (Mg_2SO_4) and evaporated. The residue is purified by flash chromatography (50% EtOAc/Hexanes) to give the title compound (0.735 g, 22%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 2.80 min; MS for $C_{13}H_{17}N_3O_3$m/z 264.3$(M+H)^+$.

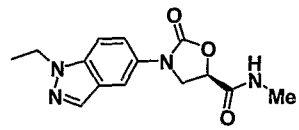
Step 4: Preparation of (R)-methyl 3-(1-ethyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxylate.

1,1'Carbonyldiimidazole (0.680 g, 0.00419 mol) and (R)-methyl 3-(1-ethyl-1H-indazol-5-ylamino)-2-hydroxypropanoate (0.735 g 0.00279 mol) in acetonitrile (10 mL) are heated at 55°C for 1 h. The reaction is diluted with ethyl acetate, washed with water and brine, the organic layer dried (Mg_2SO_4) and evaporated. The residue is purified by column chromatography (50% Hexanes/EtOAc) to give the title compound (0.334 g, 41%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 4.07 min; MS for $C_{14}H_{15}N_3O_4$ m/z 290.3$(M+H)^+$.

Step 5: Preparation of (R)-3-(1-ethyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxamide

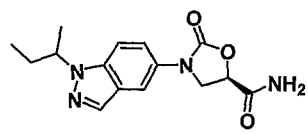
Ammonia (2M solution in methanol, 2mL) is added to solid (R)-methyl 3-(1-ethyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxylate (0.206 g, 0.000714 mol) and the mixture stirred at room temperature for 1h. The solvent is then removed *in vacuo*, the residue triturated with a minimum amount of methanol, and filtered to afford the title compound (0.183 g, 94%). HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 3.32 min; ^{1}H NMR (300 MHz, $CDCl_3$) 7.96 (s, 1H), 7.68 (dd, J = 1.3, 2.2Hz, 1H), 7.63 (d, J = 2.2Hz, 1H), 7.42 (dd, J = 1.1, 9.1Hz, 1H), 6.17 (m, 2H), 5.0 (dd, J = 6.1, 9.3Hz, 1H), 4.54-4.27 (m, 4H), 1.50(t, J = 7.1Hz, 3H); MS for $C_{13}H_{14}N_4O_3$m/z 275.3 $(M+H)^+$.

Example 6 Preparation of (R)-3-(1-ethyl-1H-indazol-5-yl)-N-methyl-2-oxooxazolidine-5-carboxamide



Methylamine (2M solution in methanol,2mL) is added to solid (R)-methyl 3-(1-ethyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxylate (0.1184 g, 0.000409 mol) and the mixture stirred at room temperature for 1h. The solvent is then removed *in vacuo*, the residue triturated with a minimum amount of methanol, and filtered to afford the title compound (0.109 g, 93%). HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 3.50 min; ^{1}H NMR (300 MHz, $CDCl_3$) 7.96 (s, 1H), 7.67 (m, 1H), 7.63(d, J = 2.2Hz, 1H), 7.41 (dd, J = 0.8, 9.9Hz,1H), 6.65 (bs, 1H), 4.98 (dd, J = 5.8, 9.6Hz, 1H), 4.41 (q, J = 7.1Hz, 2H), 4.36-4.25 (dd, J = 3.6, 9.3Hz, 2H), 2.91 (d, J = 5.0Hz, 3H), 1.50(t, J = 7.3Hz, 3H); MS for $C_{14}H_{16}N_4O_3$m/z 289.3 $(M+H)^+$.

Example 7 Preparation of (5R)-3-(1-*sec*-butyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxamide



Step 1: Preparation of 1-*sec*-butyl-1H-indazol-5-amine

Iron metal (0.61 g, 10.9 mmol) is added in portions over a period of 45 minutes to a refluxing solution of 1-*sec*-butyl-5-nitro-1H-indazole (0.8 g, 3.65 mmol) and ammonium chloride (1.95 g, 36.5 mmol) in 36 mL of 2:1 ethanol-H_2O. The rust colored mixture is refluxed for another 30 minutes and then cooled, diluted with dichloromethane. The organic

layer is separated and the aqueous phase extracted with more dichloromethane. The combined dichloromethane phases are washed with water, brine, and dried ($MgSO_4$), filtered, and concentrated to provide the title compound (0.68 g, 99%). HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 6 min; 2 mL/min rate): retention time = 1.82 min; ^1H NMR (300 MHz, $CDCl_3$) 0.76 (t, J = 9 Hz, 3H), 1.53 (d, J = 9 Hz, 3H), 1.80-2.10 (m, 2H), 3.69 (bs, 2H), 4.41-4.48 (m, 1H), 6.83 (d, J = 9 Hz, 1H), 7.22-7.25 (m, 2H), 7.79 (s, 1H).

