OXAZOLIDINONE AMIDOXIMES AS ANTIBACTERIAL AGENTS

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(54) Title: OXAZOLIDINONE AMIDOXIMES AS ANTIBACTERIAL AGENTS

(57) Abstract: The present invention relates to novel oxazolidinone amidoximes of formula (I) wherein R\textsuperscript{2}, Y\textsuperscript{1}, Y\textsuperscript{2}, X, W, and Z are as defined herein in the specification. The compounds of the present invention have potent activities against gram-positive bacteria.

\[ \text{Oxazolidinone Amidoxime Structure} \]
OXAZOLIDINONE AMIDOXIMES AS ANTIBACTERIAL AGENTS

FIELD OF INVENTION

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

BACKGROUND OF THE INVENTION

Due to ever-increasing antibiotic resistance, structurally novel antibacterials with a new mode of action have become increasingly important in the treatment of bacterial infections. Effective antibacterials should exhibit potent activity against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiple resistant staphylococci and streptococci, anaerobic organisms such as bacteroides and clostridia species, and acid-fast organisms such as Mycobacterium tuberculosis and Mycobacterium avium.

Among newer antibacterial agents, oxazolidinone compounds are the most recent synthetic class of antimicrobials active against a number of pathogenic microorganisms. This invention provides novel amidoxime derivatives of oxazolidinones, and their preparation.

INFORMATION DISCLOSURE

PCT publication WO 9964416 discloses oxazolidinone derivatives.
PCT publication WO 9964417 discloses oxazolidinone derivatives.
PCT publication WO 200021960 discloses heterocyclyl aminomethyl oxazolidinone derivatives.
PCT publication WO 200029409 discloses oxazolidinone derivatives.
PCT publication WO 200181350 discloses oxazolidinone derivatives and their salts or in vivo hydrolysable esters.
PCT publication WO 200281470 discloses oxazolidinone compounds and their salts or in vivo hydrolysable esters.
PCT publication WO 2003035648 discloses aryl substituted oxazolidinones, their salts or esters.
DE 19604223 discloses oxazolidinone derivatives.
DE 19805117 discloses oxazolidinone derivatives.
DE 19901306 discloses oxazolidinone derivatives.
DE 19905278 discloses oxazolidinone derivatives.
5 DE 19962924 discloses N-oxazolidinylmethyl-substituted (benzo)thiophene carboxamides.
EP 785201 discloses oxazolidinone derivatives.

SUMMARY OF THE INVENTION

The present invention provides a compound of formula I

\[
\begin{align*}
&Z-N-\vdash Y_1 Y_2 Y_3 X-W \\
&
\end{align*}
\]

10 or a pharmaceutically acceptable salt thereof wherein:

X is a structure of the following formula i, ii, iii, or iv

\[
\begin{align*}
&\text{i} \\
&\text{ii} \\
&\text{iii} \\
&\text{iv}
\end{align*}
\]

W is

\[
\begin{align*}
&\text{CH}_2\text{NHC}(-\text{O})\text{R}^1, \\
&(b) \quad \text{CH}_2\text{NHC}(-\text{S})\text{R}^1, \\
&(c) \quad \text{CH}_2\text{NH}–\text{het}, \\
&(d) \quad \text{CH}_2\text{O}–\text{het}, \\
&e) \quad \text{CH}_2\text{S}–\text{het}, \\
&(f) \quad \text{CH}_2\text{het}, \\
&(g) \quad \text{CH}_2\text{OH}, \\
&(h) \quad \text{CH(OH)}–\text{CH}–\text{CH}\text{R}^1, \text{ or} \\
&(i) \quad \text{CH(OH)}\text{C}≡\text{CR}^1;
\end{align*}
\]

\[Y^1, Y^2 \text{ and } Y^3 \text{ are independently}
\]

\[
\begin{align*}
&\text{(a) } \text{CH}, \\
&\text{(b) } \text{CH}_2\text{CH}, \\
&\text{(c) } \text{CH}_2\text{N}, \\
&\text{(d) } \text{CH}_2\text{S}, \\
&\text{(e) } \text{N}, \\
&\text{(f) } \text{O}, \\
&\text{(g) } \text{NHC}(-\text{O})\text{R}^1, \\
&\text{(h) } \text{NHC}(-\text{S})\text{R}^1, \\
&\text{(i) } \text{CH(OH)}\text{C}≡\text{CR}^1;
\end{align*}
\]
(b) \( \text{N} \),
(c) \( \text{N}^+\text{O}^- \), or
(d) \( \text{CF} \);

\( \text{U} \) is

5
(a) \( \text{CR}^3\text{R}^4 \),
(b) \( \text{O} \), or
(c) \( \text{S} \), \( \text{SO} \), or \( \text{SO}_2 \);

\( Z \) is \( \text{O}-\text{C}_{1-6}\text{aryl} \), optionally substituted with \( \text{OH} \), or \( \text{OC}_{1-2}\text{alkyl} \);

\( \text{R}^1 \) is

10
(a) \( \text{NH}_2 \),
(b) \( \text{NHC}_{1-4}\text{alkyl} \),
(c) \( \text{C}_{1-6}\text{alkyl} \),
(d) \( \text{C}_{2-6}\text{alkenyl} \),
(e) \( \text{CH}_2j\text{C}(=\text{O})\text{C}_{1-4}\text{alkyl} \),
(f) \( \text{OC}_{1-4}\text{alkyl} \),
(g) \( \text{SC}_{1-4}\text{alkyl} \), or
(h) \( \text{CH}_2j\text{C}_{3-7}\text{cycloalkyl} \);

\( \text{R}^2 \) is

20
(a) \( \text{C}_{1-6}\text{alkyl} \),
(b) \( \text{OC}_{1-6}\text{alkyl} \), or
(c) \( \text{CH}_2j\text{C}_{3-7}\text{cycloalkyl} \);

\( \text{R}^3 \) and \( \text{R}^4 \) are independently

25
(a) \( \text{H} \),
(b) \( \text{F} \),
(c) \( \text{CH}_3 \), or
(d) each \( \text{R}^3 \) and \( \text{R}^4 \) is together with the carbon atom to which they attach form \( \text{C}_{3-6}\text{cycloalkyl} \);

at each occurrence, \( \text{C}_{1-6}\text{alkyl} \), \( \text{C}_{2-6}\text{alkenyl} \), or \( \text{C}_{3-7}\text{cycloalkyl} \) is optionally substituted with 1-3 halo, \( \text{OR}^5 \), \( \text{CN} \), \( \text{N}_3 \), \( \text{NO}_2 \), \( \text{NR}^5\text{R}^6 \), \( \text{C}(=\text{O})\text{C}_{1-4}\text{alkyl} \), \( \text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl} \),

30 \( \text{C}(=\text{O})\text{OC}_{1-4}\text{alkyl} \), or \( \text{S}(\text{O})_n\text{C}_{1-4}\text{alkyl} \);

\( \text{R}^5 \) and \( \text{R}^6 \) are independently

35
(a) \( \text{H} \), or
(b) \( \text{C}_{1-4}\text{alkyl} \), optionally substituted with \( \text{OH} \), phenyl, or \( \text{OC}_{1-4}\text{alkyl} \);
n is 0, 1 or 2; each j is independently 0-4; and 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, which is optionally substituted with 1-3 halo, OR₅, CN, N₃, NO₂, NR₅R₆, C(=O)C₁₄alkyl, OC(=O)C₁₄alkyl, C(=O)OC₁₄alkyl, or S(O)ₙC₁₄alkyl.

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 Cᵢⱼ indicates a moiety of the integer “i” to the integer “j” carbon atoms, inclusive. Thus, for example, C₁₆ alky1 refers to alky1 of one to six carbon atoms, inclusive.

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

The term "C₃,₇-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, azetidine, 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, carbol ine, phenanthridine, acridine,
phenanthroline, isothiazole, phenazine, isoaxazole, isoxazolinone, phenoxazine,
phenothiazine, imidazolidine, imidazoline, piperidine, pip erazine, 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 thiomorpholine.), 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-ol yl, 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-oxadiazone, 1,2,4-oxadiazone,
1,2,5-oxadiazone, 1,3,4-oxadiazone, 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-dithiazole.

The term “a pharmaceutically acceptable salt” of a compound means a salt that
is pharmaceutically acceptable and that possesses the desired pharmacological activity
of the parent compound. Such salts include:

(1) acid addition salts, formed with inorganic acids such as hydrochloric acid,
hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed
with organic acids such as acetic acid, propionic acid, hexanoic acid,
cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid,
succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

(2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, 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.

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.

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".

Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer
can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 1992).

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 "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, tosylloxy, trifluorosulfonyloxy, methoxy, N,O-dimethylhydroxyl-amino, and the like.

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, 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 W is CH₂NHC(=O)R₁.

Specifically, R₁ is C₁₋₄alkyl, optionally substituted with one, two or three fluoro (F), or chloro (Cl).

Specifically, R₁ is CH₃, or CH₂CH₃, CHF₂, CF₃, or CHCl₂.

