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(71) Applicant *(for all designated States except US)*: **PHARMACIA & UPJOHN COMPANY** [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **HESTER, Jackson, B., Jr.** [US/US]; 9219 East ML Avenue, Galesburg, MI 49053 (US). **ALEXANDER, David, L.** [US/US]; 525 S. Burdick, Apt. 3702, Kalamazoo, MI 49007-5257 (US).

(74) Agent: **YANG, Lucy, X.**; Intellectual Property Legal Services, Pharmacia & Upjohn Company, 301 Henrietta Street, Kalamazoo, MI 49001 (US).

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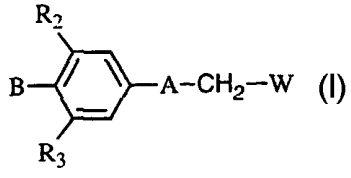
(54) Title: OXAZOLIDINONES HAVING A SULFOXIMINE FUNCTIONALITY AND THEIR USE AS ANTIMICROBIAL AGENTS



(I)

(57) Abstract: The present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof wherein: A is a structure i, ii, iii, or iv; B is (a), (b), (c) W is $NHC(=X)R_1$, or -Y-het; provided that when A is a structure iv, W is not -Y-het; Z is $S(=O)(=N\text{-}R_5)$; and R_2 and R_3 are independently H, F, Cl, methyl or ethyl; which have potent activities against Gram-positive and Gram-negative bacteria.

OXAZOLIDINONES HAVING A SULFOXIMINE FUNCTIONALITY AND THEIR USE AS ANTIMICROBIAL AGENTS

FIELD OF THE INVENTION

The present invention relates to novel oxazolidinones which have a sulfoximine functionality and their preparations. These compounds have potent activities against Gram-positive and Gram-negative bacteria.

BACKGROUND OF THE INVENTION

The oxazolidinone antibacterial agents are a novel synthetic class of antimicrobials with potent activity against a number of human and veterinary pathogens, including Gram-positive aerobic bacteria such as multiply-resistant staphylococci and streptococci, anaerobic organisms such as bacteroides and clostridia species, and acid-fast organisms such as *Mycobacterium tuberculosis* and *Mycobacterium avium*.

However, oxazolidinones generally do not demostrate an activity at a useful level against aerobic Gram-negative organisms. Thus, the use of these oxazolidinone antibacterial agents is limited to infectious states due to Gram-positive bacteria. Accordingly, it is among the objects of the present invention to provide pharmaceutical compounds which have broader antibacterial activity including the activity against aerobic Gram-negative organisms. We have now discovered that the oxazolidinones of the present invention increase the spectrum of activity to include gram-negative organisms such as *Haemophilus influenza* and *Moraxella catarrhalis*.

INFORMATION DISCLOSURE

U.S. Patent 5,688,792 discloses substituted oxazine and thiazine oxazolidinone useful as antibacticals.

PCT International Publication WO 98/54161 discloses oxazolidinone antibacterial agents having a thiocarbonyl functionality.

U.S. Patent 5,968,962 and PCT International Publication WO 99/29688 discloses phenyloxazolidinones having a C-C bond to 4-8 membered heterocyclic rings.

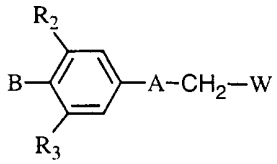
U.S. Patent 5,952,324 discloses bicyclic oxazine and thiazine oxazolidinone useful as antibacticals.

PCT publications, WO 99/64416, WO99/64417, and WO 00/21960 disclose oxazolidinone derivatives useful as antibacterial agents.

PCT publication, WO 00/10566 discloses isoxazolinones useful as antibacterial agents.

SUMMARY OF THE INVENTION

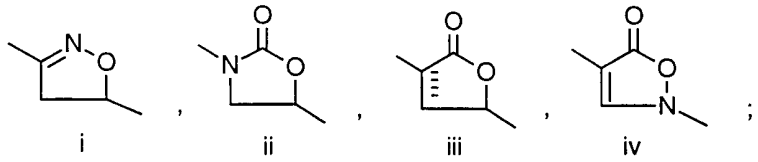
The present invention provides a compound of formula I



I

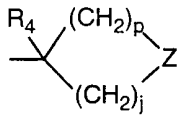
or a pharmaceutically acceptable salt thereof wherein:

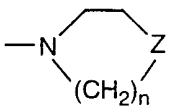
A is a structure i, ii, iii, or iv

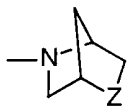


i , ii , iii , iv ;

B is

(a) 

(b) 

(c) 

W is NHC(=X)R_1, or –Y-het; povided that when A is a structure iv, W is not –Y-het;

X is O, or S; provided that when X is O, B is not the subsection (b).

Y is NH, O, or S;

Z is S(=O)(=N-R_5);

R_1 is

(a) H,

(b) NH_2,

(c) NHC_{1-4}alkyl,

(d) C_{1-4}alkyl,

(e) C_{2-4}alkenyl,

(f) OC_{1-4}alkyl,

(g) SC_{1-4}alkyl, or

(h) $(CH_2)_p C_{3-6}$cycloalkyl;

at each occurrence, alkyl or cycloalkyl in R_1 is optionally substituted with one or more F, Cl or CN;

R_2 and R_3 are independently H, F, Cl, methyl or ethyl;

R_4 is H, CH_3, or F;

R_5 is

(a) H,

(b) C_{1-4}alkyl,

(c) $C(=O)C_{1-4}$alkyl,

(d) $C(=O)OC_{1-4}$alkyl,

(e) $C(=O)NHR_6$, or

(f) $C(=S)NHR_6$;

R_6 is H, C_{1-4}alkyl, or phenyl;

at each occurrence, alkyl in R_5 and R_6 is optionally substituted with one or more halo, CN, NO_2, phenyl, C_{3-6} cycloalkyl, OR_7, $C(=O)R^7$, $OC(=O)R_7$, $C(=O)OR_7$, $S(=O)_mR_7$, $S(=O)_mNR_7R_7$, $NR_7SO_2R_7$, $NR_7SO_2NR_7R_7$, $NR_7C(=O)R_7$, $C(=O)NR_7R_7$, NR_7R_7, oxo, or oxime;

R_7 is H, C_{1-4}alkyl, or phenyl;

at each occurrence, phenyl is optionally substituted with one or more halo, CN, NO_2, phenyl, C_{3-6} cycloalkyl, OR_7, $C(=O)R^7$, $OC(=O)R_7$, $C(=O)OR_7$, $S(=O)_mR_7$, $S(=O)_mNR_7R_7$, $NR_7SO_2R_7$, $NR_7SO_2NR_7R_7$, $NR_7C(=O)R_7$, $C(=O)NR_7R_7$, or NR_7R_7;

het is a C-linked five- (5) membered heteroaryl ring having 1-4 heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen, or het is a C-linked six (6) membered heteroaryl ring having 1-3 nitrogen atoms;

p is 0, 1, or 2;

j is 1, 2, 3, 4, or 5; provided that p and j taken together are 2, 3, 4 or 5;

m is 0, 1, or 2;

n is 2 or 3; and ===== in structure iii is either a double bond or a single bond.

In another aspect, the present invention also provides:

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

a method for treating gram-positive microbial infections in humans or other warm-blooded animals 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 method for treating gram-negative microbial infections in humans or other warm-blooded animals by administering to the subject in need a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

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

DETAILED DESCRIPTION OF THE INVENTION

The following definitions are used, unless otherwise described.

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

The term "het" is a C-linked five- (5) membered heteroaryl ring having 1-4 heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen, or het is a C-linked six (6) membered heteroaryl ring having 1-3 nitrogen atoms.

Examples of "het" include 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-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 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, 1,2,4-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, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-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.

Mammal refers to human or animals.

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 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, C_{1-4} alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, and their isomeric forms thereof.

Specifically, C_{2-4} alkenyl can be vinyl, propenyl, allyl, butenyl, and their isomeric forms thereof; C_{3-6} cycloalkyl can cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and their isomeric forms thereof.

A specific value for A is structure ii as defined above.

A specific value for X is sulfur atom.

A specific value for X is oxygen atom.

A specific value for R_1 is C_{1-4}alkyl.

A more specific value for R_1 is methyl or ethyl.

A specific value for R_1 is cyclopropyl.

A specific value for R_1 is NH_2.

A specific value for R_2 and R_3 are independently H or F.

A specific value for R_2 and R_3 are that one of them is H, the other one is F.

A specific value for R_4 is H or CH_3.

A specific value for R_5 is H.

A specific value for R_5 is C_{1-4}alkyl, optionally substituted with OH.

A specific value for R_5 is CH_3, or ethyl.

A specific value for R_5 is C_{1-4}alkyl substituted with $C(=O)NHC_{1-4}$alkyl, or $C(=O)NH_2$.

A specific value for R_5 is C_{1-4}alkyl substituted with phenyl wherein the phenyl is optionally substituted with OH, methyl, NO_2, CF_3, or CN.

A specific value for R_5 is C_{1-4}alkyl substituted with phenyl wherein the phenyl is optionally substituted with NO_2.

A specific value for R_5 is $C(=O)NH_2$, or $C(=O)NHC_{1-4}$alkyl.

A specific value for R_5 is $C(=O)NHCH_3$, or $C(=O)NHCH_2CH_3$.

A specific value for R_5 is $C(=O)C_{1-4}$alkyl.

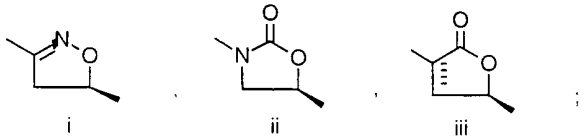
A specific value for R_5 is $C(=O)CH_3$.

A specific value for R_5 is $C(=O)OC_{1-4}$alkyl.

A specific value for R_5 is $C(=O)OCH_3$.

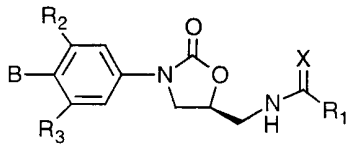
A specific value for het is isoxazol-3-yl, isoxazol-5-yl, 1,2,4-oxadiazol-3-yl, isothiazol-3-yl, 1,2,4-thiadiazol-3-yl or 1,2,5-thiadiazol-3-yl.

The preferred compounds of the present invention are those wherein structure i, ii, or iii has an optical configuration below:



i ii iii

More preferred compounds of the present invention are the compounds of formula IA:



IA

These absolute configurations are called (S)-configuration according to the Cahn-Ingold-Prelog nomenclature system. It will be appreciated by those skilled in the art that compounds of the present invention may have additional chiral centers and be isolated in optically active and racemic forms. The present invention encompasses any racemic,

optically-active, tautomeric, or stereoisomeric form, or mixture thereof, of a compound of the invention.

