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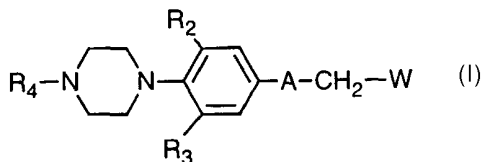
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WO 01/58885 A1

(54) Title: OXAZOLIDINONE THIOAMIDES WITH PIPERAZINE AMIDE SUBSTITUENTS



(57) Abstract: The present invention provides a compound of formula (I) which has potent activities against gram-positive and gram-negative bacteria.

OXAZOLIDINONE THIOAMIDES WITH PIPERAZINE AMIDE SUBSTITUENTS

FIELD OF THE INVENTION

The present invention relates to novel oxazolidinone thioamides which have new
5 piperazine amide substituents; 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
10 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 demonstrate an activity at a useful level
15 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 oxazolidinone thioamides of
20 the present invention increase the spectrum of activity to include gram-negative organisms
such as *Haemophilus influenza* and *Moraxella catarrhalis*.

INFORMATION DISCLOSURE

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

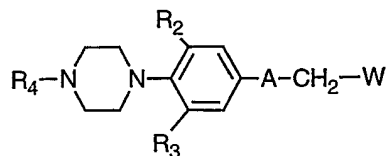
PCT International Publication WO 93/23384 discloses oxazolidinones containing a
substituted diazine moiety and their use as antimicrobials.

PCT International Publication WO 95/07271 discloses substituted oxazine and
thiazine oxazolidinones and their use as antimicrobials.

30 PCT International Publication WO 99/12914 discloses antimicrobial thiourea
derivatives.

SUMMARY OF THE INVENTION

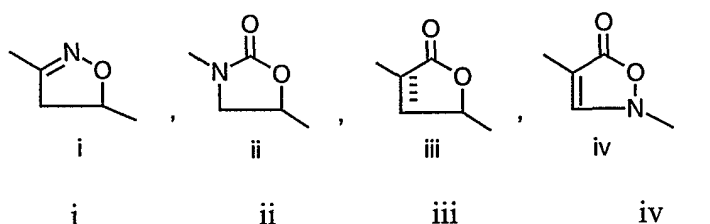
The present invention provides a compound of formula I



I

5 or a pharmaceutically acceptable salt thereof wherein:

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



W is $\text{NHC}(=\text{S})\text{R}_1$, or $-\text{Y-het}$; provided that when A is a structure iv, W is not $-\text{Y-het}$;

10 Y is NH, O, or S;

R^1 is H, NH_2 , NHC_{1-4} alkyl, C_{1-4} alkenyl, OC_{1-4} alkyl, or SC_{1-4} alkyl,

$(\text{CH}_2)_n\text{-C}_{3-6}$ cycloalkyl, or C_{1-4} alkyl, optionally substituted with 1-3 F, 1-2 Cl or CN;

R_2 and R_3 are independently H, F, Cl or C_{1-2} alkyl;

R_4 is

- 15 (a) $-\text{C}(=\text{O})\text{-CR}_5\text{R}_6\text{-O-R}_7$,
- (b) $-\text{C}(=\text{O})\text{-CH}_2\text{S}(\text{O})_n\text{-CH}_3$,
- (c) $-\text{C}(=\text{O})\text{-CH}_2\text{-S}(=\text{O})(=\text{NR}_8)\text{CH}_3$,
- (d) $-\text{C}(=\text{S})\text{-R}_9$,
- (e) $-\text{C}(=\text{O})\text{-CH}_2\text{-O-R}_{10}$,
- 20 (f) $-\text{C}(=\text{O})\text{-(CH}_2)_m\text{-C}(=\text{O})\text{-CH}_3$,
- (g) $-\text{C}(=\text{O})\text{-(CH}_2\text{OH})_2\text{-CH}_3$,
- (h) $-\text{C}(=\text{O})\text{-CH}_2\text{-CH}_2\text{-OR}_{14}$, or
- (i) $-\text{CN}$;

R_5 is H;

25 R_6 is phenyl, benzyl, CH_2OH or CH_2OCH_3 ;

or R_5 and R_6 taken together form C_{3-5} cycloalkyl;

R_7 is H, CH_3 or C_{1-4} alkanoyl;

- R₈ is H, C₁₋₄ alkyl, C₁₋₄ alkanoyl, -C(=O)NH-C₁₋₄ alkyl or -CO₂C₁₋₄ alkyl;
R₉ is C₁₋₄ alkyl, CH₂OR₁₁, S-C₁₋₄ alkyl, OC₁₋₄ alkyl, or NR₁₂R₁₃;
R₁₀ is phenyl, -CO₂-(CH₂)₂-OCH₃, -P(=O)(OH)₂, -C(=O)-NR₁₂R₁₃, or
-C(=O)-(CH₂)₂-CO₂H;
- 5 R₁₁ is H, phenyl, benzyl, CH₃ or C(=O)CH₃;
R₁₂ and R₁₃ are independently H or C₁₋₃ alkyl; or R₁₂ and R₁₃ taken together form a 5- or 6-
membered saturated heterocycle, wherein said saturated heterocycle may further contain
one or two additional hetero-atoms selected from a group consisting of O, S(O)_n or NR₇;
R₁₄ is H, CH₃ or benzyl;
- 10 n is 0, 1 or 2; and m is 0 or 1.