Step 2: Preparation of (2R)-methyl 3-(1-*sec*-butyl-1H-indazol-5-ylamino)-2-hydroxypropanoate

(R)-Methyl glycidate (0.55 g, 5.4 mmol) is added to a solution of 1-*sec*-butyl-1H-indazol-5-amine (0.68 g, 3.6 mmol) and lithium trifluoromethanesulfonate (0.84 g, 5.4 mmol) in acetonitrile (12 mL) and heated to 65°C for 16 hours. The reaction solution is concentrated *in vacuo* and the residue is purified by flash column chromatography (0-65% ethylacetate / hexanes) to obtain the title compound (0.63 g, 60%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 6 min; 2 mL/min rate): retention time = 2.13 min; MS for $C_{15}H_{21}N_3O_3$ m/z 292.0$(M+H)^+$.

Step 3: Preparation of (5R)-methyl 3-(1-*sec*-butyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxylate

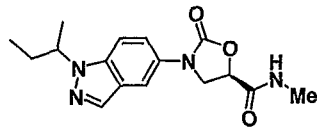
1,1'Carbonyldiimidazole (0.7 g, 4.32 mmol) is added to a solution of (2R)-methyl 3-(1-*sec*-butyl-1H-indazol-5-ylamino)-2-hydroxypropanoate (0.63 g, 2.16 mmol) in acetonitrile (22 mL) and heated at 65°C for 60 hours. The reaction mixture is diluted with dichloromethane, washed with dilute citric acid, dilute $NaHCO_3$, water, brine, and dried ($MgSO_4$), filtered and concentrated. The crude residue is subjected to flash column chromatography (0-3% MeOH / dichloromethane) to obtain the title compound (0.62 g, 90%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 6 min; 2 mL/min rate): retention time = 3.18 min; MS for $C_{16}H_{19}N_3O_4$ m/z 318.2$(M+H)^+$.

Step 4: Preparation of (5R)-3-(1-*sec*-butyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxamide.

A 2M solution of ammonia in methanol (2.5 mL) is added to (5R)-methyl 3-(1-*sec*-butyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxylate (0.16 g, 0.5 mmol) and stirred at room temperature for an hour. The reaction mixture is concentrated *in vacuo* to afford the title compound (0.15 g, 99%). HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column;

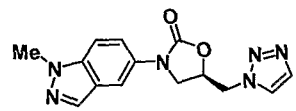
gradient elution 2%-98% MeCN with 0.1% TFA over 6 min; 2 mL/min rate): retention time = 2.62 min; ^{1}H NMR (300 MHz, $CDCl_3$) 0.73 (t, J = 9 Hz, 3H), 1.55 (d, J = 6 Hz, 3H), 1.83-2.12 (m, 2H), 4.26-4.39 (m, 2H), 4.49-4.56 (m, 1H), 4.98-5.03 (m, 1H), 5.66 (bs, 1H), 6.63 (bs, 1H), 7.43 (d, J = 9 Hz, 1H), 7.60-7.67 (m, 2H), 7.99 (s, 1H); MS for $C_{15}H_{18}N_4O_3$ m/z 303.1$(M+H)^+$.

Example 8 Preparation of (5R)-3-(1-*sec*-butyl-1H-indazol-5-yl)-N-methyl-2-oxooxazolidine-5-carboxamide



A 2M solution of methylamine in methanol (2.5 mL) is added to (5R)-methyl 3-(1-*sec*-butyl-1H-indazol-5-yl)-2-oxooxazolidine-5-carboxylate (0.16 g, 0.5 mmol) and stirred at room temperature for an hour. The reaction mixture is concentrated *in vacuo* to afford the title compound (0.16 g, 100%). HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 6 min; 2 mL/min rate): retention time = 2.75 min; ^{1}H NMR (300 MHz, $CDCl_3$) 0.73 (t, J = 9 Hz, 3H), 1.55 (d, J = 6 Hz, 3H), 1.83-2.12 (m, 2H), 2.90 (d, J = 3 Hz, 3H), 4.25-4.35 (m, 2H), 4.48-4.55 (m, 1H), 4.96-5.01 (m, 1H), 6.63 (bs, 1H), 7.43 (d, J = 9 Hz, 1H), 7.60-7.67 (m, 2H), 7.98 (s, 1H); MS for $C_{16}H_{20}N_4O_3$ m/z 317.1$(M+H)^+$.