Examples of the present invention are:

(1) N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)ethanethioamide;

(2) N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide;

(3) N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)cyclopropanecarbothioamide;

(4) N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (E)-isomer;

(5) N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)ethanethioamide (E)-isomer;

(6) N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide (E)-isomer;

(7) N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)cyclopropanecarbothioamide (E)-isomer;

(8) N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (Z)-isomer;

(9) N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)ethanethioamide (Z)-isomer;

(10) N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide (Z)-isomer;

(11) N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)cyclopropanethioamide (Z)-isomer;

(12) N-({(5*S*)-3-[3-Fluoro-4-[1-(acetylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, (Z)-isomer;

(13) N-({(5*S*)-3-[3-Fluoro-4-[1-(methylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(14) N-({(5*S*)-3-[3-Fluoro-4-[1-(acetylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(15) N-({(5*S*)-3-[3-Fluoro-4-[1-(ethylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(16) N-({(5*S*)-3-[3-Fluoro-4-[1-[(phenylmethyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(17) N-({(5*S*)-3-[3-Fluoro-4-[1-[(3-phenylpropyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(18) N-({(5*S*)-3-[3-Fluoro-4-(1-{[(methylamino)carbonyl]imino}-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(19) N-({(5*S*)-3-[3-Fluoro-4-(1-[(methoxycarbonyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(20) N-({(5*S*)-3-[3-Fluoro-4-(1-[[(ethoxycarbonyl)methyl]imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(21) N-({(5*S*)-3-[3-Fluoro-4-(1-{[[(4-nitrophenyl)amino]carbonyl]imino}-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer ;

(22) N-({(5*S*)-3-[3-Fluoro-4-[1-[(aminocarbonyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(23) N-({(5*S*)-3-[3-Fluoro-4-[1-[[(aminocarbonyl)methyl]imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(24) N-({(5*S*)-3-[3-Fluoro-4-[1-[(2-hydroxyethyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(25) N-[((5*S*)-3-{3-Fluoro-4-[1-(methylimino)-1-oxido-1λ^4,4-thiazinan-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide;

(26) N-[((5*S*)-3-{3-Fluoro-4-[1-(methylimino)-1-oxido-1λ^4,4-thiazinan-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarbothioamide;

(27) N-[((5*S*)-3-{3-Fluoro-4-(1-[(methoxycarbonyl)imino]-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide;

(28) N-[((5*S*)-3-{3-Fluoro-4-(1-[(methoxycarbonyl)imino]-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarbothioamide ;

(29) N-({(5*S*)-3-[3-Fluoro-4-[1-(methylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)cyclopropanecarbothioamide, *Z*-isomer;

(30) N-[((5*S*)-3-{3-Fluoro-4-[1-[(methoxycarbonyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarbothioamide, *Z*-isomer;

(31) N-[((5*S*)-3-{3-Fluoro-4-[1-(methylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarbothioamide, *E*-isomer;

(32) N-[((5*S*)-3-{3-Fluoro-4-[1-(methylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide, *E*-isomer;

(33) N-[((5*S*)-3-{3-Fluoro-4-[1-[[(phenylmethoxy)carbnonyl]imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide, *Z*-isomer; or

(34) N-({(5*S*)-3-[3-Fluoro-4-(1-{[(benzylamino)carbonyl]imino}-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, *Z*-isomer.

The following Schemes describe the preparation of compounds of the present invention. All of the starting materials are prepared by procedures described in these schemes or 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 claims.

The compounds of this invention can be prepared in accordance to one or more of the Schemes discussed below. Optically pure material could be obtained either by one of a number of asymmetric syntheses or alternatively by resolution from a racemic mixture.

In scheme I the starting materials of 1-a can be prepared according to the procedures described in U.S. Patent 5,688,792 or PCT International Publication WO 98/54161. A compound of 1-a is allowed to react with sodium azide in polyphosphoric acid at a temperature in a range from about 40°C to about 70°C to provide compound 1-b. Compound 1-b can be alkylated by the reaction with aldehydes or ketones and formic acid using Leuckart-Wallach or Eschweiler-Clarke reaction conditions to provide 1-c (R' = C_{1-4}alkyl). An illustration of this method for the methylation of compound 1-b is described in Preparation 3 of the present invention. In an alternative method for this

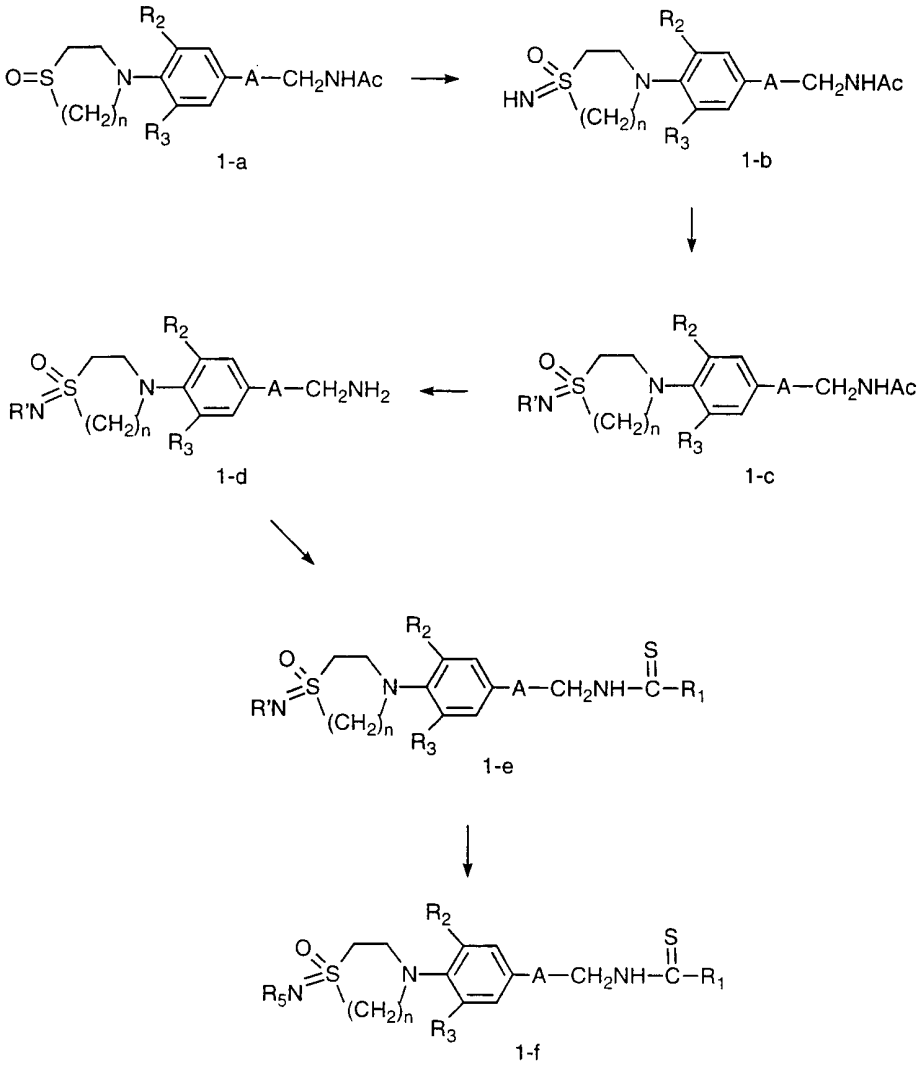
alkylation, a compound of 1-b or 1-e (R' = H) is allowed to react with an aldehyde or ketone, triethylsilane and trifluoroacetic acid. Para-formaldehyde is a convenient source of formaldehyde for this reaction and aldehydes protected as acetals can also be employed. Solvents such as toluene, dichloromethane, THF, and preferably acetonitrile with temperatures, depending on the solvent, in the range of 10^{o}-120^{o} C can be used. This method is illustrated in Examples 13 and 16. Aldehydes with various functional groups can also be employed in this reaction as illustrated by the use of ethyl glyoxalate in Example 20. The ester prepared in this example can be reduced to an alcohol with lithium borohydride (Example 24) or converted to an amide with ammonium hydroxide (Example 23). Compounds wherein R_5 is C_{1-4} alkyl substituted by NH_2 or NHalkyl can be obtained by employing an amine protecting group such as benzyloxycarbonyl or tert-butyloxycarbonyl that can subsequently be removed. Other compounds wherein R_5 is substituted alkyl can be obtained with appropriate modifications of this reductive alkylation procedure.

The acetamide 1-c is hydrolyzed to the corresponding amine, 1-d, with hydrochloric acid in a solvent such as methanol at the reflux temperature. Acylation of the amine with appropriate dithioesters and a tertiary amine base such as triethylamine provides the corresponding compound 1-e. Solvents such as CH_2Cl_2, THF or preferably MeOH and temperatures of 24°C to the reflux temperature of the solvent are suitable for this reaction. Preparations of other thiocarbonyl compounds 1-e are as described in PCT International Publication WO 98/54161. Where R' is hydrogen, 1-e may be converted to compound 1-f with additional functional groups on the sulfoximine nitrogen. Reactions with carboxylic acid chlorides or anhydrides in solvents such as pyridine at a temperature in a range from about 24-100°C provide the corresponding acyl derivatives (R_5 is $C(=O)C_{1-4}$ alkyl). Carboxylic acid anhydrides in the corresponding carboxylic acid as solvent can also be used as illustrated for acetic anhydride in acetic acid in Preparation 2. Carbamates (R_5 is $C(=O)OC_{1-4}$ alkyl) are prepared by the reactions of 1-e (R' is H) with appropriate alkyl chloroformates in pyridine at 0°C to 100°C. In addition, 4-(dimethylamino)pyridine can be used to catalyze this reaction as illustrated in Example 19. Alkyl ureas and alkyl thioureas (R_6 is C_{1-4} alkyl) are prepared by warming 1-e (R' is H) with the appropriate alkyl isocyanate or alkyl isothiocyanate at a temperature in a range from about 30°C to about 100°C. DMF is a preferred solvent for this reaction. Compounds where R_6 is phenyl or substituted phenyl are similarly preprared. Compounds where R_6 is hydrogen are prepared by the reactions of 1-e (R' is H) with sodium cyanate or sodium thiocyanate in acetic acid at

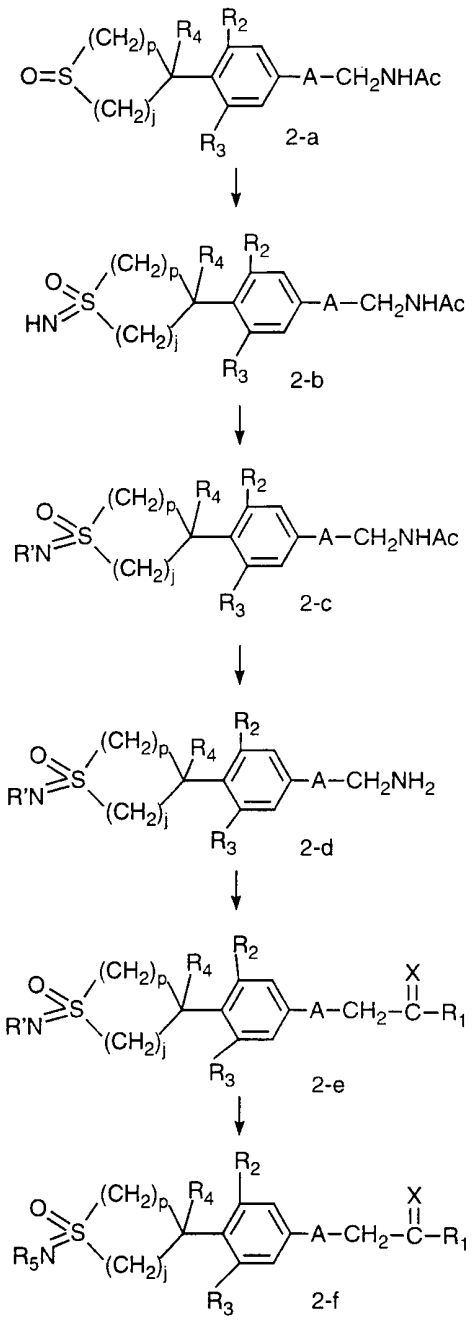
a temperature in a range from about 24°C to about 100°C. For the preparation of a compound wherein X is oxygen, the amine 1-d may be acylated with appropriate carbonyl derivatives such as carboxylic acid anhydrides, alkyl chloroformates, alkyl isocyanates and sodium cyanate in an acetic acid solution. Compounds of formula I wherein B is the subsection (c) can be prepared by the methods shown in Scheme I with the starting material, sulfoxides. The sulfoxides can be prepared according to the procedure disclosed in US patent 5,952,324.