Specifically, R₁ is CHF₂, CF₃, or CHCl₂.

Specifically, Y₁, Y₂, or Y₃ is CH.

Specifically one of the Y₁, Y₂ and Y₃ is N, the other two are CH.

Specifically, Y₁ is CF, Y₂ and Y₃ are CH.

Specifically, U is CH₂.

Specifically, U is O or S.

Specifically, R₂ is CH₃.

Specifically R₂ is cyclopenten.

Specifically, R₂ is C₁₋₄alkyl, optionally substituted with 1-3 with one, two or three fluoro (F), or chloro (Cl).

Specifically, R₃ and R₄ are independently H.

Specifically, Z is OC₁₋₄alkyl, optionally substituted with OH, or OC₁₋₄alkyl.
Specifically, Z is OC_{1-6}alkyl substituted with OC_{1-4}alkyl which may be further substituted with a phenyl.
Specifically, Z is OCH_3, or OCH_2CH_3.
Specifically, Z is OH.
Specifically, X is a structure of formula ii

$$\text{ii.}$$

Specific examples of the present invention are:

1) (5S)-N-[3-(2-methoxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl)-2-oxooxazolidin-5-ylmethyl]-acetamide,
2) (5S)-N-[3-(2-ethoxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl)-2-oxooxazolidin-5-ylmethyl]-acetamide,
3) (5R)-N-[3-(2-ethoxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl)-2-oxooxazolidin-5-ylmethyl]-propionamide,
4) (5S)-N-[3-(3-ethyl-2-methoxyimino-2,3-dihydro-benzothiazol-6-yl)-2-oxooxazolidin-5-ylmethyl]-acetamide,
5) (5S)-N-[3-(3-ethyl-2-methoxyimino-2,3-dihydro-benzothiazol-6-yl)-2-oxooxazolidin-5-ylmethyl]-propionamide,
6) (5S)-N-[3-(2-Ethoxyimino-3-ethyl-2,3-dihydro-benzothiazol-6-yl)-2-oxooxazolidin-5-ylmethyl]-acetamide,
7) (5S)-N-[3-(2-Ethoxyimino-3-ethyl-2,3-dihydro-benzothiazol-6-yl)-2-oxooxazolidin-5-ylmethyl]-propionamide,
8) (5R)-N-[3-(3,3-difluoro-2-methoxyimino-1-methyl-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,
9) (5R)-N-[3-(3,3-difluoro-2-methoxyimino-1-methyl-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-propionamide, or
10) (5R)-N-[3-(3,3-difluoro-2-methoxyimino-1-methyl-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid methyl ester.

The 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.

As shown in Scheme I, a nitrobenzazole (X = O, S, SO, or SO₂; R' = C₁-₄ alkyl; R¹, R², Y¹, Y² and Y³ are as described previously) substituted in the 2-position with an appropriate leaving group A (such as halogen or SC₁-₄ alkyl) is treated with an alkylating agent to give benzazolium salt 1b. Appropriate alkylating agents include alkyl sulfates ((R'O)₂SO₂ or R'OSO₂CF₃), halides (R'X), tosylates, triflates (R'OSO₂tolyl) or trialkyloxonium salts ((R₂)₃OBF₃), wherein R' is an alkyl group. The reaction is typically conducted neat with excess alkylating agent or in an organic solvent such as dimethylformamide, dichloromethane or tetrahydrofuran at temperatures in a range of from 0 °C to about 100 °C. Next the intermediate benzazolium salt 1b is treated with an alkoxyamine (H₂NOR') or its salt thereof such as methoxylamine hydrochloride and a suitable base according to the methods described in Chem. Pharm. Bull., 1996, vol. 24(5), pp. 1050-1058. The reaction is most conveniently conducted in water with an inorganic base such as sodium hydroxide, but may also be conducted in an organic solvent such as methanol or dimethylformamide with an organic base such as sodium methoxide or triethylamine. The reaction is performed at temperatures in a range of from 0 °C to about 100 °C.

The alkoxyimino substituted nitrobenzazole 1c may be converted to aniline 1d under a variety of mild conditions including catalytic hydrogenation, transfer
hydrogenation using a hydrogen donor such as ammonium formate in the presence of palladium catalyst or a dissolving metal reduction with iron or tin. The resulting aniline 1d is protected as the carbamate 1e and converted to the Boc-protected oxazolidinone 1f using known chemistry methods described in US Patent publication No. 6,107,519. It is understood that the syntheses of intermediates and final products described herein are generally applicable to the preparation of related derivatives bearing other groups in place of the oxazolidinone substituent (such as isoxazoline, isoxazolinone, or butenolide groups).

The Boc-protected oxazolidinone intermediate 1f is then deprotected to give the corresponding amine. It is convenient to remove the Boc group with 20 to 60% trifluoroacetic acid in dichloroethane or hydrogen chloride in dioxane at temperatures ranging from 0 °C to 24 °C. In the final step of the synthesis, the amine intermediate is then acylated using known art to give 1g. Acylations can be routinely performed by reactions of amines with carboxylic acid anhydrides or esters. These transformations are generally performed at 0 °C to 50 °C using polar solvents, such as acetonitrile, dimethylformamide, tetrahydrofuran and methanol or mixtures thereof with optional apolar solvents, such as dichloromethane. These reactions are preferably conducted in the presence of an organic or inorganic base, such as pyridine, triethylamine, or potassium carbonate. In this reaction it is often convenient to employ an excess of the tertiary amine base with the amine salt prepared by Boc deprotection without first isolating the free base. Solvents such as tetrahydrofuran, methylene chloride or preferably methanol and temperatures in the range of about 24 °C to about 50 °C can be used for this reaction.
SCHEME II

As shown in Scheme II (wherein $R' = C_{1-6}$alkyl; $R^3$, $R^4$, $R^1$, $R^2$, $Y^1$, $Y^2$ and $Y^3$ are as described previously), an appropriately substituted nitroxindole $2a$ conveniently prepared as described by in US Patent No. 4,188,325 is converted to the thione $2b$ using various thionation reagents, such as Lawesson, Davy, Belleau, Na$_2$P$_4$S$_{11}$, Na$_2$P$_4$S$_{10}$O, or alike known reagents capable of converting amides into thioamides. The reaction is most conveniently conducted using Lawesson's reagent in a suitable organic solvent, such as dioxane or tetrahydrofuran, and is typically performed at temperatures ranging from 25 °C to about 100 °C. The intermediate thione compound $2b$ is reacted with an alkoxylamine or a salt thereof, such as methoxylamine hydrochloride and a suitable base at temperatures ranging from 25 °C to about 100 °C to give alkoxylimino intermediate $2c$.

The alkoxylimino substituted nitroxindole $2c$ may be converted to aniline $2d$ under a variety of mild conditions including catalytic hydrogenation, transfer hydrogenation using a hydrogen donor such as ammonium formate in the presence of palladium catalyst or a dissolving metal reduction with iron or tin. The resulting aniline $2d$ is protected as the carbamate $2e$ and converted to the Boc-protected oxazolidinone $2f$ using known chemistry methods described in US Patent publication No. 6,107,519. It is understood that the syntheses of intermediates and final products described herein are generally applicable to the preparation of related derivatives.
bearing other groups in place of the oxazolidinone substituent (such as isoxazoline, isoxazolinone, or butenolide groups).

The Boc-protected oxazolidinone intermediate 2f is then deprotected to give the corresponding amine. It is convenient to remove the Boc group with 20 to 60% trifluoroacetic acid in dichloroethane or hydrogen chloride in dioxane at temperatures ranging from 0 °C to 24 °C. In the final step of the synthesis, the amine intermediate is then acylated using known art to give 2g. Acylations can be routinely performed by reactions of amines with carboxylic acid anhydrides or esters. These transformations are generally performed at 0 °C to 50 °C using polar solvents, such as acetonitrile, dimethylformamide, tetrahydrofuran and methanol or mixtures thereof with optional apolar solvents, such as dichloromethane. These reactions are preferably conducted in the presence of an organic or inorganic base, such as pyridine, triethylamine, or potassium carbonate. In this reaction it is often convenient to employ an excess of the tertiary amine base with the amine salt prepared by Boc deprotection without first isolating the free base. Solvents such as tetrahydrofuran, methylene chloride or preferably methanol and temperatures in the range of about 24 °C to about 50 °C can be used for this reaction.