Example 9 Preparation of (R)-5-((1H-1,2,3-triazol-1-yl)methyl)-3-(1-methyl-1H-indazol-5-yl)oxazolidin-2-one



Step 1: Preparation of (R)-5-(hydroxymethyl)-3-(1-methyl-1H-indazol-5-yl)oxazolidin-2-one

Lithium bis(trimethylsilyl)amide (1M in THF, 35.46 ml, 0.035 mol) is added dropwise to benzyl 1-methyl-1H-indazol-5-ylcarbamate (5.0g, 0.0173 mol) in THF at -78 °C and the mixture stirred for 90 minutes. R-Glycidyl butyrate (2.76 ml, 0.019 mol) is added, the reaction mixture allowed to warm to room temperature and stirred for 14 h. The reaction is quenched with saturated aqueous ammonium chloride, diluted with water and extracted with dichloromethane. The organic layer is washed with brine, dried (Na_2SO_4) and evaporated. The residue is purified by flash column chromatography (20% EtOAc/Hexane) to give the title compound (2.7 g, 52%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm

column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 3.153 min; MS (m/z): $(M+H)^+$ 249.3

Step 2: Preparation of (R)-(3-(1-methyl-1H-indazol-5-yl)-2-oxooxazolidin-5-yl)methyl methanesulfonate

Methanesulfonyl chloride (1.25 g, 0.011 mol) is added dropwise at 0 °C to (R)-5-(hydroxymethyl)-3-(1-methyl-1H-indazol-5-yl)oxazolidin-2-one (2.7 g, 0.011 mol) and triethylamine (2.29 ml, 0.016 mol) in dichloromethane (25 ml) and the mixture stirred for 45 minutes. The reaction is quenched with saturated sodium bicarbonate, diluted with water and extracted with dichloromethane. The organic layer is washed with brine, dried (Na_2SO_4) and evaporated to give product used directly in the next step without purification; HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 4.023 min.

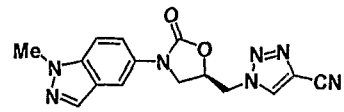
Step 3: Preparation of (R)-5-(azidomethyl)-3-(1-methyl-1H-indazol-5-yl)oxazolidin-2-one

(R)-(3-(1-Methyl-1H-indazol-5-yl)-2-oxooxazolidin-5-yl)methyl methanesulfonate (3.2 g, 0.0098 mol) and sodium azide (3.58g, 0.054 mol) in dimethylformamide (15 ml) is heated at 70 °C for 16 h. The reaction is diluted with water and extracted with dichloromethane. The organic layer is washed with brine, dried (Na_2SO_4) and evaporated. The residue is purified by flash column chromatography (20% EtOAc/Hexane) to give the title compound (1.2 g, 52%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 4.186 min; MS (m/z): $(M+H)^+$ 273.1

Step 4: Preparation of (R)-5-((1H-1,2,3-triazol-1-yl)methyl)-3-(1-methyl-1H-indazol-5-yl)oxazolidin-2-one

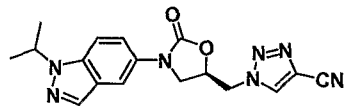
Norbornadiene (0.47 ml, 0.0044 mol) and (R)-5-(azidomethyl)-3-(1-methyl-1H-indazol-5-yl)oxazolidin-2-one (0.6 g, 0.0022 mol) in dioxane (20 ml) are heated at 70°C for 14 h. The solvent is removed under reduced pressure and the residue purified by flash column chromatography (20% EtOAc/Hexane) to give the title compound (0.18 g, 35%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 4.198 min; ^1H NMR (300 MHz, DMSO-*d6*) 7.92 (s,1H), 7.82 (s, 1H), 7.75 (s, , 1H), 7.50 (d, J = 14.5 Hz, 1H), 7.34 (d, J = 9.6 Hz, 1H), 5.07 (m, 1H), 4.80 (d, J = 4.4 Hz, 2H), 4.21 (t, J = 9.3 Hz,1H), 4. 05 (s, 3H), 4.0 (dd, J = 6.04, 3.3 Hz, 1H); MS (m/z); MS for $C_{14}H_{14}N_6O_2$ m/z 299.1$(M+H)^+$.

Example 10 Preparation of (R)-1-((3-(1-methyl-1H-indazol-5-yl)-2-oxooxazolidin-5-yl)methyl)-1H-1,2,3-triazole-4-carbonitrile



2-Chloroacrylonitrile (0.26 ml, 0.0033 mol) and (R)-5-(azidomethyl)-3-(1-methyl-1H-indazol-5-yl)oxazolidin-2-one (0.6 g, 0.0022 mol) in DMF (5 ml) are heated at 95 °C for 3 days. The solvent is removed under reduced pressure and the residue purified by PTLC (10% MeOH/DCM) to give the title compound (0.24 g, 41%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 4.003 min; ^{1}H NMR (300 MHz, DMSO-*d6*) 9.15 (s,1H), 8.03 (s, , 1H), 7.66 (m, 3H), 5.15 (m, 1H), 4.97 (d, J = 5.2 Hz, 2H), 4.31 (t, J = 9.1 Hz,1H), 4. 03 (s, 3H), 3.97 (dd, J = 5.5, 3.8 Hz, 1H); MS for $C_{15}H_{13}N_7O_2$ m/z 324.1(M+H)$^+$.