Scheme II illustrates the preparation of compounds of 2-e and 2-f. The starting material 2-a can be prepared according to the procedures described in U.S. Patent 5,968,962, PCT International Publication WO 99/29688 and PCT International Publication WO 98/54161.In this series the sulfoxides can be either *cis* or *trans* to the benzene ring attachment. The reaction of compounds 2-a with O-mesitylenesulfonylhydroxylamine (MSH) proceeds with retention of the sulfoxide stereochemistry in the products 2-b. This reaction is usually carried out at ambient temperature in solvents such as methylene chloride. Subsequent reactions in Scheme II are carried out as discussed for the corresponding steps in Scheme I. Compounds 2-e where X=O are prepared by acylating compounds 2-d with appropriate carbonyl derivatives such as carboxylic acid anhydrides, alkyl chloroformates, alkyl isocyanates and sodium cyanate in acetic acid.

SCHEME I


R2
O=S
N
A—CH2NHAc
(CH2)n
R3
1-a
HN=S
1-b
R'N=S
A—CH2NH2
1-d
1-c
A—CH2NH—C—R1
S
1-e
R5N=S
1-f

SCHEME II



The pharmaceutical compositions of this invention may be prepared by combining the compounds of formula I of this invention with a solid or liquid pharmaceutically acceptable carrier and, optionally, with pharmaceutically acceptable adjuvants and excipient employing standard and conventional techniques. Solid form compositions include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be at least one substance which may also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Inert solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, cellulosic materials, low melting wax, cocoa butter, and the like. 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.

Preferably, the pharmaceutical composition is provided employing conventional techniques in unit dosage form containing effective or appropriate amounts of the active component, that is, the compounds of formula I according to this invention.

The quantity of active component, that is the compound of formula I according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the potency of the particular compound and the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

In therapeutic use for treating, or combating, bacterial infections in warm-blooded animals, the compounds or pharmaceutical compositions thereof will be administered orally, topically, transdermally, and/or parenterally at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which will be antibacterially effective. Generally, such antibacterially effective amount of dosage of active component will be in the range of about 0.1 to about 100, 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 the patient, the severity of the bacterial infection being treated, and the particular compound being used. 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 blood-level or 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.

The compounds of formula I according to this invention are administered parenterally, i.e., by injection, for example, by intravenous injection or by other parenteral routes of administration. Pharmaceutical compositions for parenteral administration will generally contain a pharmaceutically acceptable amount of the compound according to formula I as a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as, for example, water-for-injection and a buffer to provide a suitably buffered isotonic solution, for example, having a pH of about 3.5-6. Suitable buffering agents include, for example, trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine to name but a few representative buffering agents. The compounds according to formula I generally will be dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 mg/ml to about 400 mg/ml of solution. The resulting liquid pharmaceutical composition will be administered so as to obtain the above-mentioned antibacterially effective amount of dosage. The compounds of formula I according to this invention are advantageously administered orally in solid and liquid dosage forms.

The oxazolidinone antibacterial agents of this invention have useful activity against a variety of organisms. The in vitro activity of compounds of this invention can be assessed by standard testing procedures such as the determination of minimum inhibitory concentration (MIC) by agar dilution as described in "Approved Standard. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically", 3rd. ed., published 1993 by the National Committee for Clinical Laboratory Standards, Villanova, Pennsylvania, USA. The activity of compounds of this invention against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Enterococcus faecalis*, *Moraxella catarrhalis* and *H. influenzae* is shown in Table 1.

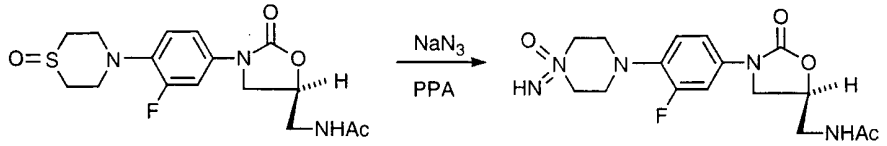
TABLE 1

Antibacterial Activity Minimum Inhibitory Concentration (μg/mL)

Example No.	SAUR 9213	SEPI 30593	EFAE 12712	SPNE 9912	SPYO 152	HINF 30063	EFAE 9217	MCAT 30607
1	1	0.5	1	0.25	0.25	4	1	2
2	1	0.25	0.5	0.25	0.25	2	0.5	2
3	1	0.25	0.5	0.25	0.25	4	1	1
4	16	2	4	1	1	8	2	4
8	8	1	2	0.5	1	8	2	2
9	0.5	0.125	0.5	0.25	0.25	2	0.5	2
10	1	0.25	0.5	0.25	0.25	2	0.5	2
11	1	0.5	0.5	0.25	0.25	4	0.5	1
12	8	1		0.5	1	16	2	8
13	1	0.5	1	0.25	0.25	8	0.5	2
14	1	0.5	1	0.25	0.25	4	0.5	2
15	2	1	1	0.5	0.5	8	1	2
16	2	1	1	0.25	0.5	>64	1	2
17	2	2	2	0.5	1	>64	1	2
18	2	1	1	0.25	0.5	8	1	4
19	1	0.5	1	0.25	0.25	2		2
20	2	1	1	4	16	8	1	4
21	0.5	0.25	0.25	<0.06	0.125	>64	0.25	0.25
22	2	.05	0.5	0.125	0.5	4	0.5	2
23	2	2	1	0.25	0.5	4	0.5	4
24	2	0.5	1	0.25	0.5	4	1	4
25	2	0.5	1	0.25	0.5	4	1	4
26	2	0.5	1	0.25	0.5	4	0.5	2
27	2	0.5	0.5	0.125	0.5	4	0.5	8
28	2	0.5	1	0.25	0.5	4	1	2
29	1	0.5	1	0.25	0.5	4	0.5	2
30	1	0.5	0.5	0.125	0.5	4	0.5	0.5
31	2	1	2	0.5	1	8	1	4
32	4	1	2	0.5	1	8	2	8
33	8	2	4	1	1	64	4	16
34	16	2	4	1	2	32	4	16
PREP 1	16	4	4	1	2	16	8	8
PREP 2	16	2	4	1	2	32	2	8
PREP 3	16	2	4	1	2	16	4	8

EXAMPLES

Preparation 1: N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (**2**)

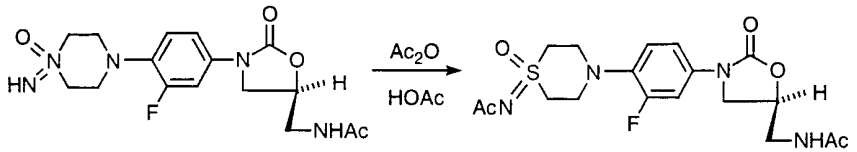


1 **2**

((*S*)-N-[[3-[3-fluoro-4-(1-oxothiomorpholin-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, (compound **1**, prepared according to the procedure described in WO95/07271, Example 3) (1.01 g, 2.73 mmol) and sodium azide (0.38g, 5.8 mmol) are added at ambient temperature, under nitrogen, with stirring to polyphosphoric acid (40 g) and the mixture is warmed at 50-55°C for 6 hours and at 60°C for 4 hours, cooled slowly to 0°C and treated, dropwise with water (20 ml) and enough 50% (w/w) sodium hydroxide to raise the pH to 10.5-11.0. This mixture is diluted with enough water to give a solution which is extracted with $CHCl_3$. The extract is dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with mixtures of MeOH-$CHCl_3$ containing 2-3% MeOH gave 691 mg of the product. Crystallization of this material from acetone-hexane gave compound **2**.

mp 165-166°C; HRMS (FAB) calcd for $C_{16}H_{22}FN_4O_4S$ ($M+H^+$) 385.1346, found 385.1352. Anal. Calcd for $C_{16}H_{21}FN_4O_4S$: C, 49.99; H, 5.51; N, 14.57. Found: C, 50.01; H, 5.56; N, 14.49.

Preparation 2: N-({(5*S*)-3-[3-Fluoro-4-(1-acetylimino-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (**7**)

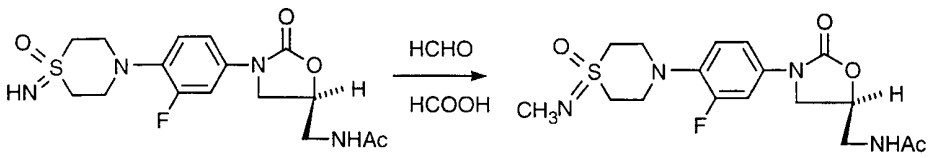


2 **7**

A stirred solution of **2** (100 mg, 0.26 mmol) in acetic acid (1 ml), under nitrogen, is treated with acetic anhydride (55 µL, 0.58 mmol), kept at ambient temperature (24°C) for 66 hours and concentrated *in vacuo*. Chromatography of the residue on silica gel with 3% MeOH-$CHCl_3$ gave the product which is recrystallized from MeOH to give 68 mg of **7**.

mp 219.5-221.0°C; HRMS (FAB) calcd for $C_{18}H_{24}FN_4O_5S$ ($M+H^+$) 427.1451, found 427.1458. Anal. Calcd for $C_{18}H_{23}FN_4O_5S$: C, 50.69; H, 5.44; N, 13.14. Found: 50.64; H, 5.49; N, 13.12.

Preparation 3: N-({(5*S*)-3-[3-Fluoro-4-(1-methylimino-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (**8**)



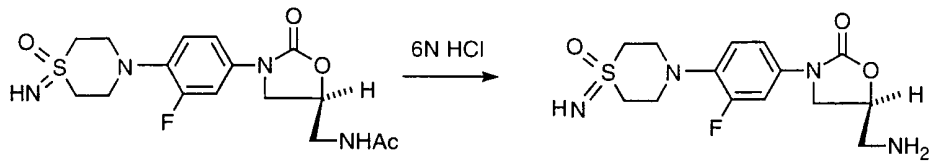
2 **8**

A stirred mixture of **2** (230 mg, 0.60 mmol), 37.5% aqueous formaldehyde (75 µL), 1.0 mmol) and formic acid (75 µL, 2.0 mmol) is warmed at 80°C for 4 hours, treated with additional formaldehyde (75 µL) and formic acid (75 µL) and warmed at 80°C for an additional 4 hours. The cooled mixture is dissolved in $CHCl_3$ and water and treated with 1 N NaOH to pH 10. It is extracted with $CHCl_3$ and the extract is dried (Na_2SO_4) and concentrated. The residue is combined with the crude product from a similar reaction with 53 mg of **2** and chromatographed on silica gel with mixtures of MeOH-$CHCl_3$ containing 2-4% MeOH to give 140 mg of **8**.

HRMS (ESI) calcd for $C_{17}H_{24}FN_4O_4S$ ($M+H^+$) 399.1502, found 399.1498.