**SCHEME III**

\[ 
\begin{align*}
\text{3a} & \quad \rightarrow \quad \text{3b} \\
\text{MeS} & \\
\text{R}^2 & \\
\text{X} & \\
\text{R}^1 & \\
\text{Y}^1, Y^2 & \\
\text{R}^3 & \\
\text{N} & \\
\text{O} & \\
\text{H} & \\
\text{O} & \\
\text{R}^1 & \\
\text{3b} & \\
\text{1g} & \\
\text{R}^2 & \\
\text{R}^3 & \\
\text{N} & \\
\text{O} & \\
\text{H} & \\
\text{R}^1 & \\
\text{1g} & \\
\end{align*} 
\]

Alternatively, as shown in Scheme III, known oxazolidinone benzazolium salt intermediates 3a described in US Patent Publication No. 6,069,160 may be reacted with hydroxylamine or a salt thereof such as hydroxylamine hydrochloride and a suitable base, or a protected source of hydroxylamine such as O-(trimethylsilyl) hydroxylamine or N,O-bis(trimethylsilyl)hydroxylamine in a protic solvent to provide 3b. The reaction is most conveniently conducted in water with an inorganic base such as sodium hydroxide, but may also be conducted in an organic solvent such as
methanol or dimethylformamide with an organic base such as sodium methoxide or triethylamine. The reaction is performed at temperatures in a range of from 0 °C to about 24 °C. If desired, hydroxyimino benzazole 3b may be further converted to alkoxyimino benzazole 1g by reaction with a suitable electrophilic alkylation agent such as an alkyl halide, sulfate or tosylate, or a reagent containing an electrophilic multiple bond such as acrylonitrile in the presence of a suitable inorganic or organic base, such as sodium hydride or lithium bis(trimethylsilyl)amide. Solvents for this transformation may include tetrahydrofuran or dimethylformamide, and the reaction is typically performed in the range of about 0 °C to 80 °C.

Schemes IV-VI describe the synthesis of aryl isoxazolinone, aryl isoxazoline and aryl butyrolactones bearing amidoxime groups.

**SCHEME IV**

Scheme IV describes the synthesis of aryl isoxazolinone amidoximes. Benzoazoxole (X = O), benzothiazole (X = S) aldehyde intermediates 4a may be prepared by known methods. The aldehyde group is conveniently protected as an acetal or other suitable protecting group and the benzazole 4b reacted with an appropriate alkylation agent as described previously. The intermediate benzazolium salt 4c is then reacted with an alkoxyamine or a salt thereof as described previously to give the desired alkoxyimino intermediate 4d. The acetal protecting group is removed using various reaction conditions that are well known in the art (see "Protecting Groups" by Philip J. Kocienski; publisher: Georg Thieme Verlag: Stuttgart, 1994).

Benzaldehyde intermediate 4e may be reacted with ethyl diazoacetate (as described by Mahmood, et al. in J. Org. Chem., 1998, Vol. 63, pp. 3333-3336) to provide ester aldehyde intermediate 4f. Addition of hydroxylamine, followed by warming to reflux
in a suitable solvent such as aqueous methanol, yields the desired isoxazolinone 4g. This intermediate is then converted to the corresponding methylacetamide 4h by reaction with N-(hydroxymethyl)acetamide acetate (prepared as described by Barnes et al. in US Patent 5,284,863) in a polar aprotic solvent such as dimethylformamide.

**SCHEME V**

Scheme II describes the synthesis of aryl isoxazoline amidoximes. Aldehyde 4e is reacted with hydroxylamine hydrochloride in a polar protic solvent, such as methanol, in the presence of a base, such as pyridine, to afford oxime 5a. The oxime is oxidized with N-chlorosuccinimide in a suitable solvent, such as dichloromethane, to give the intermediate N-hydroxyoximidoxy chloride 5b. The N-hydroxyoximidoyl chloride is reacted with an allylic compound such as allyl alcohol or N-acetylamine, in the presence of a base, such as triethylamine, in a solvent such as dichloromethane, to provide the hydroxymethyl or acetalidomethyl substituted isoxazolines. Hydroxymethyl intermediate 5c may be converted to compounds 5d in which Z is a group other than NH(C=O)Me or to a heterocyclic substituent (Z = NH-het¹, O-het¹, S-het¹ or het²) by methods known in the art.

**SCHEME VI**

Scheme VI describes the synthesis of aryl butyrolactone amidoximes. Aldehyde intermediate 4e is conveniently converted to phenyl acetic acid intermediate
6a following methods described by Hester, et al. in US Patent 5,708,169. The synthesis of the saturated and unsaturated 3-arylbutyrolactone system parallels that described in Biorganic & Medicinal Chemistry Letters, 1994, Vol. 4, No. 16, pp. 1925-1930. The lithiated dianion of the phenyl acetic acid intermediate 6a is reacted with R-benzyloxymethoxyxiran in THF. The resulting \( \gamma \)-hydroxyacid is cyclized with catalytic p-toluenesulfonic acid to provide lactone 6b as a mixture of diastereomers. The Z-group functionality may be introduced by a known sequence of hydrogenolytic benzyl deprotection, mesylate formation, nucleophilic substitution by azide ion, hydrogenolytic reduction and acetyl formation with acetic anhydride. Alternatively, heterocyclic substituents (Z = NH-het\(^1\), O-het\(^1\), S-het\(^1\) or het\(^2\)) may be introduced from appropriate intermediates by methods known in the art. The saturated butyrolactone is then brominated with N-bromosuccinimide, and the double bond introduced by elimination with pyridine in a suitable solvent such as pyridine to provide 6d.

Following the Schemes I-III, compounds of the present invention illustrated below can be prepared:

1. (5S)-N-[3-(2-methoxyimino-3-methyl-2,3-dihydro-benzoxazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

2. (5S)-N-[3-(2-ethoxyimino-3-methyl-2,3-dihydro-benzoxazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

3. (5S)-N-[3-(3-ethyl-2-methoxyimino-2,3-dihydro-benzoxazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

4. (5S)-N-[3-[1-(2-fluoro-ethyl)-2-methoxyimino-2,3-dihydro-1H-indol-5-yl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide,
(5) (5S)-N-[3-(3-isopropyl-2-methoxyimino-2,3-dihydro-benzooxazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

(6) N-[3-(2-methoxyimino-3-methyl-2,3-dihydro-benzooxazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-propionamide,

(7) (5S)-N-[3-(2-methoxyimino-3-methyl-2,3-dihydro-benzthiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

(8) (5S)-N-[3-(3-ethyl-2-methoxyimino-2,3-dihydro-benzthiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

(9) (5S)-N-[3-(3-isopropyl-2-methoxyimino-2,3-dihydro-benzthiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

(10) (5S)-N-[3-(2-methoxyimino-3-methyl-2,3-dihydro-benzthiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-propionamide,

(11) (5S)-N-[3-(4-fluoro-2-methoxyimino-3-methyl-2,3-dihydro-benzooxazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,
(12) (5S)-N-[3-(4-fluoro-2-methoxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

(13) (5S)-N-[3-(2-hydroxyimino-3-methyl-2,3-dihydro-benzoxazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

(14) (5S)-N-[3-(2-hydroxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

(15) (5S)-N-[3-[2-(2-hydroxy-ethoxyimino)-3-methyl-2,3-dihydro-benzoxazol-6-yl]-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

(16) (5S)-N-[3-(2-hydroxyimino-1-methyl-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

(17) (5S)-N-[3-(2-methoxyimino-1-methyl-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

(18) (5S)-N-[3-(1-isopropyl-2-methoxyimino-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,
(19) (5S)-N-[3-(1-ethyl-2-methoxyimino-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

(20) (5S)-N-[3-(3,3-difluoro-2-methoxyimino-1-methyl-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

(21) (5S)-N-[3-(2-methoxyimino-1,3,3-trimethyl-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

(22) (5S)-N-[3-(7-fluoro-2-methoxyimino-1-methyl-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

Medical and Veterinary Uses

The compounds of the present invention may be used for the treatment of infectious diseases caused by a variety of bacterial organisms.

Examples 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 compounds 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 compounds 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 (5th ed) Washington, DC: American Society for Microbiology Press, 2003. The antibacterial activity is presented in Table 1 in the form of MIC value (Minimum Inhibitory concentrations). The MIC value is the lowest concentration of drug which prevented macroscopically visible growth under the conditions of the test.

<table>
<thead>
<tr>
<th>Example</th>
<th>S. aureus (UC-76)</th>
<th>S. pyogenes (C203)</th>
<th>S. pneumoniae (SV-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>
Routes of Administration

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

Parenteral administrations include indirect injections to generate a systemic effect or direct injections to the afflicted area. Examples of parenteral administrations are subcutaneous, intravenous, intramuscular, intradermal, intrathecal, intraocular, intranasal, intraventricular injections or infusions techniques.

Topical administrations include the treatment of infectious areas or organs readily accessibly by local application, such as, for example, eyes, ears including 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 compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For oral administration, the compounds can be formulated by combining the active compounds with pharmaceutically acceptable carriers well known in the art.