Example 11 (R)-1-((3-(1-isopropyl-1H-indazol-5-yl)-2-oxooxazolidin-5-yl)methyl)-1H-1,2,3-triazole-4-carbonitrile



Step 1: Preparation of benzyl 1-isopropyl-1H-indazol-5-ylcarbamate

Benzyl chloroformate (3.59 mL, 0.0251 mol) is added dropwise to a solution of 1-isopropyl-1H-indazol-5-amine (4.00 g, 0.0228 mol) and pyridine (3.70 mL, 0.0457 mol) in dichloromethane (50 mL) at 0 °C. The reaction is allowed to warm to room temperature and stirred overnight. The solvent is evaporated *in vacuo*, the residue dissolved in dichloromethane and washed with saturated citric acid solution and brine. The organic layers are dried ($MgSO_4$) and concentrated to afford the title compound (6.88 g, 97%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 5.07 min; MS for $C_{18}H_{19}N_3O_2$ m/z 310.4(M+H)$^+$.

Step 2: Preparation of (R)-5-(hydroxymethyl)-3-(1-isopropyl-1H-indazol-5-yl)oxazolidin-2-one

Lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.0M solution in THF, 24.2 mL, 0.0242 mol) is added to a solution of benzyl 1-isopropyl-1H-indazol-5-ylcarbamate (3.75 g, 0.0121 mol) in tetrahydrofuran (35 mL) at -78 °C and stirred for 30 minutes. (*R*)-(-)-Glycidyl butyrate (1.89 mL, 0.0133 mol) is added, the mixture allowed to warm to room temperature and stirred overnight. The reaction is diluted with dichloromethane, washed with saturated

ammonium chloride solution and brine, dried ($MgSO_4$), and concentrated. The residue is purified by column chromatography (20% Hexanes/EtOAc) to afford the title compound (1.43 g, 43%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 3.84 min; MS for $C_{14}H_{17}N_3O_3$ m/z 276.3$(M+H)^+$.

Step 3: Preparation of (R)-(3-(1-isopropyl-1H-indazol-5-yl)-2-oxooxazolidin-5-yl)methyl methanesulfonate

Methanesulfonyl chloride (0.402 mL, 0.00519 mol) is added to (R)-5-(hydroxymethyl)-3-(1-isopropyl-1H-indazol-5-yl)oxazolidin-2-one (1.43 g, 0.00519 mol) and triethylamine (1.09 mL, 0.00779 mol) in dichloromethane (10 mL) at 0 °C. The reaction is stirred for 30 minutes, diluted with dichloromethane, washed with saturated sodium bicarbonate solution and brine, dried ($MgSO_4$), and concentrated to afford the title compound. The material is used directly in the next step without purification; HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 4.55 min; MS for $C_{15}H_{19}N_3O_5S$ m/z 354.4$(M+H)^+$.

Step 4: Preparation of (R)-5-(azidomethyl)-3-(1-isopropyl-1H-indazol-5-yl)oxazolidin-2-one

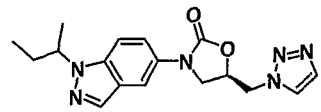
Sodium azide (1.69 g, 0.0260 mol) and (R)-(3-(1-isopropyl-1H-indazol-5-yl)-2-oxooxazolidin-5-yl)methyl methanesulfonate (1.84 g, 0.00519 mol) in dimethylformamide (10 mL) are heated at 70 °C overnight. The reaction is diluted with EtOAc, washed with water and brine, dried ($MgSO_4$), and concentrated. The residue is purified by column chromatography (50% EtOAc/Hexanes) to afford the title compound (1.13 g, 73%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 3.84 min; MS for $C_{14}H_{16}N_6O_2$ m/z 301.3$(M+H)^+$.

Step 5: Preparation of (R)-1-((3-(1-isopropyl-1H-indazol-5-yl)-2-oxooxazolidin-5-yl)methyl)-1H-1,2,3-triazole-4-carbonitrile

2-Chloroacrylonitrile (0.0800 mL, 0.000999 mol) and (R)-5-(azidomethyl)-3-(1-isopropyl-1H-indazol-5-yl)oxazolidin-2-one (0.200 g, 0.000666 mol) in dimethylformamide (2 mL) are heated at 85 °C for 3 days. The solvent is removed *in vacuo* and the residue purified by preparative thin layer chromatography (10% MeOH/dichloromethane) to afford the title compound (0.100 g, 43%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time

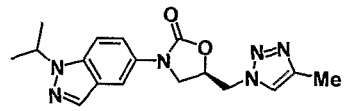
= 4.68 min; ^{1}H NMR (300 MHz, $CDCl_3$) 8.40 (s, 1H), 7.95 (s, 1H), 7.56-7.39 (m, 3H), 5.12-5.06 (m, 1H), 4.88-4.77 (m, 3H), 4.28 (t, J = 9.3 Hz, 1H), 3.97 (dd, J = 6.0, 9.3 Hz, 1H), 1.56 (d, J = 2.5 Hz, 6H); MS for $C_{17}H_{17}N_7O_2$ m/z 352.4$(M+H)^+$

Example 12 (5R)-5-((1H-1,2,3-triazol-1-yl)methyl)-3-(1-sec-butyl-1H-indazol-5-yl)oxazolidin-2-one