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,

15 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.

20 The invention may also contain 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.

25 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,
30 i.e., the prefix C_{i-j} indicates a moiety of the integer "i" to the integer "j" carbon atoms,
inclusive. Thus, for example, C₁₋₇ alkyl refers to alkyl of one to seven carbon atoms,
inclusive.

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).

5 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.

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

A specific value for R₁ is C₁₋₄ alkyl.

10 A specific value for R₁ is ethyl.

A specific value for R₂ and R₃ are independently H or F.

A specific value for R₂ is H.

A specific value for R₃ is F.

A specific value for R₄ is C(=O)-CH(CH₂-phenyl)(OH).

15 A specific value for R₄ is C(=O)-CH₂-SO₂-CH₃.

A specific value for R₄ is C(=O)-CH(OH)(CH₂OH).

A specific value for R₄ is C(=O)-C(=O)-CH₃.

A specific value for R₄ is C(=O)-CH(OH)(CH₂-O-CH₃).

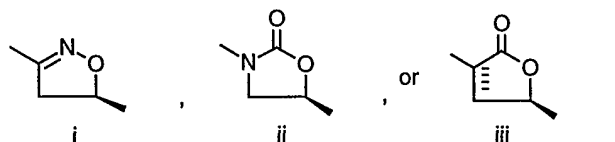
A specific value for R₄ is C(=O)-CH₂CH₂-OH.

20 A specific value for R₄ is C(=O)-CH₂-O-CO₂-(CH₂)₂-OCH₃.

A specific value for R₄ is C(=S)-CH₃.

A specific value for R₄ is CN.

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



25

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 may have additional chiral centers and be isolated in optically active or racemic form. The present invention encompasses any racemic, optically-active, tautomeric, or stereoisomeric form, or mixture thereof, of a compound of the invention.

30

A more preferred compounds of the present invention is wherein A is structure ii that is optically pure enantiomer with the (S)-configuration at C5 of the oxazolidinone ring.

Examples of the present invention are:

- (1) N{[(5S)-3-(3-fluoro-4-{4-[2-(methylsulfinyl)acetyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}propanethioamide,
- (2) N-[[[(5S)-3-(3-fluoro-4-{4-[2-(methylsulfanyl)acetyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}propanethioamide,
- (3) N-[[[(5S)-3-(3-fluoro-4-{4-[2-(methylsulfonyl)acetyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}propanethioamide,
- (4) N-((5S)-3-[4-(4-ethanethioly-1-piperazinyl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl}propanethioamide,
- (5) N-((5S)-3-[4-(4-cyano-1-piperazinyl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl}propanethioamide,
- (6) N-((5S)-3-(3-fluoro-4-{4-[2-(methylaminocarbonyloxy)acetyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl}propanethioamide,
- (7) N-((5S)-3-(3-fluoro-4-{4-[2-[(2-methoxyethoxy)carbonyloxy]acetyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl}propanethioamide,
- (8) N-(((5S)-3-{3-fluoro-4-[4-((2S)-2-hydroxy-3-methoxypropanoyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl}propanethioamide,
- (9) N-(((5S)-3-{3-fluoro-4-[4-((2S)-2,3-dimethoxypropanoyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl}propanethioamide,
- (10) N-(((5S)-3-{3-fluoro-4-[4-((2S)-3-hydroxy-2-methoxypropanoyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl}propanethioamide,
- (11) N-((5S)-3-[3-fluoro-4-(4-acetoacetyl-1-piperazinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl}propanethioamide,
- (12) N-((5S)-3-[3-fluoro-4-(4-pyruvoyl-1-piperazinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl}propanethioamide,
- (13) N-((5S)-3-[3-fluoro-4-[4-(3-hydroxypropanoyl)-1-piperazinyl]phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl}propanethioamide,
- (14) N-[[[(5S)-3-(3-fluoro-4-{4-[(1-hydroxycyclopropyl)carbonyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}propanethioamide,
- (15) N-(((5S)-3-{3-fluoro-4-[4-(2-phenoxyacetyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl}propanethioamide,