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

For topical applications, the pharmaceutical composition may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion such as suspensions, emulsion, or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, poloxorbate 60, cetyl esters wax, ceteary alcohol, 2-octyldecanol, 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 compounds 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 compounds 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 compounds 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

In the discussion above and in the examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>bm</td>
<td>broad multiplet</td>
</tr>
<tr>
<td>BOC</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>bd</td>
<td>broad doublet</td>
</tr>
<tr>
<td>bs</td>
<td>broad singlet</td>
</tr>
<tr>
<td>bt</td>
<td>broad triplet</td>
</tr>
<tr>
<td>CDI</td>
<td>1,1\textit{O}-carbodiimidazole</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
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<td>dimethylformamide</td>
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<td>DMAP</td>
<td>dimethylaminopyridine</td>
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<tr>
<td>DIEA</td>
<td>diisopropylethylamine</td>
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<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
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<tr>
<td>eq.</td>
<td>equivalents</td>
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<tr>
<td>g</td>
<td>grams</td>
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<td>hours</td>
</tr>
<tr>
<td>HPLC</td>
<td>high pressure liquid chromatography</td>
</tr>
<tr>
<td>HATU</td>
<td>N-[(dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-yl-methylene]-N-methylmethanaminium hexafluorophosphate N-oxide</td>
</tr>
<tr>
<td>LG</td>
<td>leaving group</td>
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<td>m</td>
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<tr>
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</tr>
<tr>
<td>TBS</td>
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</tr>
<tr>
<td>TFA</td>
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<tr>
<td>THF</td>
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<tr>
<td>TLC</td>
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<tr>
<td>p-TLC</td>
<td>preparative thin layer chromatography</td>
</tr>
<tr>
<td>(\mu)L</td>
<td>microliter</td>
</tr>
<tr>
<td>N</td>
<td>normality</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
</tbody>
</table>
HCl = hydrochloric acid
ACN = acetonitrile
MS = mass spectrometry
rt = room temperature
5 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
15 min = minutes
Boc = tert-butoxycarbonyl
CBZ = benzylxycarbonyl
DCC = 1,3-dicyclohexylcarbodiimide
PyBop = benzotriazole-1-yl-oxy-trispyrrolidinophosphonium

hexafluorophosphate

Example 1 Preparation of (5S)-N-[3-(2-methoxyimino-3-methyl-2,3-dihydrobenzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide

Step 1: Preparation of 3-methyl-2-methylsulfanyl-6-nitro-benzothiazol-3-i um methyl sulfate

2-Methylsulfanyl-6-nitro-benzothiazole (5.00 g, 0.0221 mol) and dimethyl sulfate (10 ml) are heated at 100 ºC for 20 hours. The reaction mixture is cooled and diluted with ether (50 ml). The resulting white precipitate is filtered, washed thoroughly with ether and dried under vacuum (10 g, 98%).

Step 2: Preparation of 3-methyl-6-nitro-3H-benzothiazol-2-one O-methyl-oxime

Methoxylamine hydrochloride (0.676 g, 8.09 mmol) is added in one portion to 3-methyl-2-methylsulfanyl-6-nitro-benzothiazol-3-i um methyl sulfate (2.50 g, 5.39 mmol) in pyridine (10 ml) and heated at 65 ºC for 20 hours. The reaction is evaporated under vacuum, the residue diluted with ethyl acetate, washed with 2N hydrochloric acid and brine, dried (MgSO₄), and evaporated to give the title
compound as a bright orange solid (1.24 g, 96%); HPLC r.t. 5.684 min; MS for C₅H₉N₅O₃S m/z 240 (M+H)⁺.

Step 3: Preparation of 6-amino-3-methyl-3H-benzothiazol-2-one O-methyl-oxime

3-Methyl-6-nitro-3H-benzothiazol-2-one O-methyl-oxime (1.20 g, 5.02 mmol) and palladium on carbon (10%, wet Degussa type E101 NE/W, 0.250 g) are suspended in ethyl acetate (20 ml) and placed under a hydrogen atmosphere (balloon) overnight. The catalyst is filtered and the clear colorless filtrate evaporated under vacuum to give the title compound as a white solid (1.05 g, 99%), HPLC r.t. 2.837 min; MS for C₉H₁₁N₅OS m/z 210 (M+H)⁺.

Step 4: Preparation of (2-methoxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl)-carbamic acid benzyl ester

Benzyl chloroformate (0.75 ml, 5.26 mmol) is added dropwise to 6-amino-3-methyl-3H-benzothiazol-2-one O-methyl-oxime (1.00 g, 4.78 mmol) and pyridine (0.64 ml, 7.89 mmol) in dichloromethane (10 ml) at 0 °C. The mixture is allowed to warm to room temperature and stirred for 15 minutes. The reaction is diluted with dichloromethane, washed with 2N hydrochloric acid and brine, dried (MgSO₄) and evaporated to give the title compound as a white solid (1.55 g, 95%), HPLC r.t. 6.058 min; MS for C₁₇H₁₇N₅O₃S m/z 344 (M+H)⁺.

Step 5: Preparation of (5S)-[3-(2-methoxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid tert-butyl ester

Lithium t-butoxide (1.0 M solution in THF, 13.1 ml, 13.1 mmol) is added at 0 °C to (2-methoxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl)-carbamic acid benzyl ester (1.50 g, 4.37 mmol) and (3-chloro-2-hydroxy-propyl)-carbamic acid tert-butyl ester (1.34 g, 6.55 mmol) in DMF (10 ml). The reaction mixture is allowed to warm at room temperature and stirred for 24h. The reaction is quenched with saturated aqueous ammonium chloride, diluted with water and extracted with dichloromethane. The organic layer is washed with brine, dried (Na₂SO₄) and evaporated. The residue is purified by flash column chromatography (50% EtOAc/Hexane) to give the title compound as a white solid (1.43 g, 80%); MS for C₁₈H₂₄N₄O₃S m/z 409 (M+H)⁺.
Step 6: Preparation of (5R)-6-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-3-methyl-3H-benzothiazol-2-one O-methyl-oxime

(5S)-3-(2-Methoxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid tert-butyl ester (0.65 g, 1.59 mmol) is stirred with 50% TFA/DCM (10 ml) for 1 h at room temperature. The solvent is evaporated to give the title compound as the TFA salt (0.68 g, 99%); MS for C_{13}H_{16}N_{4}O_{5}S m/z 309 (M+H)^+.

Step 7: Preparation of (5S)-N-[3-(2-methoxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide

Acetic anhydride (0.133 ml, 1.30 mmol) is added to (5R)-6-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-3-methyl-3H-benzothiazol-2-one O-methyl-oxime (0.500 g, 1.19 mmol) and pyridine (0.290 ml, 3.55 mmol) in dichloromethane (5 ml) 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_{2}SO_{4}), and evaporated under vacuum to give the title compound as a white solid (0.225 g, 54%); HPLC r.t. 4.212 min.

{\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3})} \delta 7.74 (d, J = 2.2 Hz, 1H), 7.41 (dd, J = 2.5, 8.8 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 4.69-4.66 (m, 1H), 4.08 (t, J = 8.8 Hz, 1H), 3.75 (s, 3H), 3.72 (dd, J = 6.9, 11.3 Hz, 1H), 3.39 (m, 5H), 1.82 (s, 3H); MS for C_{13}H_{18}N_{4}O_{5}S m/z 351.5 (M+H)^+.

Example 2 Preparation of 5(S)-N-[3-(2-ethoxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide

![Chemical structure](image)

Step 1: Preparation of 3-methyl-6-nitro-3H-benzothiazol-2-one O-ethyl-oxime

O-Ethylhydroxylamine hydrochloride (0.789 g, 8.09 mmol) is added in one portion to 3-methyl-2-methylsulfanyl-6-nitro-benzothiazol-3-ium methyl sulfate (2.50 g, 5.39 mmol) in pyridine (10 ml) and heated at 65 °C for 20 hours. The reaction is evaporated under vacuum, the residue diluted with ethyl acetate, washed with 2N hydrochloric acid and brine, dried (MgSO_{4}), and evaporated to give the title
compound as a bright orange solid (1.3 g, 95%); HPLC r.t. 6.142 min; MS for 
\[ C_{10}H_{11}N_{3}O_{3}S \text{ m/z 254 (M+H)}^+ \].

Step 2: Preparation of 6-amino-3-methyl-3H-benzothiazol-2-one O-ethyl-oxime

3-Methyl-6-nitro-3H-benzothiazol-2-one O-ethyl-oxime (1.25 g, 4.94 mmol) and palladium on carbon (10%, wet Degussa type E101 NE/W, 0.250 g) are suspended in ethyl acetate (20 ml) and placed under a hydrogen atmosphere (balloon) overnight. The catalyst is filtered and the clear colorless filtrate evaporated under vacuum to give the title compound as a white solid (1.10 g, 99%); MS for 
\[ C_{10}H_{13}N_{3}OS \text{ m/z 224 (M+H)}^+ \].

Step 3: Preparation of (2-ethoxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl)-carbamic acid benzyl ester

Benzyl chloroformate (0.74 ml, 5.17 mmol) is added dropwise to 6-amino-3-methyl-3H-benzothiazol-2-one O-ethyl-oxime (1.05 g, 4.70 mmol) and pyridine (0.57 ml, 7.05 mmol) in dichloromethane (10 ml) at 0 °C. The mixture is allowed to warm to room temperature and stirred for 15 minutes. The reaction is diluted with dichloromethane, washed with 2N hydrochloric acid and brine, dried (MgSO\(_4\)) and evaporated to the title compound as a white solid (1.6 g, 95%), HPLC r.t. 6.387 min; MS for 
\[ C_{18}H_{19}N_{3}O_{3}S \text{ m/z 358 (M+H)}^+ \].