Dichloroacetaldehyde (0.087 g, 0.77 mmol) and *p*-toluenesulfonyl hydrazide (0.14 g, 0.77 mmol) are stirred at 0 °C in MeOH (2.6 mL) and acetic acid (0.022 mL) for an hour. To this mixture is added (5S)-5-(aminomethyl)-3-(1-*sec*-butyl-1H-indazol-5-yl)oxazolidin-2-one (0.22 g, 0.77 mmol) in triethylamine (0.54 mL, 3.85 mmol) and DMF (4.5 mL). After stirring at room temperature for 48 hours, the reaction mixture is concentrated *in vacuo*. The residue is purified by preparative TLC (5% methanol-dichloromethane) to obtain the title compound (0.04 g, 15%). HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 6 min; 2 mL/min rate): retention time = 2.59 min; ^{1}H NMR (300 MHz, $CDCl_3$) 0.71 (t, J = 9 Hz, 3H), 1.53 (d, J = 6 Hz, 3H), 1.81-2.07 (m, 2H), 3.96-4.01 (m, 1H), 4.20 (t, J = 9 Hz, 1H), 4.46-4.53 (m, 1H), 4.79 (d, J = 6 Hz, 2H), 5.03-5.08 (m, 1H), 7.36-7.49 (m, 3H), 7.74 (s, 1H), 7.80 (s, 1H), 7.94 (s, 1H); MS for $C_{17}H_{20}N_6O_2$ m/z 341.3$(M+H)^+$.

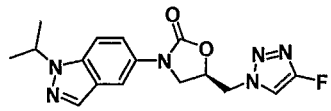
Example 13 (R)-3-(1-isopropyl-1H-indazol-5-yl)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one



Dichloroacetone (0.124 mL, 0.00129 mol) is added to a solution of *p*-toluenesulfonylhydrazide (0.240 g, 0.00129 mol) and acetic acid (0.0370 mL, 0.000644 mol) in methanol (5 mL) at room temperature. The resulting slurry is allowed to react at room temperature for 1 h to generate N'-(1,1-dichloropropan-2-ylidene)-4-methylbenzenesulfonohydrazide. (S)-5-(Aminomethyl)-3-(1-isopropyl-1H-indazol-5-yl)oxazolidin-2-one (0.500 g, 0.00129 mol), as a TFA-salt, and triethylamine (0.359 mL, 0.00258 mol) in dimethylformamide (10 mL) is added and the mixture stirred overnight at room temperature. The solvent is then removed *in vacuo* and the residue purified by preparative thin layer chromatography (10%MeOH/dichloromethane) to afford the title compound (0.163 g, 37%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 4.07

min; ^{1}H NMR (300 MHz, DMSO-d_6) 8.04 (s, 1H), 7.87, (s, 1H), 7.77 (d, J = 9.1 Hz, 1H), 7.66 (d, J = 1.4 Hz, 1H), 7.57 (dd, J = 2.2, 9.1 Hz, 1H), 5.13-5.05 (m, 1H), 4.95 (m, 1H), 4.75 (d, J = 5.2 Hz, 2H), 4.27 (t, J = 9.1 Hz, 1H), 3.91 (dd, J = 5.8, 6.3 Hz, 1H), 2.22 (s, 3H), 1.45 (d, J = 6.6 Hz, 6H); MS for $C_{17}H_{20}N_6O_2$m/z 341.4(M+H)$^+$.

Example 14 Preparation of (R)-3-(1-iIsopropyl-1H-indazol-5-yl)-5-((4-fluoro-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one



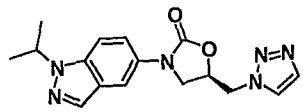
Step 1: Preparation of (R)-3-(1-isopropyl-1H-indazol-5-yl)-5-((4-tributylstannyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one

Ethynyltributylstannane (0.462 mL, 0.00160 mol) and (R)-5-(azidomethyl)-3-(1-isopropyl-1H-indazol-5-yl)oxazolidin-2-one (0.480 g, 0.00160 mol) in toluene (3 mL) are heated to 70 °C for 3 days. The reaction is evaporated and the residue purified by column chromatography (1.75% MeOH/dichloromethane) to afford the title compound (0.678 g, 69%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 7.08 min; MS for $C_{28}H_{44}N_6O_2Sn$ m/z 616.4(M+H)$^+$.