- (16) N-((5*S*)-3-[3-fluoro-4-[4-((2*S*)-2,3-dihydroxypropanoyl)-1-piperazinyl]phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- (17) N-((5*S*)-3-[3-fluoro-4-[4-((2*R*)-2,3-dihydroxypropanoyl)-1-piperazinyl]phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- 5 (18) N-(((5*S*)-3-(3-fluoro-4-{4-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- (19) N-(((5*S*)-3-{3-fluoro-4-[4-((2*S*)-2-hydroxy-3-phenylpropanoyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- (20) N-(((5*S*)-3-{3-fluoro-4-[4-((2*R*)-2-hydroxy-3-phenylpropanoyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- 10 (21) N-(((5*S*)-3-{3-fluoro-4-[4-((2*R*)-2-hydroxy-2-phenylacetyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide, or
- (22) N-(((5*S*)-3-{3-fluoro-4-[4-((2*S*)-2-acetoxy-2-phenylacetyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide.

15 Scheme I describes 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 Schemes I are as defined below or as in the claims. Optically pure material could be obtained either by one of a number of asymmetric syntheses or

20 alternatively by resolution from a racemic mixture.

In step 1 of Scheme I, a suitably protected piperazine (II) is allowed to react with an activated carboxylic acid derivative to give compounds III. In this reaction activated carboxylic acid derivatives can include acyl halides and acid anhydrides or mixed anhydrides which are allowed to react with II in the presence of a tertiary amine base such

25 as triethylamine or pyridine in solvents such as methylene chloride, tetrahydrofuran (THF) or excess pyridine. Temperatures in the range of about 0°C to about 24°C are generally suitable for this reaction. Alternatively coupling agents which are well known for amide forming reactions can be used with appropriate carboxylic acids in step 1. Reagents such as dicyclohexylcarbodiimide (DCC) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

30 hydrochloride (EDC) can be used with activating agents such as 1-hydroxybenzotriazole (HOBT) or 4-(dimethylamino)pyridine (DMAP) in this reaction. Solvents such as THF or dimethylformamide (DMF) and temperatures in the range of 0°C to 24°C are suitable. Compounds where R₄ is cyano are prepared by allowing compounds II to react with

cyanogen bromide in solvents such as methanol. Sodium acetate is a suitable base for this reaction which can be carried out at temperatures in the range of 0°C to 24°C (See Example 5). Protecting groups (P) are chosen for their compatibility with other functional groups on the molecule. Benzyloxycarbonyl (Cbz) and *tert*-butoxycarbonyl (Boc) are generally
5 suitable protecting groups for these compounds; however, it is sometimes necessary to employ other protecting groups. Example 1 illustrates the use of the phthalimide protecting group. In this example, the sulfoxide is sensitive to the acidic conditions required for Boc group removal. The phthalimide can be removed under non-acidic conditions with hydrazine hydrate or methylamine.

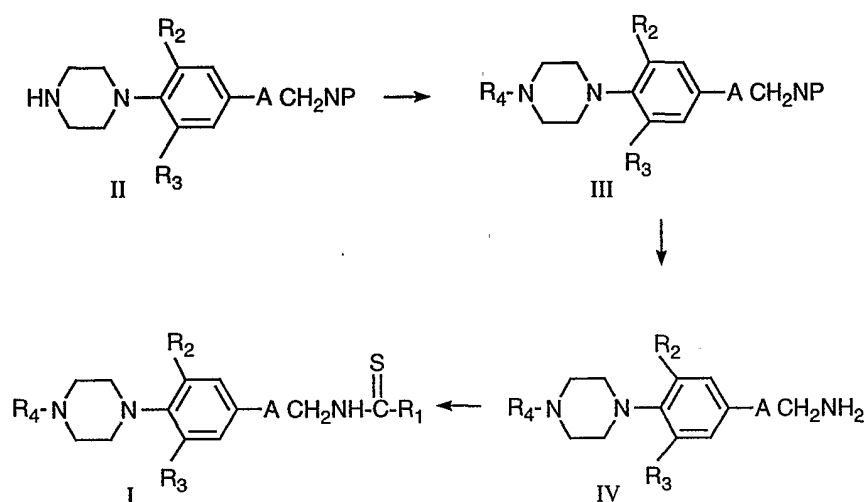
10 In step 2 of Scheme 1, the protecting group (P) is removed to give the corresponding amines (IV). It is convenient to remove the Boc group with hydrogen chloride in dioxane at 0°C to 24°C; however, other deprotection strategies can be employed. Deprotection of Cbz groups can generally be accomplished by hydrogenation with a palladium catalyst.