Example 1 N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)ethanethioamide (**4**)

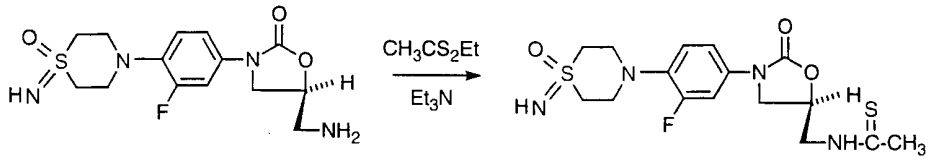
Step 1:



2 **3**

A stirred mixture of **2** (691 mg, 1.80 mmol), MeOH (30 ml) and 6N hydrochloric acid (10 mL) is gently refluxed for 21 hours, cooled and neutralized (pH7) with 1 N NaOH. It is concentrated *in vacuo* and the residue is dissolved in a small amount of water, adjusted to pH 11 with NaOH and extracted with $CHCl_3$ and 5% MeOH-CH_2Cl_2. The extracts are dried (Na_2SO_4) and concentrated to give 535 mg of **3**.

Step 2:

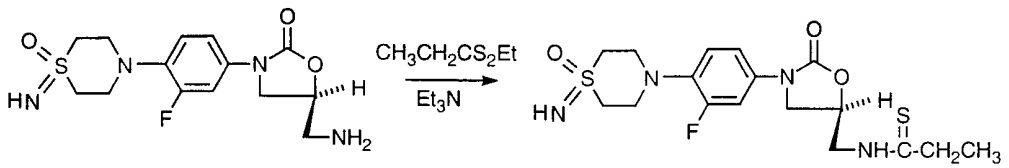


3 4

A stirred solution of **3** (371 mg, 1.08 mmol) in MeOH (10 ml) is treated with triethylamine (302 µL, 2.17 mmol) and ethyl dithioacetate (162 µL, 1.41 mmol) and warmed at 40°C, under nitrogen, for 17 hours. The solid product is chromatographed on silica gel with 2% MeOH-CH_2Cl_2 and the resulting product is crystallized from EtOH-CH_3CN to give 298 mg of **4**.

mp 197-198°C; HRMS (FAB) calcd for $C_{16}H_{22}FN_4O_3S_2$ ($M+H^+$) 401.1117, found 401.1115. Anal. Calcd for $C_{16}H_{21}FN_4O_3S_2$: C, 47.98; H, 5.28; N, 13.99. Found: C, 47.98; H, 5.34; N, 14.01.

Example 2 N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide (**5**)

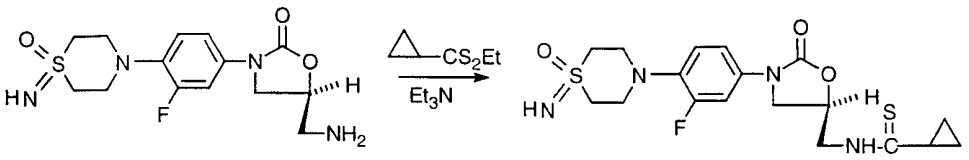


3 5

As described in Example 1, Step 2 the reaction of **3** with ethyl dithiopropionate and triethylamine in methanol gave **5** which is crystallized from MeOH.

mp 189-190°C; HRMS (FAB) calcd for $C_{17}H_{24}FN_4O_3S_2$ ($M+H^+$) 415.1273, found 415.1278. Anal calcd for $C_{17}H_{23}FN_4O_3S_2$: C, 49.26; H, 5.59; N, 13.52. Found: C, 49.89; H, 5.81; N, 13.18.

Example 3 N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)cyclopropanecarbothioamide (**6**)

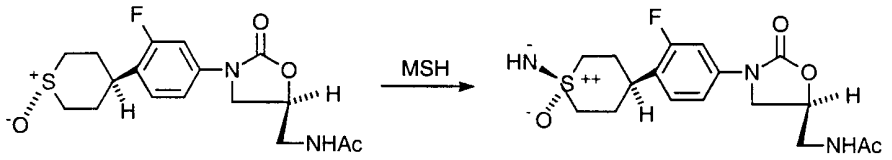


3 6

As described in Example 1, Step 2 the reaction of **3** with ethyl dithiocyclopropane-carboxylate and triethylamine in MeOH gave **6** which is crystallized from MeOH.

mp 209-210°C (dec); HRMS (FAB) calcd for $C_{18}H_{24}FN_4O_3S_2$ ($M+H^+$) 427.1273, found 427.1289. Anal. Calcd for $C_{18}H_{23}FN_4O_3S_2$: C, 50.69; H, 5.43; N, 13.14. Found: C, 50.70; H, 5.50; N, 13.00.

Example 4 N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, E-Isomer (**10**)



9 10

Step 1:

A stirred, ice cold solution of ethyl O-(mesitylenesulfonyl)acetohydroxamate (1.28 g, 4.49 mmol) in dioxane (3 ml), under nitrogen, is treated dropwise during 5 minutes with 70% perchloric acid (0.48 ml, 5.57 mmol) and kept in the ice bath for 4 hours. It is then poured with stirring into ice water (30 ml), stirred for 30 minutes at 0°C and filtered. The solid is ished with cold water and dissolved in a small amount of diethyl ether. The solution is ished with water, dried (K_2CO_3) and the product (O-mesitylenesulfonyl-hydroxylamine, MSH) is crystallized, under nitrogen from cold Et_2O-pentane. A CH_2Cl_2 solution of this product is used in Step 2.

Step 2:

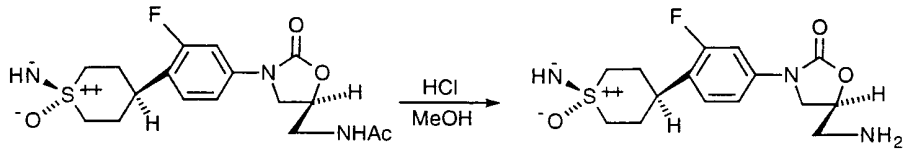
A stirred solution of **9** ((*S*)-*trans*-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (prepared according to the procedure described in WO95/07271, Example 9, Step 1) (470 mg, 1.28 mmol) in CH_2Cl_2 (5 ml) is treated with a CH_2Cl_2 solution of the MSH prepared in Step 1 and kept at ambient temperature (24°C) for 19 hours. It is mixed with water and 5% MeOH-CH_2Cl_2, treated with 1 N NaOH to pH 11 and extracted with 5% MeOH-CH_2Cl_2. The extract is dried

(Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 2.5% MeOH - 0.1% NH_4OH-CH_2Cl_2 gives **10** which can be crystallized from MeOH:

Mp 225-226°C; HRMS (FAB) calcd for $C_{17}H_{23}FN_3O_4S$ ($M+H^+$) 384.1393, found 384.1398. Anal calcd for $C_{17}H_{22}FN_3O_4S$: C, 53.25; H, 5.78; N, 10.96. Found: C, 53.18; H, 5.90; N, 10.79.

Example 5 N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)ethanethioamide, E-Isomer (**12**)

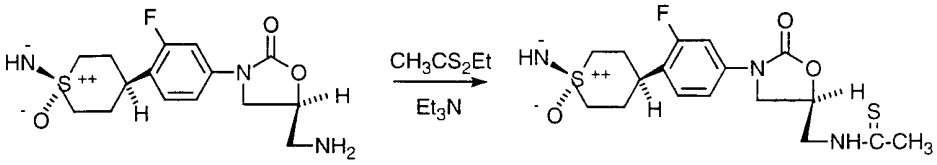
Step 1



10 **11**

A stirred mixture of **10** (586 mg, 1.53 mmol), MeOH (24 ml) and water (4 ml) is treated with concentrated hydrochloric acid (4 ml), refluxed for 22 hours, neutralized with 50% NaOH and concentrated *in vacuo* to remove MeOH. The residue is diluted with brine, treated with 1N NaOH to pH 11 and extracted with 5% MeOH-CH_2Cl_2. The extract is dried (Na_2SO_4) and concentrated to give 464 mg of **11**.

Step 2:

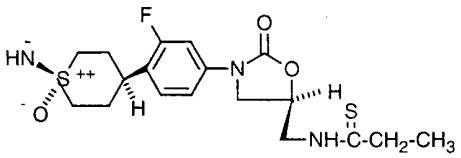


11 **12**

A stirred solution of **11** (159 mg, 0.47 mmol) in MeOH (5 ml) is treated with ethyl dithioacetate (73 µL, 0.64 mmol) and triethylamine (130 µL, 0.93 mmol), kept at about 40°C for 24 hours, cooled and concentrated under a stream of nitrogen. Chromatography of the residue on silica gel first with 2% MeOH - 0.1% Et_3N-$CHCl_3$,and then with 4% EtOH-0.1% Et_3N-$CHCl_3$ and crystallization of the product from acetone give 94 mg of the title compound **12**.

Mp 193-194°C (dec); HRMS (FAB) calcd for $C_{17}H_{23}FN_3O_3S_2$ ($M+H^+$) 400.1165, found 400.1157. Anal calcd for $C_{17}H_{22}FN_3O_3S_2$: C, 51.11; H, 5.55; N, 10.52. Found: C, 51.07; H, 5.61; N, 10.37.

Example 6 N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, E-Isomer (**13**)

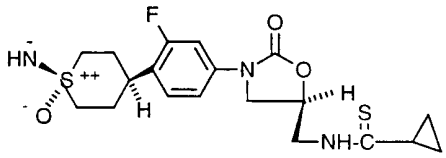


13

As described in Example 5, Step 2 the reaction of **11** with ethyl dithiopropionate and triethylamine in MeOH at 40°C gives **13** which is cyrstallized from acetone.

Mp 191-192 °C (dec); HRMS (FAB) calcd for $C_{18}H_{25}FN_3O_3S_2$: ($M+H^+$) 414.1321, found 414.1329. Anal. Caled for $C_{18}H_{24}FN_3O_3S_2$: C, 52.28; H, 5.85; N, 10.16. Found: C, 52.30; H, 5.90; N, 10.14.

Example 7 N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)cyclopropanecarbothioamide, E-Isomer (**14**)

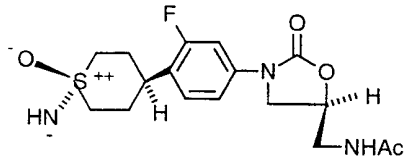


14

As described in Example 5, Step 2 the reaction of **11** with ethyl dithiocyclopropanecarboxylate and triethylamine in MeOH at 40°C gives **14** which is crystallized from acetone-MeOH.

Mp. 210-211 °C (dec); HRMS (FAB) calcd for $C_{19}H_{25}FN_3O_3S_2$: ($M+H^+$) 426.1321, found 426.1309. Anal. Calcd for $C_{19}H_{24}FN_3O_3S_2$: C, 53.63; H, 5.68; N, 9.87. Found: C, 53.68; H, 5.74; N, 9.84.

Example 8 N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, Z-Isomer (**15**)

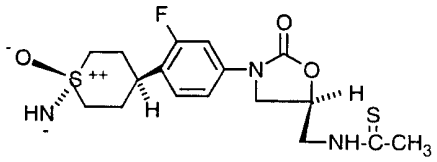


15

As described in Example 4 the reaction of (*S*)-*cis*-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (see WO 98/54161, Example 7, Step 1) with MSH gave **15** which is crystallized from EtOAc.

mp 189.5-190.5°C; HRMS (FAB) calcd for $C_{17}H_{23}FN_3O_4S$ ($M+H^+$) 384.1393, found 384.1389. Anal. Calcd for $C_{17}H_{22}FN_3O_4S$: C, 53.25; H, 5.78; N, 10.96. Found: C, 53.21; H, 5.82; N, 10.88.