Step 4: Preparation of (SS)-[3-(2-ethoxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid tert-butyl ester

Lithium t-butoxide (1.0 M solution in THF, 13.0 ml, 13.0 mmol) is added at 0 °C to (2-ethoxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl)-carbamic acid benzyl ester (1.55 g, 4.34 mmol) and (3-chloro-2-hydroxy-propyl)-carbamic acid tert-butyl ester (1.35 g, 6.50 mmol) in DMF (10 ml). The reaction mixture is allowed to warm at room temperature and stirred for 24h. 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\(_2\)SO\(_4\)) and evaporated. The residue is purified by flash column chromatography (50% EtOAc/Hexane) to give the title compound as a white solid (1.43 g, 78%); MS for 
\[ C_{19}H_{26}N_{4}O_{3}S \text{ m/z 423 (M+H)}^+ \].
Step 5: Preparation of (5R)-6-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-3-methyl-3H-benzothiazol-2-one O-ethyl-oxime

(5S)-3-(2-Ethoxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-carboxylic acid tert-butyl ester (0.70 g, 1.66 mmol) is stirred with 50% TFA/DCM (10 ml) for 1 h at room temperature. The solvent is evaporated to the title compound as the TFA salt (0.72 g, 99%); MS for C_{14}H_{18}N_{4}O_{8} S m/z 323 (M+H)^{+}.

Step 6: Preparation of (5S)-N-[3-(2-ethoxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl)]-2-oxo-oxazolidin-5-ylmethyl]-acetamide

Acetic anhydride (0.112 ml, 1.11 mmol) is added to 6-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-3-methyl-3H-benzothiazol-2-one O-ethyl-oxime (0.436 g, 1.00 mmol) and pyridine (0.245 ml, 3.00 mmol) in dichloromethane (5 ml) 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_{2}SO_{4}), and evaporated under vacuum to give the title compound as a white solid (0.22 g, 60%); HPLC r.t. 4,253 min.

^1^H NMR (300 MHz, CDCl_{3}) δ 7.73 (d, J= 2.2 Hz, 1H), 7.4 (dd, J= 2.2, 8.8 Hz, 1H), 7.12 (d, J= 8.8 Hz, 1H), 4.69- 4.66 (m, 1H), 4.08 (t, J= 9.0 Hz, 1H), 4.00 (q, J= 7.1 Hz, 2H), 3.71 (dd, J= 6.6, 8.7 Hz, 1H), 3.38 (t, J= 5.9 Hz, 2H), 3.33 (s, 3H), 1.82 (s, 3H), 1.20 (t, J=7.1 Hz, 3H); MS for C_{16}H_{20}N_{4}O_{4} S m/z 365 (M+H)^{+}.

Example 3 Preparation of (5R)-N-[3-(2-ethoxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl)]-2-oxo-oxazolidin-5-ylmethyl]-propionamide

Propionic anhydride (0.129 ml, 1.01 mmol) is added to (5R)-6-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-3-methyl-3H-benzothiazol-2-one O-ethyl-oxime (0.400 g, 0.917 mmol) and pyridine (0.224 ml, 2.75 mmol) in dichloromethane (5 ml) 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_{2}SO_{4}), and evaporated. The residue is purified by
PTLC (10% MeOH/DCM) to give the title compound as a white solid (0.21 g, 61%);
HPLC r.t. 4.532 min.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.72 (d, \(J=2.2\) Hz, 1H), 7.39 (dd, \(J=2.2, 8.8\) Hz, 1H), 7.12 (d, \(J=8.8\) Hz, 1H), 4.70-4.67 (m, 1H), 4.08 (t, \(J=9.0\) Hz, 1H), 3.99 (q, \(J=7.1\) Hz, 2H), 3.71 (dd, \(J=6.6, 8.6\) Hz, 1H), 3.43-3.38 (m, 2H), 3.30 (s, 3H), 2.09 (q, \(J=7.7\) Hz, 2H), 1.20 (t, \(J=6.9\) Hz, 3H), 0.95 (t, \(J=7.4\) Hz, 3H); MS for
\(C_{17}H_{22}NaO_4S\) m/z 379 (M+H)+.

Example 4  Preparation of (5S)-N-[3-(3-ethyl-2-methoxyimino-2,3-dihydro-
benzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide

\[\text{Me} \overset{\text{N}}{\text{O}_2} \text{N} \overset{\text{S}}{\text{Me}} \overset{\text{N}}{\text{O}_2} \text{N} \overset{\text{S}}{\text{Me}} \]

Step 1: Preparation of 3-ethyl-2-methylsulfanyl-6-nitro-benzothiazol-3-ium ethyl
sulfate

2-Methylsulfanyl-6-nitro-benzothiazole (5.00 g, 0.0221 mol) and diethyl
sulfate (10 ml) are heated at 100 °C for 20 hours. The reaction mixture is cooled and
diluted with ether (50 ml). The resulting white precipitate is filtered, washed
thoroughly with ether and dried under vacuum (8.9 g, 82%); mp.

Step 2: Preparation of 3-ethyl-6-nitro-3H-benzothiazol-2-one O-methyl-oxime

Methoxylamine hydrochloride (0.638 g, 7.64 mmol) is added in one portion to
3-ethyl-2-methylsulfanyl-6-nitro-benzothiazol-3-ium ethyl sulfate (2.50 g, 5.09 mmol)
in pyridine (10 ml) and heated at 65 °C for 20 hours. The reaction is evaporated under
vacuum, the residue diluted with ethyl acetate, washed with 2N hydrochloric acid and
brine, dried (MgSO\(_4\)), and evaporated to give the title compound as a bright orange
solid (1.29 g, 92%); HPLC r.t. 6.138 min; MS for \(C_{10}H_{11}N_3O_2S\) m/z 254 (M+H)+.

Step 3: Preparation of 6-amino-3-ethyl-3H-benzothiazol-2-one O-methyl-oxime

3-Ethyl-6-nitro-3H-benzothiazol-2-one O-methyl-oxime (1.25 g, 4.94 mmol)
and palladium on carbon (10%, wet Degussa type E101 NE/W, 0.250 g) are
suspended in ethyl acetate (20 ml) and placed under a hydrogen atmosphere (balloon)
overnight. The catalyst is filtered and the clear colorless filtrate evaporated under
vacuum to give the title compound as a white solid (1.00 g, 91%); MS for C_{10}H_{13}N_{3}OS m/z 224 (M+H)^+.

Step 4: Preparation of (3-ethyl-2-methoxyimino-2,3-dihydro-benzothiazol-6-yl)-carbamic acid benzyl ester

Benzyl chloroformate (0.70 ml, 4.93 mmol) is added dropwise to 6-amino-3-ethyl-3H-benzothiazol-2-one O-methyl-oxime (1.00 g, 4.48 mmol) and pyridine (0.54 ml, 6.72 mmol) in dichloromethane (10 ml) at 0 °C. The mixture is allowed to warm to room temperature and stirred for 15 minutes. The reaction is diluted with dichloromethane, washed with 2N hydrochloric acid and brine, dried (MgSO_4) and evaporated to give the title compound as a white solid (1.48 g, 93%), HPLC r.t. 6.388 min; MS for C_{18}H_{19}N_{3}O_{3}S m/z 358 (M+H)^+.

Step 5: Preparation of (5S)-[3-(3-ethyl-2-methoxyimino-2,3-dihydro-benzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid tert-butyl ester

Lithium tert-butoxide (1.0 M solution in THF, 11.8 ml, 11.8 mmol) is added at 0 °C to (3-ethyl-2-methoxyimino-2,3-dihydro-benzothiazol-6-yl)-carbamic acid benzyl ester (1.40 g, 3.92 mmol) and (3-chloro-2-hydroxy-propyl)-carbamic acid tert-butyl ester (1.27 g, 5.88 mmol) in DMF (10 ml). The reaction mixture is allowed to warm at room temperature and stirred for 24h. 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 (50% EtOAc/Hexane) to give the title compound as a white solid (1.26 g, 76%); MS for C_{19}H_{26}N_{4}O_{5}S m/z 423 (M+H)^+.

Step 6: Preparation of (5R)-6-(5-aminomethyl)-2-oxo-oxazolidin-3-yl)-3-ethyl-3H-benzothiazol-2-one O-methyl-oxime

(5S)-[3-(3-Ethyl-2-methoxyimino-2,3-dihydro-benzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid tert-butyl ester (0.60 g, 1.42 mmol) is stirred with 50% TFA/DCM (10 ml) for 1 h at room temperature. The solvent is evaporated to give the title compound as the TFA salt (0.62 g, 99%); MS for C_{14}H_{18}N_{4}O_{3}S m/z 323 (M+H)^+. 

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Step 7: Preparation of (5S)-N-[3-(3-ethyl-2-methoxyimino-2,3-dihydro-benzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide

Acetic anhydride (0.129 ml, 1.26 mmol) is added to (5R)-6-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-3-ethyl-3H-benzothiazol-2-one O-methyl-oxime (0.50 g, 1.15 mmol) and pyridine (0.280 ml, 3.44 mmol) in dichloromethane (5 ml) 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 (Na₂SO₄), and evaporated under vacuum to give the title compound as a white solid (0.32 g, 74%); HPLC r.t. 4.579 min.