Step 2: Preparation of (R)-3-(1-isopropyl-1H-indazol-5-yl)-5-((4-fluoro-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one

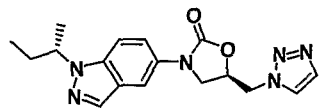
Selectfluor fluorinating agent (1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) (0.399 g, 0.00113 mol) and (R)-3-(1-isopropyl-1H-indazol-5-yl)-5-((4-tributylstannyl-1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one (0.660 g, 0.00107 mol) in acetonitrile (10 mL) are stirred at room temperature for 2 days. The reaction is diluted with water, extracted into dichloromethane, dried ($MgSO_4$), and concentrated. The residue is purified by preparative HPLC to afford the title compound (0.070 g, 19%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 4.16 min; ^{1}H NMR (300 MHz, DMSO-d_6) 8.22 (s, 1H), 8.19 (s, 1H), 7.81 (s, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.26 (dd, J = 7.1, 8.5 Hz, 1H), 5.24-5.16 (m, 1H), 5.0 (m, 1H), 4.86 (d, J = 4.7 Hz, 2H), 4.18 (t, J = 8.8 Hz, 1H), 3.82 (dd, J = 5.5, 8.8 Hz, 1H), 1.46 (d, J = 6.6 Hz, 6H); MS for $C_{16}H_{17}N_6O_2F$ m/z 345.4(M+H)$^+$.

Example 15 Preparation of (R)-3-(1-isopropyl-1H-indazol-5-yl)-5-((1H-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one



Dichloroacetaldehyde, hydrate (0.169 g, 0.00129 mol) is added to a solution of *p*-toluenesulfonylhydrazide (0.240 g, 0.00129 mol) and acetic acid (0.0370 mL, 0.000644 mol) in methanol (5 mL) at room temperature. The mixture is stirred for 1 h to generate N'-(1,1-dichloropropan-2-ylidene)-4-methylbenzenesulfonohydrazide. (S)-5-(aminomethyl)-3-(1-isopropyl-1H-indazol-5-yl)oxazolidin-2-one (0.500 g, 0.00129 mol), as a TFA-salt, and triethylamine (0.359 mL, 0.00258 mol) in dimethylformamide (10 mL), is added in one portion and the mixture stirred overnight at room temperature. The solvent is removed from the reaction *in vacuo* and the residue purified by preparative thin layer chromatography (10%MeOH/dichloromethane) to afford the title compound (0.060 g, 14%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 10 min; 2 mL/min rate): retention time = 3.97 min; ^{1}H NMR (300 MHz, DMSO-d_6) 8.18 (s, 1H), 8.04 (s, 1H), 7.87, (s, 1H), 7.77 (s, 1H), 7.67 (d, J = 10.7 Hz, 1H), 7.56 (dd, J = 2.2, 9.3 Hz, 1H), 5.15-5.11 (m, 1H), 4.96 (m, 1H), 4.84 (d, J = 4.9 Hz, 2H), 4.29 (t, J = 9.3 Hz, 1H), 3.93 (dd, J = 5.5, 9.3 Hz, 1H), 1.45 (d, J = 6.6 Hz, 6H); MS for $C_{16}H_{18}N_6O_2$m/z 327.4$(M+H)^+$.

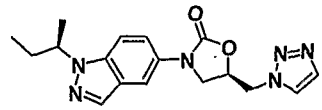
Example 16 Preparation of (R)-5-((1H-1,2,3-triazol-1-yl)methyl)-3-((S)-1-sec-butyl-1H-indazol-5-yl)oxazolidin-2-one



Dichloroacetaldehyde (0.087 g, 0.77 mmol) and *p*-toluenesulfonyl hydrazide (0.14 g, 0.77 mmol) are stirred at room temperature in MeOH (2.6 mL) and acetic acid (0.022 mL) for an hour. To this mixture is added (5S)-5-(aminomethyl)-3-((S)-1-*sec*-butyl-1H-indazol-5-yl)oxazolidin-2-one (0.31 g, 0.77 mmol) in triethylamine (0.54 mL, 3.85 mmol) and DMF (4.5 mL). After stirring at room temperature for 16 hours, the reaction mixture is diluted with dichloromethane and washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The crude residue is purified by preparative TLC (5% MeOH-10% acetonitrile-dichloromethane) to afford the title compound (0.043 g, 16%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 6 min; 2 mL/min rate): retention time = 2.60 min; ^{1}H NMR (300 MHz, $CDCl_3$) _ 0.72 (t, J = 9 Hz, 3H), 1.54 (d, J = 6 Hz, 3H), 1.83-2.09 (m, 2H), 3.97-4.02 (m, 1H), 4.20 (t, J = 9 Hz, 1H),

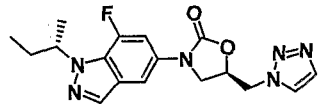
4.49-4.57 (m, 1H), 4.79 (d, J = 6 Hz, 2H), 5.04-5.09 (m, 1H), 7.36-7.50 (m, 3H), 7.75 (s, 1H), 7.81 (s, 1H), 7.96 (s, 1H); MS for $C_{17}H_{20}N_6O_2$ m/z 341.3$(M+H)^+$.