Example 9 N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)ethanethioamide, Z-Isomer (**17**)

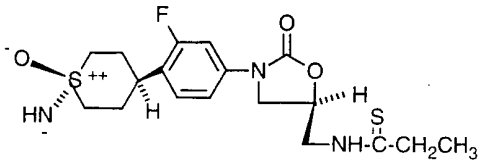


17

As described in Example 5 compound **15** is hydrolyzed with 6N hydrochloric acid in methanol and the resulting amine (**16**) is condensed with ethyl dithioacetate and triethylamine in methanol to give **17** which is crystallized from MeOH.

Mp 206-207°C; HRMS (FAB) calcd for $C_{17}H_{23}FN_3O_3S_2$ ($M+H^+$) 400.1165, found 400.1171. Anal. Calcd for $C_{17}H_{22}FN_3O_3S_2$: C, 51.11; H, 5.55; N, 10.52. Found: C, 51.65; H, 5.77; N, 10.28.

Example 10 N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, Z-Isomer (**18**)

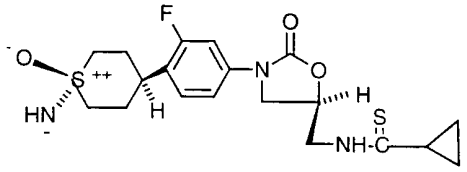


18

As described in Example 9 the amine (**16**) is allowed to react with ethyl dithiopropionate and triethylamine in methanol to give **18** which is recrystallized from methanol.

Mp 211-213°C; HRMS (FAB) calcd for $C_{18}H_{25}FN_3O_3S_2$ ($M+H^+$) 414.1321, found 414.1313. Anal. Calcd for $C_{18}H_{24}FN_3O_3S_2$: C, 52.28; H, 5.85; H, 10.16. Found: C, 52.33; H, 5.95; H, 10.11.

Example 11 N-({(5*S*)-3-[3-Fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)cyclopropanethioamide, Z-Isomer (**19**)

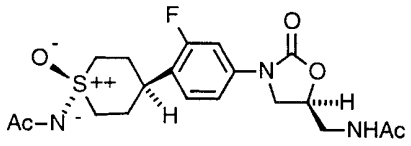


19

As described in Example 9 the amine (**16**) is allowed to react with ethyl dithiocyclopropanecarboxylate and triethylamine in methanol to give **19** which is recrystallized from methanol.

Mp 220-221°C; HRMS (FAB) calcd for $C_{19}H_{25}FN_3O_3S_2$ ($M+H^+$) 426.1321, found 426.1317. Anal. Calcd for $C_{19}H_{24}FN_3O_3S_2 \cdot 0.55$ MeOH: C, 52.99; H, 5.96; N, 9.48. Found: C, 52.50; H, 5.80; N, 9.49.

Example 12. N-({(5*S*)-3-[3-Fluoro-4-[1-(acetylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, *Z*-isomer (**20**).

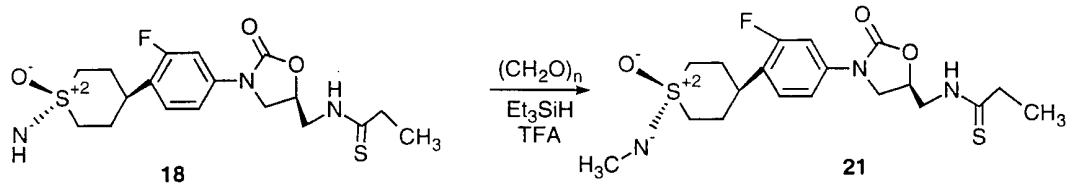


20

As described in Preparation 2, compound **15** (Example 8) is allowed to react with acetic anhydride in acetic acid to give **20** which is recrystallized from CH_2Cl_2-MeOH.

Mp 237.5-239 °C; HRMS(FAB) calcd for $C_{19}H_{25}FN_3O_5S$ ($M+H^+$) 426.1499, found 426.1508. Anal. calcd for $C_{19}H_{24}FN_3O_5S$: C, 53.63; H, 5,68; N, 9.88. Found: C, 53.69; H, 5.74; N, 9.89.

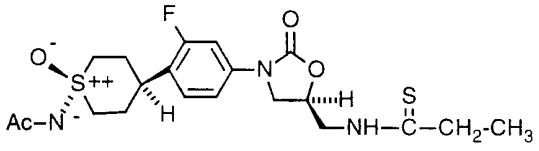
Example 13. N-({(5*S*)-3-[3-Fluoro-4-[1-(methylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer (**21**).



A stirred suspension of **18** (Example 10) (50 mg, 0.12 mmol) and paraformaldehyde (11 mg, 0.37 mmol) in acetonitrile (1 mL) is treated with triethylsilane (60 μL, 0.38 mmol) and trifluoroacetic acid (28 μL, 0.36 mmol) and kept at ambient temperature, under nitrogen, for 5 hours. It is then diluted with water, neutralized to pH 11 and extracted with 5% MeOH-CH_2Cl_2. The extracts are dried (Na_2SO_4) and concentrated. The residue, combined with the product of a second 0.30 mmol reaction, is chromatographed on silica gel with 3% MeOH-$CHCl_3$. Crystallization of the product from MeOH gives 130 mg of **21**.

HRMS(FAB) calcd for $C_{19}H_{27}FN_3O_3S_2$ ($M+H^+$) 428.1478, found 428.1481. Anal. calcd for $C_{19}H_{26}FN_3O_3S_2$: C, 53.37; H, 6.13; N, 9.83. Found: C, 53.34; H, 6.15; N, 9.83.

Example 14. N-({(5*S*)-3-[3-Fluoro-4-[1-(acetylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer (**22**).

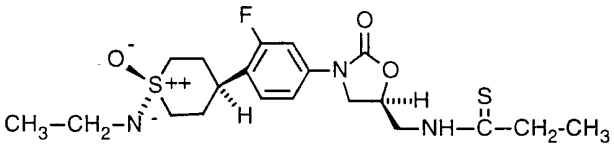


22

As described in Preparation 2, Compound **18** (Example 10) is allowed to react with acetic anhydride in acetic acid to give **22** which is recrystallized from MeOH.

Mp 214.0-214.5 °C (dec), HRMS(FAB) calcd for $C_{20}H_{27}FN_3O_4S_2$ ($M+H^+$) 456.1427, found 456.1430. Anal. calcd for $C_{20}H_{26}FN_3O_4S_2$: C, 52.73; H, 5.75; N, 9.22. Found: C, 52.57; H, 5.76; N, 9.20.

Example 15. N-({(5*S*)-3-[3-Fluoro-4-[1-(ethylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer (**23**).

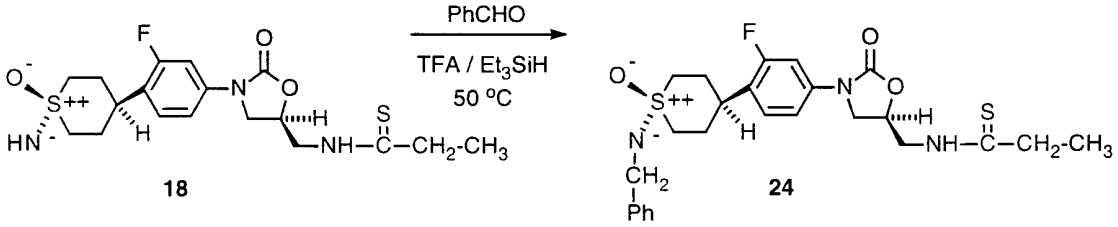


23

Compound **23** is prepared according to the procedure described in Example 13 by substituting acetaldehyde for paraformaldehyde. It is purified by silica gel chromatography with 2% MeOH-$CHCl_3$ and recrystallization from MeOH.

Mp 200-201 °C; HRMS(FAB) calcd for $C_{20}H_{29}FN_3O_3S_2$ ($M+H^+$) 442.1634, found 442.1645.

Example 16. N-({(5*S*)-3-[3-Fluoro-4-[1-[(phenylmethyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer (**24**).

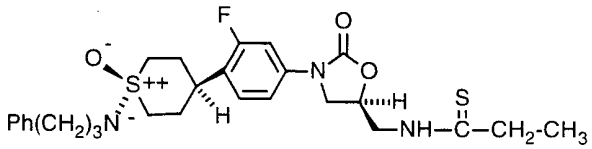


18 **24**

A stirred suspension of **18** (Example 10) (151 mg, 0.37 mmol) in acetonitrile (3 mL) is treated with benzaldehyde (115 µL, 1.13 mmol), trifluoroacetic acid (85 µL, 1.10 mmol) and triethylsilane (175 µL, 1.10 mmol) and kept at 50 °C, under nitrogen, for 20 hours. It is then mixed with water, neutralized to pH 11 and extracted with 5% MeOH-CH_2Cl_2. The extract is dried ($NaSO_4$) and concentrated. Chromatography of the residue on silica gel first with 2% MeOH-$CHCl_3$ and then with 15% acetone-1% MeOH-$CHCl_3$ and crystallization of the resulting product from MeOH gives **24**.

Mp 207-208 °C; HRMS(FAB) calcd for $C_{25}H_{31}FN_3O_3S_2$ ($M+H^+$) 504.1790, found 504.1796. Anal. calcd for $C_{25}H_{30}FN_3O_3S_2$: C, 59.62; H, 6.00; N, 8.34. Found: C, 59.55; H, 6.03; N, 8.33.

Example 17. N-({(5*S*)-3-[3-Fluoro-4-[1-[(3-phenylpropyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer (**25**).

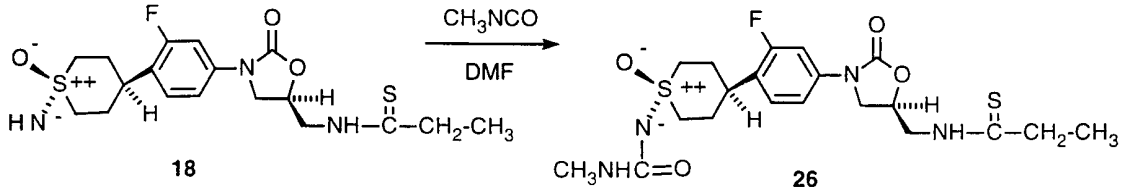


25

Compound **25** is prepared by the procedure described in Example 16 by substituting 3-phenylpropionaldehyde for benzaldehyde.

Mp 165.5-167 °C; HRMS(FAB) calcd for $C_{27}H_{35}FN_3O_3S_2$ ($M+H^+$) 532.2104, found 532.2114. Anal. calcd for $C_{27}H_{34}FN_3O_3S_2$: C, 60.99; H, 6.45; N, 7.90. Found: 60.65; H, 6.53; N, 7.78.

Example 18. N-({(5*S*)-3-[3-Fluoro-4-(1-{[(methylamino)carbonyl]imino}-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer (**26**).