^1H NMR (300 MHz, CDCl₃) δ 7.74 (d, J= 2.2 Hz, 1H), 7.40 (dd, J= 2.2, 8.9 Hz, 1H), 7.16 (d, J= 8.8 Hz, 1H), 4.69-4.66 (m, 1H), 4.08 (t, J= 8.7 Hz, 1H), 3.86 (q, J= 6.9 Hz, 2H), 3.75 (s, 3H), 3.71 (dd, J= 6.4, 11.5 Hz, 1H), 3.39 (t, J= 5.7 Hz, 2H), 1.82 (s, 3H), 1.17 (t, J= 6.9 Hz, 3H); MS for C₁₆H₂₀N₄O₄S m/z 365 (M+H)^+. 

Example 5 Preparation of (5S)-N-[3-(3-ethyl-2-methoxyimino-2,3-dihydro-benzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-propionamide

Propionic anhydride (0.129 ml, 1.01 mmol) is added to (5R)-6-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-3-ethyl-3H-benzothiazol-2-one O-methyl-oxime (0.400 g, 0.917 mmol) and pyridine (0.224 ml, 2.75 mmol) in dichloromethane (5 ml) 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 (Na₂SO₄), and evaporated. The residue is purified by PTLC (10% MeOH/DCM) to give the title compound as a white solid (0.195 g, 56%); HPLC r.t. 4.450 min.

^1H NMR (300 MHz, CDCl₃) δ 7.74 (d, J= 2.1Hz, 1H), 7.39 (dd, J= 2.2, 8.9 Hz, 1H), 7.16 (d, J= 8.7 Hz, 1H), 4.70-4.67(m, 1H), 4.08 (t, J= 8.7 Hz, 1H), 3.87 (q, J= 7.1 Hz, 2H), 3.75 (s,3H), 3.71 (dd, J= 6.3, 8.6 Hz, 1H), 3.41 (t, J = 5.7Hz, 2H), 2.09 (q, J= 7.5 Hz, 2H), 1.17 (t, J=7.2 Hz, 3H), 0.95 (t, J=7.5 Hz, 3H); MS for C₁₇H₂₂N₄O₄S m/z 379 (M+H)^+. 

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Example 6  Preparation of (5S)-N-[3-(2-Ethoxyimino-3-ethyl-2,3-dihydro-benzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide

\[
\begin{align*}
\text{Step 1: Preparation of 3-ethyl-6-nitro-3H-benzothiazol-2-one O-ethyl-oxime} \\
\text{O-Ethylhydroxylamine hydrochloride (0.744 g, 7.64 mmol) is added in one} \\
\text{portion to 3-ethyl-2-methylsulfanyl-6-nitro-benzothiazol-3-ium ethyl sulfate (2.50 g,} \\
\text{5.09 mmol) in pyridine (10 ml) and heated at 65 °C for 20 hours. The reaction is} \\
evaporated under vacuum, the residue diluted with ethyl acetate, washed with 2N 
\text{hydrochloric acid and brine, dried (MgSO}_4\text{), and evaporated to give the title} \\
\text{compound as a bright orange solid (1.29 g, 95%); HPLC rt 6.572 min; MS for} \\
\text{C}_{11}\text{H}_{13}\text{N}_{5}\text{O}_{3}\text{S m/z 268 (M+H)}^+.
\end{align*}
\]

\[
\text{Step 2: Preparation of 6-Amino-3-ethyl-3H-benzothiazol-2-one O-ethyl-oxime} \\
\text{3-Ethyl-6-nitro-3H-benzothiazol-2-one O-ethyl-oxime (1.25 g, 4.68 mmol) and} \\
palladium on carbon (10%, wet Degussa type E101 NE/W, 0.250 g) are} \\
suspended in ethyl acetate (20 ml) and placed under a hydrogen atmosphere (balloon) 
\text{overnight. The catalyst is filtered and the clear colorless filtrate evaporated under} \\
vacuum to give the title compound as a white solid (1.10 g, 99%); MS for} \\
\text{C}_{11}\text{H}_{15}\text{N}_{3}\text{OS m/z 238 (M+H)}^+.
\]

\[
\text{Step 3: Preparation of (2-ethoxyimino-3-ethyl-2,3-dihydro-benzothiazol-6-yl)-} \\
carbamic acid benzyl ester \\
\text{Benzyl chloroformate (0.66 ml, 4.64 mmol) is added dropwise to 6-amino-3-} \\
eythyl-3H-benzothiazol-2-one O-ethyl-oxime (1.00 g, 4.21 mmol) and pyridine (0.51} \\
\text{ml, 6.31 mmol) in dichloromethane (10 ml) at 0 °C. The mixture is allowed to warm} \\
to room temperature and stirred for 15 minutes. The reaction is diluted with 
\text{dichloromethane, washed with 2N hydrochloric acid and brine, dried (MgSO}_4\text{) and} \\
evaporated to give the title compound as a white solid (1.47 g, 96%), HPLC rt 6.721 
\text{min; MS for C}_{19}\text{H}_{21}\text{N}_{5}\text{O}_{3}\text{S m/z 372 (M+H)}^+.
\]

\[
\text{Step 4: Preparation of (S,S)-[3-(2-ethoxyimino-3-ethyl-2,3-dihydro-benzothiazol-6-} \\
yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid tert-butyl ester}
\]
Lithium t-butoxide (1.0 M solution in THF, 11.3 ml, 11.3 mmol) is added at 0 °C to (2-ethoxyimino-3-ethyl-2,3-dihydro-benzothiazol-6-yl)-carbamic acid benzyl ester (1.40 g, 3.77 mmol) and (3-chloro-2-hydroxy-propyl)-carbamic acid tert-butyl ester (1.22 g, 5.66 mmol) in DMF (10 ml). The reaction mixture is allowed to warm at room temperature and stirred for 24 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 (Na₂SO₄) and evaporated. The residue is purified by flash column chromatography (50% EtOAc/Hexane) to give the title compound as a white solid (1.20 g, 73%); MS for C₂₀H₂₈N₄O₃S m/z 437 (M+H)⁺.

Step 5: Preparation of (5R)-6-(5-Aminomethyl-2-oxo-oxazolidin-3-yl)-3-ethyl-3H-benzothiazol-2-one O-ethyl-oxime

(5S)-[3-(2-Ethoxyimino-3-ethyl-2,3-dihydro-benzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid tert-butyl ester (0.60 g, 1.37 mmol) is stirred with 50% TFA/DCM (10 ml) for 1 h at room temperature. The solvent is evaporated to give the title compound as the TFA salt (0.62 g, 99%); MS for C₁₅H₂₀N₄O₃S m/z 337 (M+H)⁺.

Step 6: Preparation of (5S)-N-[3-(2-ethoxyimino-3-ethyl-2,3-dihydro-benzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide

Acetic anhydride (0.125 ml, 1.22 mmol) is added to (5R)-6-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-3-ethyl-3H-benzothiazol-2-one O-ethyl-oxime (0.500 g, 1.11 mmol) and pyridine (0.270 ml, 3.33 mmol) in dichloromethane (5 ml) 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 (Na₂SO₄), and evaporated under vacuum to give the title compound as a white solid (0.30 g, 71%); HPLC r.t. 4.579 min.

1H NMR (300 MHz, CDCl₃) δ 7.72 (d, J= 2.2 Hz, 1H), 7.39 (dd, J= 2.5, 8.8 Hz, 1H), 7.15 (d, J= 8.8 Hz, 1H), 4.69-4.66 (m, 1H), 4.08 (t, J= 8.8 Hz, 1H), 3.97 (q, J= 6.9 Hz, 2H), 3.71 (dd, J= 6.3, 8.9 Hz, 1H), 3.39 (t, J= 5.5 Hz, 2H), 1.83 (s, 3H), 1.20(t, J= 6.8 Hz, 3H), 1.17 (t, J=7.2 Hz, 3H); MS for C₁₇H₂₂N₄O₄S m/z 379 (M+H)⁺.
Example 7  Preparation of (5S)-N-[3-(2-Ethoxyimino-3-ethyl-2,3-dihydrobenzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-propionamide

Propionic anhydride (0.128 ml, 0.99 mmol) is added to (5R)-6-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-3-ethyl-3H-benzothiazol-2-one O-ethyl-oxime (0.400 g, 0.908 mmol) and pyridine (0.222 ml, 2.72 mmol) in dichloromethane (5 ml) 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 (Na₂SO₄), and evaporated. The residue is purified by PTLC (10% MeOH/DCM) to give the title compound as a white solid (0.25 g, 72%); HPLC r.t. 4.788 min.