Example 17 Preparation of (R)-5-((1H-1,2,3-triazol-1-yl)methyl)-3-((R)-1-sec-butyl-1H-indazol-5-yl)oxazolidin-2-one



Dichloroacetaldehyde (0.085 g, 0.75 mmol) and *p*-toluenesulfonyl hydrazide (0.14 g, 0.75 mmol) are stirred at room temperature in MeOH (2.5 mL) and acetic acid (0.022 mL) for an hour. To this mixture is added (5S)-5-(aminomethyl)-3-((R)-1-*sec*-butyl-1H-indazol-5-yl)oxazolidin-2-one (0.3 g, 0.75 mmol) in triethylamine (0.52 mL, 3.75 mmol) and DMF (4.4 mL). After stirring at room temperature for 16 hours, the reaction mixture is diluted with dichloromethane and washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The crude residue is purified by preparative TLC (5% MeOH-10% acetonitrile-dichloromethane) to afford the title compound (0.046 g, 18%). HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 6 min; 2 mL/min rate): retention time = 2.69 min; ^{1}H NMR (300 MHz, $CDCl_3$) _ 0.72 (t, J = 9 Hz, 3H), 1.54 (d, J = 6 Hz, 3H), 1.81-2.11 (m, 2H), 3.99-4.02 (m, 1H), 4.20 (t, J = 9 Hz, 1H), 4.47-4.54 (m, 1H), 4.79 (d, J = 6 Hz, 2H), 5.04-5.09 (m, 1H), 7.36-7.50 (m, 3H), 7.74 (s, 1H), 7.81 (s, 1H), 7.96 (s, 1H); MS for $C_{17}H_{20}N_6O_2$ m/z 341.3$(M+H)^+$.

Example 18 Prepartion of 5-(*S*)-5-((1H-1,2,3-triazol-1-yl)methyl)-3-((S)-1-*sec*-butyl-7-fluoro-1*H*-indazol-5-yl)oxazolidin-2-one



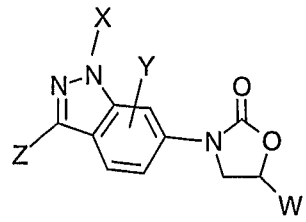
Dichloroacetaldehyde (0.07 g, 0.62 mmol) and *p*-toluenesulfonyl hydrazide (0.116 g, 0.62 mmol) are stirred at 0 °C in MeOH (2.0 mL) and acetic acid (0.018 mL) for an hour. To this mixture is added (5S)-5-(aminomethyl)-7-fluoro-3-((S)-1-*sec*-butyl-1H-indazol-5-yl)oxazolidin-2-one (0.26 g, 0.62 mmol) in triethylamine (0.43 mL, 3.1 mmol) and DMF (3.5 mL). After stirring at room temperature for 18 hours, the reaction mixture is diluted with dichloromethane and washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The crude residue is purified by preparative TLC (5% MeOH-10% acetonitrile-dichloromethane) to afford the title compound (0.03 g, 14%); HPLC (SYMMETRY C_{18} 3.5 μM, 4.6 x 30 mm column; gradient elution 2%-98% MeCN with 0.1% TFA over 6 min; 2 mL/min rate): retention time = 3.01 min; ^{1}H NMR (300 MHz, $CDCl_3$) _ 0.95 (t, J = 9 Hz,

3H), 1.75 (d, J = 6 Hz, 3H), 2.01-2.32 (m, 2H), 4.16-4.21 (m, 1H), 4.40 (t, J = 9 Hz, 1H), 4.96-5.01 (m, 3H), 5.26-5.30 (m, 1H), 7.39-7.45 (m, 2H), 7.59 (d, J = 15 Hz, 1H), 7.98 (d, J = 15 Hz, 1H), 8.17 (s, 1H); MS for $C_{17}H_{19}FN_6O_2$ m/z 359.1$(M+H)^+$.

CLAIMS

We claim:

1. A compound of formula I



I

or a pharmaceutically acceptable salt thereof wherein:

W is $C(=O)NHR^1$, $C(=S)NHR^1$, or CH_2het;

Y is H, or F;

R^1 is (a) H,

(d) C_{16}alkyl, or

(e) OC_{1-6}alkyl;

X is (a) H,

(d) C_{1-6}alkyl, or

(e) C_{3-7}cycloalkyl;

Z is

(f) H,

(g) halo,

(h) C_{1-6}alkyl,

(i) OC_{1-6}alkyl, or

(j) SC_{1-6}alkyl;

het is a five-(5) or six-(6) membered heterocyclic ring having 1-4 heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen within the ring, wherein ezch carbon atom I het is optionally substituted with C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, halo, OR^2, CN, NO_2, NR^2R^2, oxo, CF_3, OCF_3, $C(=O)C_{1-4}$alkyl, $OC(=O)C_{1-4}$alkyl, or $C(=O)OR^2$;

at each occurrence, C_{1-6}alkyl is optionally substituted with aryl, het, halo, CN, OR^2, NO_2, N_3, NR^2R^2, or C_{1-4}alkyl; and R^2 is H or C_{1-4}alkyl.