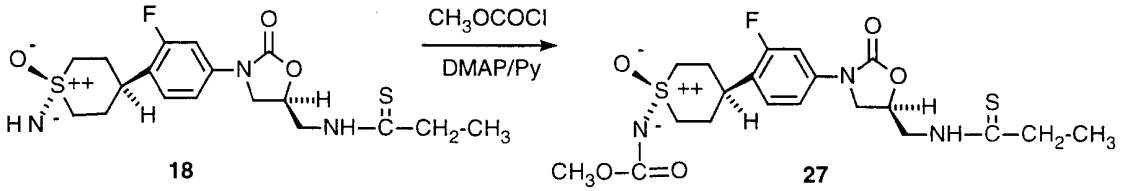


18 **26**

A stirred solution of **18** (Example 10) (152 mg, 0.37 mmol) in dimethylformamide (3 mL), under nitrogen, is treated with methylisocyanate (24 μL, 0.41 mmol) and kept at ambient temperature (24 °C) or 67 hours. It is concentrated *in vacuo* and the residue is chromatographed on silica gel with 30% acetone-1% MeOH-$CHCl_3$. Crystallization of the product from MeOH gives 133 mg of **26**.

Mp 203-204 °C; HRMS(FAB) calcd for $C_{20}H_{28}FN_4O_4S_2$ ($M+H^+$) 471.1536, found 471.1538. Anal. calcd for $C_{20}H_{27}FN_4O_4S_2$: C, 51.05; H, 5.78; N, 11.91. Found: C, 51.01; H, 5.83; N, 11.88.

Example 19. N-({(5*S*)-3-[3-Fluoro-4-(1-[(methoxycarbonyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer (**27**).

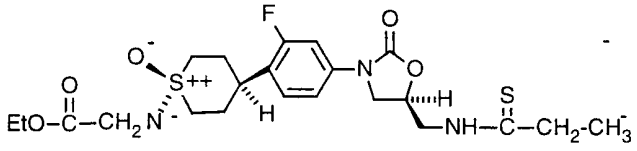


18 27

A stirred solution of **18** (Example 10) (151 mg, 0.365 mmol) and 4-(dimethylamino)pyridine (5.3 mg, 0.043 mol) in pyridine (3 mL), under nitrogen, is treated with methyl chloroformate (56 μL, 0.72 mmol) and kept at ambient temperature (24 °C) for 5 hours. Additional methyl chloroformate (56 μL) is added and the mixture is kept at ambient temperature for 2 hours and concentrated *in vacuo*. Chromatography of the residue on silica gel with 2% MeOH-$CHCl_3$ and crystallization of the product from acetonitrile-MeOH gives 132 mg of **27**.

Mp 217-218 °C; HRMS(FAB) calcd for $C_{20}H_{27}FN_3O_5S_2$ (M+H$^+$) 472.1376, found 472.1385. Anal. calcd for $C_{20}H_{26}FN_3O_5S_2$: C, 50.92; H, 5.56; N, 8.91. Found: C, 51.02; H, 5.59; N, 8.90.

Example 20. N-({(5*S*)-3-[3-Fluoro-4-(1-[[(ethoxycarbonyl)methyl]imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer (**28**).

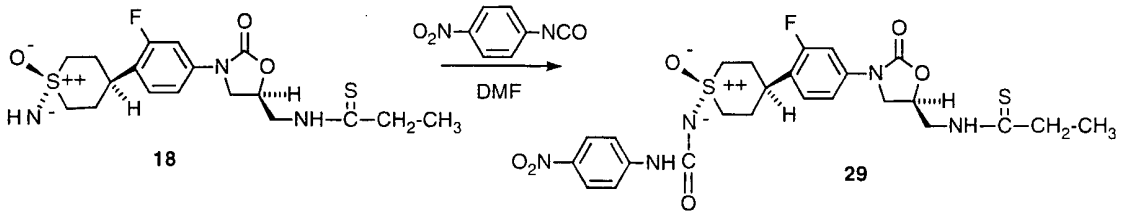


28

Compound **28** is prepared by the procedure described in Example 16 by substituting ethyl glyoxalate for benzaldehyde. It is purified by silica gel chromatography with 20% acetone-1% MeOH-$CHCl_3$ and crystallization from MeOH.

Mp 183.5-184.5 °C; HRMS(FAB) calcd for $C_{22}H_{31}FN_3O_5S_2$ (M+H$^+$) 500.1689, found 500.1699. Anal. calcd for $C_{20}H_{30}FN_3O_5S_2$: C, 52.89; H, 6.05; N, 8.41. Found: C, 52.76; H, 6.04; N, 8.39.

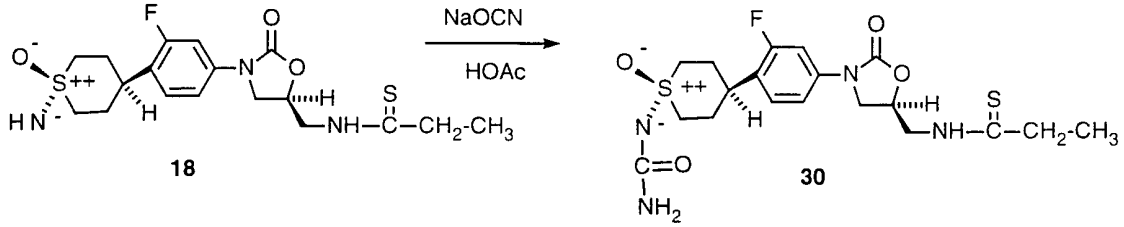
Example 21. N-({(5*S*)-3-[3-Fluoro-4-(1-{[[(4-nitrophenyl)amino]carbonyl]imino}-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer (**29**).



A stirred mixture of **18** (Example 10) (151 mg, 0.37 mmol), 4-nitrophenylisocyanate (79 mg, 0.48 mmol) and dimethylformamide (3 mL) is kept, under nitrogen, for 18 hours and concentrated *in vacuo*. Chromatography of the residue on silica gel first with 4% MeOH-$CHCl_3$ and then with 12.5% acetone-1% MeOH-$CHCl_3$ gives the product which is triturated with MeOH-CH_2Cl_2 to give 166 mg of **29**.

Mp 222-228 °C; HRMS(FAB) calcd for $C_{25}H_{29}FN_5O_6S_2$ ($M+H^+$) 578.1543, found 578.1534. Anal. calcd for $C_{25}H_{28}FN_5O_6S_2$; C, 51.98; H, 4.89; N, 12.12. Found: C, 51.83; H, 4.91; N, 12.01.

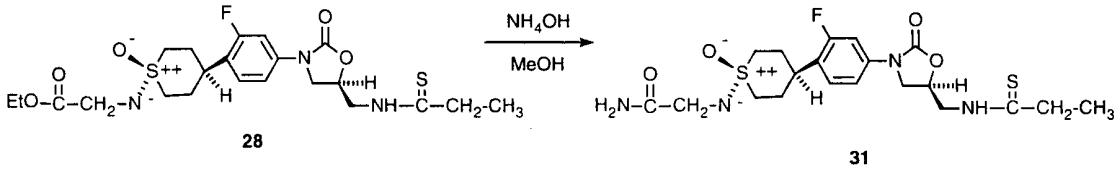
Example 22. N-({(5*S*)-3-[3-Fluoro-4-[1-[(aminocarbonyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer (**30**).



A stirred solution of **18** (Example 10) (151 mg, 0.365 mmol) in acetic acid (5 mL) is treated with sodium isocyanate (245 mg, 3.77 mmol) and kept, under nitrogen, at ambient temperature for 19 hours. It is then concentrated *in vacuo*. A mixture of the residue in water and 5% MeOH-CH_2Cl_2 is neutralized to pH5 with 1N NaOH and then concentrated *in vacuo*. A mixture of the residue, MeOH and silica gel is concentrated and the residue is extracted with 5% MeOH-$CHCl_3$. The extract is concentrated and the residue is chromatographed on silica gel first with 5% MeOH-$CHCl_3$ and then with 4% MeOH-$CHCl_3$. Crystallization of the product from MeOH-$CHCl_3$ gives 50 mg of **30**.

Mp 236-238 °C (dec); HRMS(FAB) calcd for $C_{19}H_{26}FN_4O_4S_2$ ($M+H^+$) 457.1379, found 457, 1382. Anal. calcd for $C_{19}H_{25}FN_4O_4S_2$: C, 49.98; H, 5.52; N, 12.27. Found: C, 49.65; H, 5.61; N, 12.05.

Example 23. N-({(5*S*)-3-[3-Fluoro-4-[1-[[(aminocarbonyl)methyl]imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer (**31**).

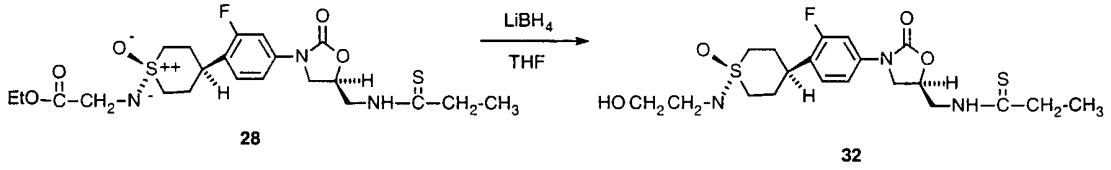


28 31

A stirred suspension of **28** (Example 20) (161 mg, 0.322 mmol) in MeOH (13 mL) is treated with 28% ammonium hydroxide (3.2 mL), kept at ambient temperature for 65 hours and concentrated *in vacuo*. Chromatography of the residue on silica gel with 6% MeOH-$CHCl_3$ and crystallization of the product from MeOH gives 98 mg of **31**.

Mp 221-222 °C; HRMS(FAB) calcd for $C_{20}H_{28}FN_4O_4S_2$ ($M+H^+$) 471.1536, found 471.1540. Anal. calcd for $C_{20}H_{27}FN_4O_4S_2$: C, 51.05; H, 5.78; N, 11.91. Found: C, 51.02; H, 5.80; N, 11.90.

Example 24. N-({(5*S*)-3-[3-Fluoro-4-[1-[(2-hydroxyethyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer (**32**).

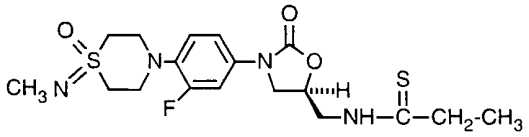


28 32

A stirred solution of **28** (Example 20) (240 mg, 0.48 mmol) in THF (5 mL) is treated with a 2.0 M solution of lithium borohydride in THF (0.24 mL, 0.48 mmol) and kept, under nitrogen, at ambient temperature for 4 hours. It is then mixed with a little water, treated, dropwise with enough 10% aqueous $NaHSO_4$ to give pH 2, stirred for 5 minutes and poured into saturated aqueous $NaHCO_3$. The pH is raised to 10 with 1N NaOH and the mixture is extracted with 5% MeOH-CH_2Cl_2. The extract is dried ($NaSO_4$) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-CH_2Cl_2 and crystallization of the product from MeOH gives 73 mg of **32**.

Mp 180-181 °C (dec); HRMS(FAB) calcd for $C_{20}H_{29}FN_3O_4S_2$ ($M+H^+$) 458.1583, found 458.1580. Anal. calcd for $C_{20}H_{28}FN_3O_4S_2$: C, 52.50; H, 6.17; N, 9.18. Found: C, 52.64; H, 6.34, N, 8.98.

Example 25. N-[((5*S*)-3-{3-Fluoro-4-[1-(methylimino)-1-oxido-1λ^4,4-thiazinan-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide (**33**).