¹H NMR (300 MHz, CDCl₃) δ 7.72 (d, J = 2.0 Hz, 1H), 7.38 (dd, J = 2.2, 8.9 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 4.69-4.66 (m, 1H), 4.08 (t, J = 8.8 Hz, 1H), 3.99 (q, J = 6.9 Hz, 2H), 3.87 (q, J = 7.1 Hz, 2H), 3.71 (dd, J = 6.3, 8.9 Hz, 1H), 3.40 (m, 2H), 2.09 (q, J = 7.7 Hz, 2H), 1.20 (t, J = 6.9 Hz, 3H), 1.17 (t, J = 7.14 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H); MS for C₁₈H₂₄N₄O₄S m/z 393 (M+H)⁺.

Example 8  Preparation of (5R)-N-[3-(3,3-difluoro-2-methoxyimino-1-methyl-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide

Step 1: Preparation of 3,3-difluoro-1-methyl-5-nitro-1,3-dihydro-indol-2-one
(Diethylamino)sulfur trifluoride (4.04 ml, 30.6 mmol) is added dropwise to 1-methyl-5-nitro-1H-indole-2,3-dione (3.00 g, 14.6 mmol) in dichloromethane (50 ml) at -78 °C. The reaction is allowed to warm to room temperature and stirred for 48 hours. The mixture is poured into cold saturated sodium bicarbonate solution and the product extracted with dichloromethane. The extract is washed with brine, dried (Na₂SO₄), and evaporated. The residue is purified by flash chromatography (20% EtOAc/Hexane) to give the title compound as a yellow solid (2.09 g, 63%); HPLC r.t. 4.88 min; MS for C₉H₆F₂N₂O₃ m/z 227.0 (M-H)⁻.
Step 2: Preparation of 5-amino-3,3-difluoro-1-methyl-1,3-dihydro-indol-2-one

Iron powder (1.56 g, 28.05 mmol) is added in small portions to 3,3-difluoro 1-methyl-5-nitro-1, 3-dihydro-indol-2-one (1.60 g, 7.01 mmol) and ammonium chloride (3.72 g, 70.1 mmol) in ethanol (70 ml) and water (35 ml) at 90 °C. The reaction mixture is stirred vigorously and heated for 30 minutes, cooled to room temperature, and diluted with dichloromethane (150 ml). The mixture is filtered through celite, the organic layer separated and washed with water and brine, dried (Na₂SO₄), and evaporated to give the title compound as a brown solid (1.30 g, 93.5%); HPLC r.t. 1.96 min; MS for C₉H₈F₂N₂O m/z 199.1 (M+H)⁺.

Step 3: Preparation of (3,3-difluoro-1-methyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-carbamic acid benzyl ester

Benzyl chloroformate (0.547 ml, 3.89 mmol) is added dropwise to a mixture of 5-amino-3,3-difluoro-1-methyl-1,3-dihydro-indol-2-one (0.70 g, 3.53 mmol) and pyridine (0.571 ml, 7.06 mmol) in dichloromethane (6 ml) at 0 °C. The reaction mixture is stirred at 0 °C for 30 minutes, allowed to warm at room temperature and then poured into water. The organic layer is separated, washed with brine and dried (Na₂SO₄). Evaporation gave the title compound as a yellowish-orange solid (1.15 g, 98%); HPLC r.t. 5.65 min; MS for C₁₇H₁₄F₂N₂O₃ m/z 333.2 (M+H)⁺.

Step 4: Preparation of (3,3-difluoro-1-methyl-2-thioxo-2,3-dihydro-1H-indol-5-yl)-carbamic acid benzyl ester

(3,3-Difluoro-1-methyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-carbamic acid benzyl ester (1.10 g, 3.3 mmol) and Lawesson’s reagent (1.0 g, 2.48 mmol) in dioxane (7 ml) are heated overnight at 65 °C. The reaction is evaporated under vacuum and the residue purified by recrystallization from dichloromethane/hexane to give the title compound as a brown solid (1.0 g, 87%); HPLC r.t. 6.28 min; MS for C₁₇H₁₄F₂N₂O₂S m/z 347.0 (M-H)⁻.

Step 5: Preparation of (3,3-difluoro-2-methoxyimino-1-methyl-2,3-dihydro-1H-indol-5-yl)-carbamic acid benzyl ester

(3,3-Difluoro-1-methyl-2-thioxo-2,3-dihydro-1H-indol-5-yl)-carbamic acid benzyl ester (0.50 g, 1.43 mmol) and methoxylamine hydrochloride (0.48 g, 5.74
mmol) in pyridine (5 ml) are heated overnight at 70 °C. The reaction mixture is evaporated, the residue diluted with ethyl acetate, washed with 2N hydrochloric acid, water and brine, dried (\( \text{Na}_2\text{SO}_4 \)) and evaporated. The residue is purified by flash column chromatography (20% \( \text{EtOAc/Hexane} \)) to give the title compound as a light yellow solid (0.20 g, 39%); HPLC r.t. 6.16 min; MS for C_{18}H_{17}F_{2}N_{3}O_{3} m/z 362.0 (M+H)^+.

Step 6: Preparation of (5R)-N-[3-(3,3-difluoro-2-methoxyimino-1-methyl-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide

Lithium t-butoxide (1M solution in THF, 0.83 ml, 0.828 mmol) is added dropwise to (3,3-difluoro-2-methoxyimino-1-methyl-2,3-dihydro-1H-indol-5-yl)-carbamic acid benzyl ester (0.100 g, 0.276 mmol) and methanol (0.0225 ml, 0.558 mmol) in DMF (1ml) at 0°C. The mixture is stirred for 20 minutes and acetic acid 1-(acetylamino-methyl)-2-chloro-ethyl ester (0.107 g, 0.553 mmol) added in one portion. The reaction is allowed to warm to room temperature and stirred for 72 hours. Saturated aqueous ammonium chloride is added, the organic layer separated, washed with brine, dried (\( \text{Na}_2\text{SO}_4 \)), and evaporated. The residue is purified by PTLC (10% MeOH / DCM) to give the title compound as a white solid (0.356 g, 35%); HPLC r.t. 4.36 min.

\(^1\text{H} \text{NMR} (300 \text{ MHz, CDCl}_3-d) \delta 7.55-7.66 (m, 2H), 6.68-6.76 (m, 1H), 6.05 (t, 1H), 4.78 (m, 1H), 4.05 (t, J = 8.8 Hz, 1H), 3.92 (s, 3H), 3.61-3.81 (m, 3H), 3.59 (s, 3H), 2.03 (s, 3H); MS for C_{16}H_{18}F_{2}N_{4}O_{4} m/z 369.0 (M+H)^+.

Example 9 Preparation of (5R)-N-[3-(3,3-difluoro-2-methoxyimino-1-methyl-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-propionamide

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

Lithium t-butoxide (1M solution in THF, 1.41ml, 1.41mmol) is added dropwise to (3,3-difluoro-2-methoxyimino-1-methyl-2,3-dihydro-1H-indol-5-yl)-carbamic acid benzyl ester (0.17 g, 0.470 mmol) and (3-chloro-2-hydroxy-propyl)-
carbamic acid tert-butyl ester (0.147 g, 0.705 mmol) in DMF (5 ml) at 0°C. The reaction mixture is allowed to warm to room temperature and stirred for 72 h. Saturated aqueous ammonium chloride is added, the organic layer separated, washed with brine, dried (Na₂SO₄), and evaporated. The residue is purified by PTLC (10% MeOH / DCM) to give the title compound as a white solid (0.15 g, 75%); HPLC r.t. 5.55 min; MS for C₁₉H₂₄F₂N₂O₅ m/z 427.0 (M+H)+.

Step 2: Preparation of (5R)-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-3,3-difluoro-1-methyl-1,3-dihydro-indol-2-one O-methyl-oxime

(5R)-[3-(3,3-Difluoro-2-methoxyimino-1-methyl-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid tert-butyl ester (0.15 g, 0.35 mmol) is treated with 50% TFA / DCM (2 ml) for 30 minutes at room temperature. The reaction mixture is evaporated under vacuum to give product as the TFA salt (0.093 g, 60%); HPLC r.t. 3.65 min; MS for C₁₄H₁₆F₂N₄O₃ m/z 327.3 (M+H)+.

Step 3: Preparation of (5R)-N-[3-(3,3-difluoro-2-methoxyimino-1-methyl-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-propionamide

Propionic anhydride (0.0295 ml, 0.231 mmol) is added to (5R)-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-3,3-difluoro-1-methyl-1,3-dihydro-indol-2-one O-methyl-oxime (0.042 g, 0.115 mmol) and diisopropyl ethylamine (0.080 ml, 0.463 mmol) in dichloromethane (2 ml) at 0 °C. The mixture is allowed to warm at room temperature and stirred for 1 hour. The reaction is diluted with dichloromethane, washed with water, citric acid and brine, dried (Na₂SO₄), and evaporated. The residue is purified by PTLC (5%MeOH / DCM) to give the title compound as an off white solid (0.0196 g, 40%); HPLC r.t. 4.56 min.