2. A compound of claim 1 wherein Z is H.

3. A compound of claim 2 wherein W is $C(=O)NHR^1$.

4. A compound of claim 3 wherein R^1 is H or CH_3.

5. A compound of claim 2 wherein W is CH_2het.

6. A compound of claim 2 wherein W is 1,2,3-triazole-1-yl methyl.

7. A compound of claim 1 wherein X is methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, or sec-butyl.

8. A compound of claim 1 which is:

(1) (*R*)-3-(1-isopropyl-1*H*-indazol-5-yl)-2-oxooxazolidine-5-carboxamide,

(2) (*R*)-3-(1-isopropyl-1*H*-indazol-5-yl)-*N*-methyl-2-oxooxazolidine-5-carboxamide,

(3) (*R*)-3-(1-methyl-1*H*-indazol-5-yl)-2-oxooxazolidine-5-carboxamide,

(4) (*R*)-*N*-methyl-3-(1-methyl-1*H*-indazol-5-yl)-2-oxooxazolidine-5-carboxamide,

(5) (*R*)-3-(1-ethyl-1*H*-indazol-5-yl)-2-oxooxazolidine-5-carboxamide,

(6) (*R*)-3-(1-ethyl-1*H*-indazol-5-yl)-*N*-methyl-2-oxooxazolidine-5-carboxamide,

(7) (5*R*)-3-(1-*sec*-butyl-1*H*-indazol-5-yl)-2-oxooxazolidine-5-carboxamide,

(8) (5*R*)-3-(1-*sec*-butyl-1*H*-indazol-5-yl)-*N*-methyl-2-oxooxazolidine-5-carboxamide,

(9) (*R*)-5-((1H-1,2,3-triazol-1-yl)methyl)-3-(1-methyl-1*H*-indazol-5-yl)oxazolidin-2-one,

(10) (*R*)-1-((3-(1-methyl-1*H*-indazol-5-yl)-2-oxooxazolidin-5-yl)methyl)-1*H*-1,2,3-triazole-4-carbonitrile,

(11) (*R*)-1-((3-(1-isopropyl-1*H*-indazol-5-yl)-2-oxooxazolidin-5-yl)methyl)-1*H*-1,2,3-triazole-4-carbonitrile,

(12) (5*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-3-(1-sec-butyl-1*H*-indazol-5-yl)oxazolidin-2-one,

(13) (*R*)-3-(1-isopropyl-1H-indazol-5-yl)-5-((4-methyl-1*H*-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one,

(14) (*R*)-3-(1-isopropyl-1H-indazol-5-yl)-5-((4-fluoro-1*H*-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one,

(15) (*R*)-3-(1-isopropyl-1*H*-indazol-5-yl)-5-((1*H*-1,2,3-triazol-1-yl)methyl)oxazolidin-2-one,

(16) (*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-3-((*S*)-1-sec-butyl-1*H*-indazol-5-yl)oxazolidin-2-one,

(17) (*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-3-((*R*)-1-sec-butyl-1*H*-indazol-5-yl)oxazolidin-2-one, or

(18) (*R*)-5-((1*H*-1,2,3-triazol-1-yl)methyl)-3-((*S*)-1-*sec*-butyl-7-fluoro-1*H*-indazol-5-yl)oxazolidin-2-one.

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

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

11. The method of claim 10 wherein the compound of claim 1 is administered orally, parenterally, topically, rectally, or intranasally.

12. The method of claim 10 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.

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

14. The bacteria infection of claim 10 which is ear infections, eye infections, respiratory tract infections, skin and skin structure infections, bacterial endocarditis, osteomyelitis, endocarditis or diabetic foot.

15. The bacteria infection of claim 10 which is caused by gram-positive bacteria, gram negative bacteria, anaerobic organisms, and acid-fast organisms.

16. The bacteria infection of claim 10 which is caused by bacteria comprising staphylococci, streptococci, Enterococci, Haemophilus, Moraxella, bacteroides, clostridia, Mycobacteria, or Chlamydia.

17. The bacteria of claim 16 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*.

18. The bacteria infections of claim 10 which is caused by multi-drug resistant S. aureus.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2007/000259

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/14 C07D413/04 A61K31/422 A61P31/04

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 A61K

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.
Y	US 2004/044052 A1 (THOMAS RICHARD CHARLES [US] ET AL) 4 March 2004 (2004-03-04) claims 1,6,66-70; compound 86	1-18
Y	WO 2004/074282 A (UPJOHN CO [US]; POEL TONI-JO [US]) 2 September 2004 (2004-09-02) cited in the application page 9, line 32 - page 10, line 5 page 24; claims 1,2,10-14; examples 1-4	1-18
Y	US 5 182 403 A (BRICKNER STEVEN J [US]) 26 January 1993 (1993-01-26) cited in the application column 1, line 20 - line 24; claims; figures B,E; examples 64-66,82-84,92,93	1-18

☐ 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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 June 2007	02/07/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hanisch, Inken

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2007/000259

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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10-18 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/IB2007/000259

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