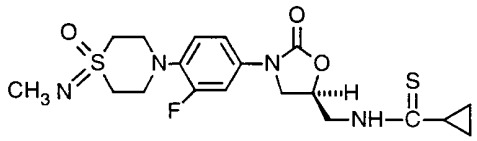


33

Compound **33** is prepared by the procedure described in Example 13 by substituting compound **5** (Example 2) for compound **18**. It is purified by silica gel chromatography first with 20% acetone-1% MeOH-$CHCl_3$ and then with 4% MeOH-$CHCl_3$.

HRMS(FAB) calcd for $C_{18}H_{26}FN_4O_3S_2$ ($M+H^+$) 429.1430, found 429.1436.

Example 26. N-[((5*S*)-3-{3-Fluoro-4-[1-(methylimino)-1-oxido-1λ^4,4-thiazinan-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarbothioamide (**34**).

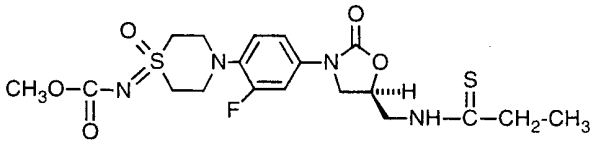


34

Compound **34** is prepared by the procedure described in Example 13 by substituting compound **6** (Example 3) for compound **18**. It is purified by silica gel chromatography with 3% MeOH-CH_2Cl_2.

HRMS(FAB) calcd for $C_{19}H_{26}FN_4O_3S_2$ ($M+H^+$) 441.1430, found 441.1425. Anal. calcd for $C_{19}H_{25}FN_4O_3S_2$: C, 51.80, H, 5.72; N, 12.72. Found: C, 51.60; H, 6.03; N, 12.34.

Example 27. N-[((5*S*)-3-{3-Fluoro-4-(1-[(methoxycarbonyl)imino]-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide (**35**).

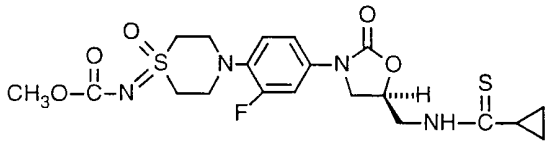


35

Compound **35** is prepared by the procedure described in Example 19 by substituting compound **5** (Example 2) for compound **18**. It is purified by silica gel chromatography with 3% MeOH-$CHCl_3$ and crystallization from acetonitrile-MeOH.

Mp 211-212 °C (dec); HRMS(FAB) calcd for $C_{19}H_{26}FN_4O_5S_2$ ($M+H^+$) 473.1328, found 473.1329. Anal. calcd for $C_{19}H_{25}FN_4O_5S_2$: C, 48.29; H, 5.33; N, 11.86. Found: C, 48.34; H, 5.41; N, 11.87.

Example 28. N-[((5*S*)-3-{3-Fluoro-4-(1-[(methoxycarbonyl)imino]-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarbothioamide (**36**).

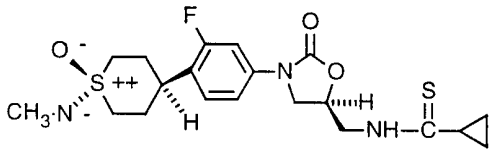


36

Compound **36** is prepared by the procedure described in Example 19 by substituting compound **6** (Example 3) for compound **18**. It is purified by silica gel chromatography first with 2.5% MeOH-$CHCl_3$ and then with 10% acetone-$CHCl_3$ and crystallization from acetonitrile-MeOH.

Mp 208-209 °C (dec). Anal. calcd for $C_{20}H_{25}FN_4O_5S_2$; C, 49.57; H, 5.20; N, 11.56. Found: C, 49.55; H, 5.22; N, 11.58.

Example 29. N-({(5*S*)-3-[3-Fluoro-4-[1-(methylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)cyclopropanecarbothioamide, *Z*-isomer (**37**).

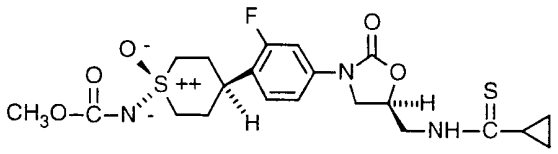


37

Compound **37** is prepared by the procedure described in Example 13 by substituting compound **19** (Example 11) for compound **18**. It is purified by crystallization from MeOH-CH_2Cl_2.

Mp 201-202 °C (dec); HRMS(FAB) calcd for $C_{20}H_{27}FN_3O_3S_2$ ($M+H^+$) 440.1478, found 440.1475. Anal. calcd for $C_{20}H_{26}FN_3O_3S_2$: C, 54.65; H, 5.96; N, 9.56. Found: C, 54.12; H, 6.16; N, 9.44.

Example 30. N-[((5*S*)-3-{3-Fluoro-4-[1-[(methoxycarbonyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarbothioamide, *Z*-isomer (**38**).

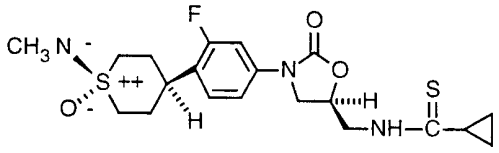


38

Compound **38** is prepared according to the procedure described in Example 19 by substituting compound **19** (Example 11) for compound **18**. It is purified by silica gel chromatography with 7.5% acetone-1% MeOH-$CHCl_3$ and crystallization from MeOH-CH_2Cl_2.

Mp 219-220 °C (dec); HRMS(FAB) calcd for $C_{21}H_{27}FN_3O_5S_2$ ($M+H^+$) 484.1376, found 484.1389. Anal. calcd for $C_{21}H_{26}FN_3O_5S_2$: C, 52.16; H, 5.42; N, 8.69. Found: C, 52.35; H, 5.50; N, 8.58.

Example 31. N-[((5*S*)-3-{3-Fluoro-4-[1-(methylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarbothioamide, *E*-isomer (**39**).

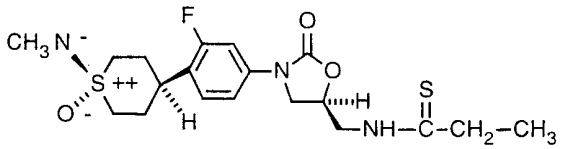


39

Compound **39** is prepared by the procedure described in Example 13 by substituting compound **14** (Example 7) for compound **18**. It is purified by silica gel chromatography first with 3% MeOH-$CHCl_3$ and then with 1% MeOH-EtOAc.

HRMS(FAB) calcd for $C_{20}H_{27}FN_3O_3S_2$ ($M+H^+$) 440.1478, found 440.1473.

Example 32. N-[((5*S*)-3-{3-Fluoro-4-[1-(methylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide, *E*-isomer (**40**).

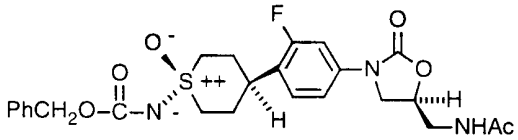


40

Compound **40** is prepared by the procedure described in Example 13 by substituting compound **13** (Example 6) for compound **18**. It is purified by silica gel chromatography with 1% MeOH-EtOAc.

HRMS(FAB) calcd for $C_{19}H_{27}FN_3O_3S_2$ ($M+H^+$) 428.1478, found 428.1484.

Example 33. N-[((5*S*)-3-{3-Fluoro-4-[1-[[(phenylmethoxy)carbnonyl]imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide, *Z*-isomer (**41**).

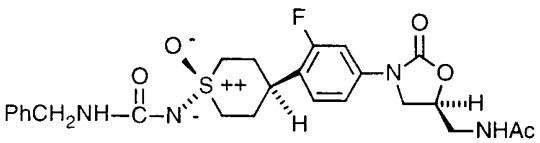


41

Compound **41** is prepared according to the procedure described in Example 19 by substituting compound **15** (Example 8) for compound **18** and benzyl chloroformate for methyl chloroformate. It is purified by silica gel chromatography with 3% MeOH-$CHCl_3$ and recrystallization from MeOH.

Mp 213-214 °C (dec); HRMS(FAB) calcd for $C_{25}H_{29}FN_3O_6S$ ($M+H^+$) 518.1761, found 518.1763. Anal. calcd for $C_{25}H_{28}FN_3O_6S$: C, 58.01; H, 5.45; N, 8.12. Found: C, 57.91; H, 5.63; N, 8.11.

Example 34. N-({(5*S*)-3-[3-Fluoro-4-(1-{[(benzylamino)carbonyl]imino}-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, *Z*-isomer (**42**).



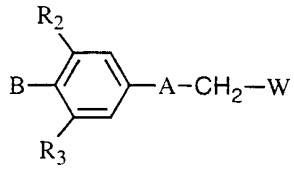
42

Compound **42** is prepared according to the procedure described in Example 18 by substituting compound **15** (Example 8) for compound **18** and benzylisocyanate for methylisocyanate. It is purified by crystallization from MeOH.

Mp 238.5-239.5 °C (dec); HRMS(FAB) calcd for $C_{25}H_{30}FN_4O_5S$ ($M+H^+$) 517.1921, found 517.1927. Anal. calcd for $C_{25}H_{29}FN_4O_5S$: C, 58.13; H, 5.66; N, 10.85. Found: C, 57.96; H, 5.80; N, 10.90.

CLAIMS

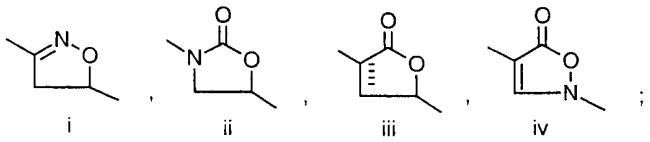
1. A compound of formula I



I

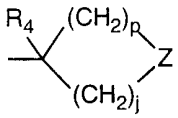
or a pharmaceutically acceptable salt thereof wherein:

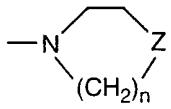
A is a structure i, ii, iii, or iv

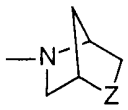


i , ii , iii , iv ;

B is

(a)  ,

(b)  , or

(c)  ;

W is NHC(=X)R_1, or -Y-het; povided that when A is a structure iv, W is not –Y-het;

X is O, or S; provided that when X is O, B is not the subsection (b).

Y is NH, O, or S;

Z is S(=O)(=N-R_5);

R_1 is

(a) H,

(b) NH_2,

(c) NHC_{1-4}alkyl,

(D) C_{1-4}alkyl,

(e) C_{2-4}alkenyl,

(f) OC_{1-4}alkyl,

(g) SC_{1-4}alkyl, or

(h) $(CH_2)_p C_{3-6}$cycloalkyl;

at each occurrence, alkyl or cycloalkyl in R_1 is optionally substituted with one or more F, Cl or CN;

R_2 and R_3 are independently H, F, Cl, methyl or ethyl;

R_4 is H, CH_3, or F;

R_5 is

(a) H,

(b) C_{1-4}alkyl,

(c) $C(=O)C_{1-4}$alkyl,

(d) $C(=O)OC_{1-4}$alkyl,

(e) $C(=O)NHR_6$, or

(f) $C(=S)NHR_6$;

R_6 is H, C_{1-4}alkyl, or phenyl;

at each occurrence, alkyl in R_5 and R_6 is optionally substituted with one or more halo, CN, NO_2, phenyl, C_{3-6} cycloalkyl, OR_7, $C(=O)R^7$, $OC(=O)R_7$, $C(=O)OR_7$, $S(=O)_mR_7$, $S(=O)_mNR_7R_7$, $NR_7SO_2R_7$, $NR_7SO_2NR_7R_7$, $NR_7C(=O)R_7$, $C(=O)NR_7R_7$, NR_7R_7, oxo, or oxime;

R_7 is H, C_{1-4}alkyl, or phenyl;

at each occurrence, phenyl is optionally substituted with one or more halo, CN, NO_2, phenyl, C_{3-6} cycloalkyl, OR_7, $C(=O)R^7$, $OC(=O)R_7$, $C(=O)OR_7$, $S(=O)_mR_7$, $S(=O)_mNR_7R_7$, $NR_7SO_2R_7$, $NR_7SO_2NR_7R_7$, $NR_7C(=O)R_7$, $C(=O)NR_7R_7$, or NR_7R_7;

het is a C-linked five- (5) membered heteroaryl ring having 1-4 heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen, or het is a C-linked six (6) membered heteroaryl ring having 1-3 nitrogen atoms;

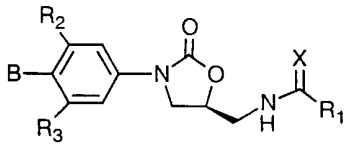
p is 0, 1, or 2;

j is 1, 2, 3, 4, or 5; provided that k and j taken together are 2, 3, 4 or 5;

m is 0, 1, or 2;

n is 2 or 3; and ----- in structure iii is either a double bond or a single bond.