¹H NMR (300 MHz, CDCl₃-d) δ 7.54-7.67 (m, 2H), 6.68-6.76 (m, 1H), 6.04 (t, 1H), 4.76-4.79 (m, 1H), 4.04 (t, J = 8.8 Hz, 1H), 3.91 s (3H), 3.61-3.83 (m, 3H), 3.58 (s, 3H), 2.25 (q, J = 7.8 Hz, 2H), 1.13 (t, J = 7.8 Hz, 3H); MS for C₁₇H₂₀F₂N₄O₄ m/z 383.3 (M+H)+.

Example 10 Preparation of (5R)-N-[3-(3,3-difluoro-2-methoxyimino-1-methyl-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid methyl ester
Methyl chloroformate (0.054 ml, 0.70 mmol) is added to (5R)-(5-aminomethyl-2-oxo-oxazolidin-3-yl)-3,3-difluoro-1-methyl-1,3-dihydro-indol-2-one O-methyl-oxime (0.155 g, 0.352 mmol) and diisopropyl ethylamine (0.365 ml, 2.11 mmol) in dichloromethane (3ml) at 0 °C and stirred for 30 minutes at 0 °C. The reaction mixture is diluted with dichloromethane, washed with water, citric acid and brine, dried (Na$_2$SO$_4$), and evaporated. The residue is purified by PTLC (5% MeOH / DCM) to give the title compound as an off white solid (0.05 g, 37%); HPLC r.t. 4.75 min; %.

$^1$H NMR (300 MHz, CDCl$_3$-$d$) δ 7.59-7.68 (m, 2H), 6.68-6.77 (m, 2H), 5.17 (t, 1H), 4.76 (m, 1H), 4.05 (t, J = 8.8 Hz, 1H), 3.92 (s, 3H), 3.82 (t, J = 7.2 Hz, 1H), 3.69 (s, 3H), overlapping 3.58 (s, 3H) and 3.49-3.63 (m, 2H)[$^1$]MS for C$_{16}$H$_{18}$F$_2$N$_4$O$_5$ m/z 385.0 (M+H)$^+$. 

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CLAMS

What is claimed is:

1. A compound of formula I

\[
\begin{align*}
\text{Z} \equiv \text{N} \equiv \text{U} \equiv \text{Y}^1 \equiv \text{Y}^2 \equiv \text{X} \equiv \text{W}
\end{align*}
\]

or a pharmaceutically acceptable salt thereof wherein:

X is a structure of the following formula i, ii, iii, or iv

\[
\begin{align*}
i & : \quad \text{N} \equiv \text{O} \equiv \text{N} \equiv \text{O} \\
ii & : \quad \text{N} \equiv \text{O} \equiv \text{O} \\
iii & : \quad \text{O} & \equiv & \text{O} \\
iv & : \quad \text{N} \equiv \text{O} \\
\end{align*}
\]

W is

(a) \(\text{CH}_2\text{NHC} (=\text{O})\text{R}^1\),
(b) \(\text{CH}_2\text{NHC} (=\text{S})\text{R}^1\),
(c) \(\text{CH}_2\text{NH} – \text{het}\),
(d) \(\text{CH}_2\text{O} – \text{het}\),
(e) \(\text{CH}_2\text{S} – \text{het}\),
(f) \(\text{CH}_2\text{het}\),
(g) \(\text{CH}_2\text{OH}\),
(h) \(\text{CH(OH)} – \text{CH} = \text{CHR}^1\), or
(i) \(\text{CH(OH)C} = \equiv \text{CR}^1\);

Y\(^1\), Y\(^2\) and Y\(^3\) are independently

(a) \(\text{CH}\),
(b) \(\text{N}\),
(c) \(\text{N}^+ – \text{O}^–\), or
(d) \(\text{CF}\);

U is

(a) \(\text{CR}^3\text{R}^4\),
(b) \(\text{O}\), or
(c) \(\text{S}, \text{SO}, \text{or SO}_2\);

Z is O-C\(_{1-6}\)alkyl, optionally substituted with OH, or O-C\(_{1-2}\)alkyl;
R¹ is

(a) NH₂,
(b) NHC₄₋₆alkyl,
(c) C₁₋₄alkyl,
(d) C₆₋₉alkenyl,
(e) (CH₂)₂C(=O)C₁₋₄alkyl,
(f) OC₁₋₄alkyl,
(g) SC₁₋₄alkyl, or
(h) (CH₂)₂C₃₋₇cycloalkyl;

R² is

(a) C₁₋₄alkyl,
(b) OC₁₋₄alkyl, or
(c) (CH₂)₂C₃₋₇cycloalkyl;

R³ and R⁴ are independently

(a) H,
(b) F,
(c) CH₃, or
(d) each R³ and R⁴ is together with the carbon atom to which they attach form C₃₋₆ cycloalkyl;

at each occurrence, C₁₋₄alkyl, C₆₋₉alkenyl, or C₃₋₇cycloalkyl is optionally substituted with 1-3 halo, OR⁵, CN, N₃, NO₂, NR⁵R⁶, C(=O)C₁₋₄alkyl, OC(=O)C₁₋₄alkyl, C(=O)OC₁₋₄alkyl, or S(O)ₙC₁₋₄alkyl,

R⁵ and R⁶ are independently

(a) H, or
(b) C₁₋₄alkyl, optionally substituted with OH, phenyl, or OC₁₋₄ alkyl;
n is 0, 1 or 2;
each j is independently 0-4; and

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,

which is optionally substituted with 1-3 halo, OR⁵, CN, N₃, NO₂, NR⁵R⁶, C(=O)C₁₋₄alkyl, OC(=O)C₁₋₄alkyl, C(=O)OC₁₋₄alkyl, or S(O)ₙC₁₋₄alkyl.
2. A compound of claim 1 wherein X is a structure of formula ii

\[ \begin{array}{c}
\text{N} \\
\text{O} \\
\text{O} \\
\text{C} \\
\end{array} \]

ii.

3. A compound of claim 2 wherein W is
(a) $\text{CH}_2\text{NHC}(=\text{O})\text{R}^1$, or
(b) $\text{CH}_2\text{NHC}(=\text{S})\text{R}^1$.

4. A compound of claim 3 wherein $\text{R}^1$ is $\text{CH}_3$, $\text{CH}_2\text{CH}_3$, $\text{CHF}_2$, $\text{CF}_3$, or $\text{CHCl}_2$.

5. A compound of claim 2 wherein $\text{Y}^1$, $\text{Y}^2$, or $\text{Y}^3$ is $\text{CH}$.

6. A compound of claim 2 wherein $\text{Y}^1$ is $\text{CF}$, $\text{Y}^2$ and $\text{Y}^3$ are $\text{CH}$.

7. A compound of claim 2 wherein $\text{U}$ is $\text{CH}_2$, or $\text{CF}_2$.

8. A compound of claim 2 wherein $\text{U}$ is $\text{O}$ or $\text{S}$.

9. A compound of claim 2 wherein $\text{R}^2$ is $\text{CH}_3$, or $\text{CH}_2\text{CH}_3$.

10. A compound of claim 2 wherein $\text{Z}$ is $\text{OC}_{1-4}\text{alkyl}$.

11. A compound of claim 1 which is
(1) $\text{(S})-\text{N}[3-(2\text{-methoxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl})]-2\text{-oxo-oxazolidin-5-ylmethyl]}\text{-acetamide}$,
(2) $\text{S})-\text{N}[3-(2\text{-ethoxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl})]-2\text{-oxo-oxazolidin-5-ylmethyl]}\text{-acetamide}$,
(3) $\text{(R})-\text{N}[3-(2\text{-ethoxyimino-3-methyl-2,3-dihydro-benzothiazol-6-yl})]-2\text{-oxo-oxazolidin-5-ylmethyl]}\text{-propionamide}$,
(4) $\text{(S})-\text{N}[3-(3\text{-ethyl-2-methoxyimino-2,3-dihydro-benzothiazol-6-yl})]-2\text{-oxo-oxazolidin-5-ylmethyl]}\text{-acetamide}$,
(5) \((5S)\)-N-[3-(3-ethyl-2-methoxyimino-2,3-dihydro-benzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-propionamide,

(6) \((5S)\)-N-[3-(2-Ethoxyimino-3-ethyl-2,3-dihydro-benzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

(7) \((5S)\)-N-[3-(2-Ethoxyimino-3-ethyl-2,3-dihydro-benzothiazol-6-yl)-2-oxo-oxazolidin-5-ylmethyl]-propionamide,

(8) \((5R)\)-N-[3-(3,3-difluoro-2-methoxyimino-1-methyl-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-acetamide,

(9) \((5R)\)-N-[3-(3,3-difluoro-2-methoxyimino-1-methyl-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-propionamide, or

(10) \((5R)\)-N-[3-(3,3-difluoro-2-methoxyimino-1-methyl-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]-carbamic acid methyl ester.

12. A pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

13. A use of a compound of claim 1 for the preparation of a medicament for treating bacteria infectious diseases.

14. The use of of claim 13 wherein the compound of claim 1 is administered parenterally, topically, rectally, or intranasally.

15. The bacteria infectious diseases of claim 13 which is ear infections, eye infections, respiratory tract infections, skin and skin structure infections, joint and bone infections, bacterial endocarditis, osteomyelitis, or diabetic foot.