2. A compound of formula I which is a compound of formula IA:



IA.

3. A compound of claim 2 wherein R_1 is C_{1-4}alkyl.

4. A compound of claim 2 wherein R_1 is ethyl.

5. A compound of claim 2 wherein R_1 is methyl.

6. A compound of claim 2 wherein R_1 is C_{3-6}cycloalkyl.

7. A compound of claim 2 wherein R_1 is cyclopropyl.

8. A compound of claim 2-7 wherein X is sulfur atom.

9. A compound of claim 2-7 wherein X oxygen atom.

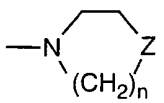
10. A compound of claim 8 wherein one of R_2 and R_3 is H, the other one is F.

11. A compound of claim 9 wherein one of R_2 and R_3 is H, the other one is F.

12. A compound of claim 8 wherein R_4 is H.

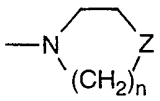
13. A compound of claim 9 wherein R_4 is H.

14. A compound of claim 8 wherein structure B is



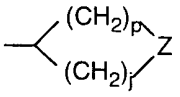
wherein Z is $S(=O)(=NR_5)$.

15. A compound of claim 9 wherein structure B is



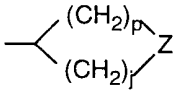
wherein Z is $S(=O)(=NR_5)$.

16. A compound of claim 8 wherein structure B is



wherein Z is $S(=O)(=NR_5)$

17. A compound of claim 8 wherein structure B is



wherein Z is $S(=O)(=NR_5)$.

18. A compound of claim 15-18 wherein R_5 is H.

19. A compound of claim 15-18 wherein R_5 is C_{1-4}alkyl, optionally substituted with OH; or C_{1-4}alkyl substituted with $C(=O)NHC_{1-4}$alkyl, $C(=O)NH_2$ or phenyl; wherein the phenyl is optionally substituted with OH, methyl, NO_2, CF_3, or CN.

20. A compound of claim 20 wherein R_5 is CH_3, or ethyl.

21. A compound of claim 20 wherein R_5 is C_{1-4}alkyl substituted with phenyl wherein the phenyl is optionally substituted with NO_2.

22. A compound of claim 15-18 wherein R_5 is $C(=O)C_{1-4}$alkyl, $C(=O)OC_{1-4}$alkyl, $C(=O)NH_2$, or $C(=O)NHC_{1-4}$alkyl.

23. A compound of claim 23 wherein R_5 is $C(=O)NHCH_3$, or $C(=O)NHCH_2CH_3$.

24. A compound of claim 15-18 wherein R_5 is $C(=O)CH_3$.

25. A compound of claim 15-18 wherein R_5 is $C(=O)OCH_3$.

26. A compound of claim 2 which is

(1) N-({(5*S*)-3-[3-fluoro-4-(1-imino-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)ethanethioamide;

(2) N-({(5*S*)-3-[3-fluoro-4-(1-imino-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide;

(3) N-({(5*S*)-3-[3-fluoro-4-(1-imino-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)cyclopropanecarbothioamide;

(4) N-({(5*S*)-3-[3-fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (E)-isomer;

(5) N-({(5*S*)-3-[3-fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)ethanethioamide (E)-isomer;

(6) N-({(5*S*)-3-[3-fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide (E)-isomer;

(7) N-({(5*S*)-3-[3-fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)cyclopropanecarbothioamide (E)-isomer;

(8) N-({(5*S*)-3-[3-fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide (Z)-isomer;

(9) N-({(5*S*)-3-[3-fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)ethanethioamide (Z)-isomer;

(10) N-({(5*S*)-3-[3-fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide (Z)-isomer;

(11) N-({(5*S*)-3-[3-fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)cyclopropanethioamide (Z)-isomer;

(12) N-({(5*S*)-3-[3-fluoro-4-[1-(acetylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, *Z*-isomer;

(13) N-({(5*S*)-3-[3-fluoro-4-[1-(methylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(14) N-({(5*S*)-3-[3-fluoro-4-[1-(acetylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(15) N-({(5*S*)-3-[3-fluoro-4-[1-(ethylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(16) N-({(5*S*)-3-[3-fluoro-4-[1-[(phenylmethyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(17) N-({(5*S*)-3-[3-fluoro-4-[1-[(3-phenylpropyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(18) N-({(5*S*)-3-[3-fluoro-4-(1-{[(methylamino)carbonyl]imino}-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(19) N-({(5*S*)-3-[3-fluoro-4-(1-[(methoxycarbonyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(20) N-({(5*S*)-3-[3-fluoro-4-(1-[[(ethoxycarbonyl)methyl]imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(21) N-({(5*S*)-3-[3-fluoro-4-(1-{[[(4-nitrophenyl)amino]carbonyl]imino}-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer ;

(22) N-({(5*S*)-3-[3-fluoro-4-[1-[(aminocarbonyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(23) N-({(5*S*)-3-[3-fluoro-4-[1-[[(aminocarbonyl)methyl]imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(24) N-({(5*S*)-3-[3-fluoro-4-[1-[(2-hydroxyethyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(25) N-[((5*S*)-3-{3-fluoro-4-[1-(methylimino)-1-oxido-1λ^4, 4-thiazinan-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide;

(26) N-[((5*S*)-3-{3-fluoro-4-[1-(methylimino)-1-oxido-1λ^4, 4-thiazinan-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarbothioamide;

(27) N-[((5*S*)-3-{3-fluoro-4-(1-[(methoxycarbonyl)imino]-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide;

(28) N-[((5*S*)-3-{3-fluoro-4-(1-[(methoxycarbonyl)imino]-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarbothioamide ;

(29) N-({(5*S*)-3-[3-fluoro-4-[1-(methylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)cyclopropanecarbothioamide, *Z*-isomer;

(30) N-[((5*S*)-3-{3-fluoro-4-[1-[(methoxycarbonyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarbothioamide, *Z*-isomer;

(31) N-[((5*S*)-3-{3-fluoro-4-[1-(methylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarbothioamide, *E*-isomer;

(32) N-[((5*S*)-3-{3-fluoro-4-[1-(methylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide, *E*-isomer;

(33) N-[((5*S*)-3-{3-fluoro-4-[1-[[(phenylmethoxy)carbnonyl]imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide, *Z*-isomer; or

(34) N-({(5*S*)-3-[3-Fluoro-4-(1-{[(benzylamino)carbonyl]imino}-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, *Z*-isomer.

27. A compound of claim 2 which is

(1) N-({(5*S*)-3-[3-fluoro-4-(1-imino-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)ethanethioamide;

(2) N-({(5*S*)-3-[3-fluoro-4-(1-imino-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide;

(3) N-({(5*S*)-3-[3-fluoro-4-(1-imino-1-oxido-1λ^4, 4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)cyclopropanecarbothioamide;

(4) N-({(5*S*)-3-[3-fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)ethanethioamide (Z)-isomer;

(5) N-({(5*S*)-3-[3-fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide (Z)-isomer; or

(6) N-({(5*S*)-3-[3-fluoro-4-(1-imino-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)cyclopropanethioamide (Z)-isomer.

28. A compound of claim 2 which is

(1) N-({(5*S*)-3-[3-fluoro-4-[1-(methylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(2) N-({(5*S*)-3-[3-fluoro-4-[1-(acetylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(3) N-({(5*S*)-3-[3-fluoro-4-(1-[(methoxycarbonyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(4) N-({(5*S*)-3-[3-Fluoro-4-(1-{[[(4-nitrophenyl)amino]carbonyl]imino}-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer ;

(5) N-({(5*S*)-3-[3-fluoro-4-[1-(methylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)cyclopropanecarbothioamide, *Z*-isomer; or

(6) N-[((5*S*)-3-{3-fluoro-4-[1-[(methoxycarbonyl)imino]-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarbothioamide, *Z*-isomer.

29. A compund of claim 2 which is

(1) N-({(5*S*)-3-[3-Fluoro-4-[1-(methylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(2) N-({(5*S*)-3-[3-Fluoro-4-[1-(ethylimino)-1-oxidohexahydro-1λ^4-thiopyran-4-yl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(3) N-({(5*S*)-3-[3-Fluoro-4-(1-{[(methylamino)carbonyl]imino}-1-oxidohexahydro-1λ^4-thiopyran-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide, *Z*-isomer;

(4) N-[((5*S*)-3-{3-Fluoro-4-[1-(methylimino)-1-oxido-1λ^4,4-thiazinan-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide; or

(5) N-[((5*S*)-3-{3-Fluoro-4-[1-(methylimino)-1-oxido-1λ^4,4-thiazinan-4-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]cyclopropanecarbothioamide.

30. Use of a compound of formula I, as shown in Claim 1, for the manufacturing of medicinals for the treatment of microbial infections.

31. The use of claim 30 wherein said compound of formula I is administered orally, parenterally, transdermally, or topically in a pharmaceutical composition.

32. The use of claim 30 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.

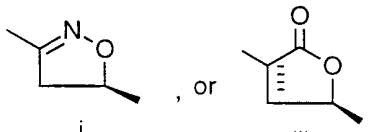
33. The use of claim 30 wherein said compound is administered in an amount of from about 1 to about 50 mg/kg of body weight/day.

34. A use for treating microbial infections of claim 30 wherein the infection is skin infection.

35. A use for treating microbial infections of claim 30 wherein the infection is eye infection.

36. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

37. A compound of claim 1 wherein structure i, or iii is



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INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 00/32451

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/10 C07D413/10

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)
IPC 7 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, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 54161 A (HESTER JACKSON B JR ;NIDY ELDON GEORGE (US); PERRICONE SALVATORE C) 3 December 1998 (1998-12-03) cited in the application the whole document	1-37
Y	WO 95 07271 A (UPJOHN CO ;BARBACHYN MICHAEL R (US); BRICKNER STEVEN J (US); HUTCH) 16 March 1995 (1995-03-16) cited in the application the whole document; in particular, page 30, claim 1 and page 29, chart 2, the compound with the formula 14	1-37

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"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
29 March 2001	16/05/2001

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	Fink, D

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. onal Application No
PCT/US 00/32451

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