In step 3 of Scheme 1, the amines (IV) are converted to compounds of formula I.
15 Thioamides are prepared by allowing compounds IV to react with dithioesters and a tertiary amine base such as triethylamine. In this reaction it is often convenient to employ an excess of the tertiary amine base with an amine salt prepared by Boc deprotection in step 2 without first isolating the free base. Solvents such as THF, methylene chloride or preferably methanol and temperatures in the range of about 24°C to about 50°C can be used
20 for this reaction. Other thiocarbonyl compounds of formula I can be prepared according to the procedures disclosed in PCT International Publication WO 98/54161.

If desired R₄ of compounds I or III can be modified to give additional compounds of formula I. This is illustrated in Example 4 where the acetamide of **14** is allowed to react with Lawesson's reagent to give the thioamide **15**, a compound of formula I. In Example 1
25 it is shown in step 3 that the sulfide **3** can be oxidized to the sulfoxide **4** with sodium periodate in methanol-water. This intermediate **4** can subsequently be converted to a compound of formula I. The reaction of sulfoxides such as **4** (Example 1) with sodium azide in polyphosphoric acid at temperatures in the range of 40°C to 70°C gives sulfoximine intermediates that can also be converted to the corresponding compounds of
30 formula I (R₄ is -C(=O)-CH₂-S(=O)(=NR₈)CH₃). Other sulfoximine analogs can be obtained as described in Case 6295. In Example 3 it is shown that the sulfide intermediate **8** can be oxidized to the sulfone **11** with osmium tetroxide and 4-methylmorpholine N-oxide in acetone-water. Intermediate **11** can subsequently be converted to compound **13**, a

compound of formula I. In Example 6 it is shown that the alcohol **19** will react with methylisocyanate and a cuprous chloride catalyst in DMF at 24°C to give **20** which can be converted to **22**, a compound of formula I. And in Example 7 acylation of the alcohol **23** with 2-methoxyethyl chloroformate in pyridine gives **24**, a compound of formula I. In a similar manner, using chemistry known in the art, other R₄ substituents of compounds I or III of Scheme I can be modified to give additional compounds of formula I.

SCHEME I



10

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 excipients 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.

25

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
5 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
10 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
15 100, 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
20 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
25 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
30 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
5 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
10 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*, *Streptococcus pneumoniae*, *Enterococcus faecalis*,
15 *Moraxella catarrhalis* and *H. influenzae* is shown in Table 1.

TABLE 1

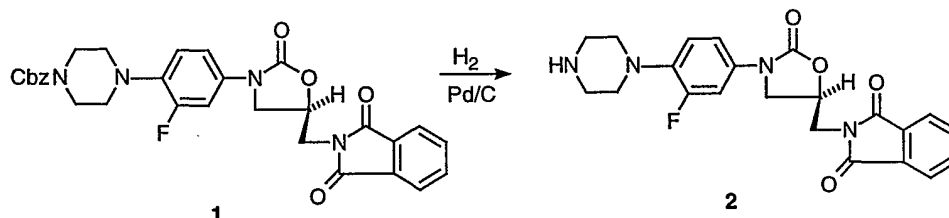
Antibacterial Activity Minimum Inhibitory Concentration ($\mu\text{g/mL}$)

	SAUR 9213 MIC	SEPI 30593 MIC	EFAE 12712 MIC	SPNE 9912 MIC	HINF 30063 MIC	HINF 30063 MIC	EFAE 9217 MIC	MCAT 30607 MIC
EX 1	4	1	2	.05	2	8	1	8
EX 2	2	1	1	<0.5	1	>64	1	4
EX 3	2	0.5	1	0.25	0.5	8	0.5	2
EX 4	0.5	0.25	0.5	0.125	0.125	1	0.5	1
EX 5	0.25	0.25	0.25	0.125	0.125	2	0.25	1
EX 7	2	1	2	0.25	0.25	4	2	4
EX 8	2	1	2	0.5	0.5	16	1	2
EX 9	4	2	4	1	1	32	2	4
EX 10	4	2	2	1	1	16	1	4
EX 12	2	1	1	0.5	0.5	8	1	2
EX 13	2	1	1	0.5	0.5	8	1	2
EX 14	4	1	2	0.5	1	32	1	2
EX 15	2	0.5	1	0.25	0.5	32	0.5	2
EX 16	4	0.5	1	0.5	0.5	8	0.5	2
EX 17	4	0.5	1	0.25	0.5	8	0.5	2
EX 18	4	1	2	0.5	1	32	2	4
EX 19	2	2	2	<0.5	1	>64	2	8
EX 20	1	1	1	<0.5	1	64	1	4
EX 21	4	1	2	1	2	64	2	4
EX 22	8	4	4	2	4	>64	4	8

Example 1 Preparation of N{[(5S)-3-(3-fluoro-4-{4-[2-(methylsulfinyl)acetyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}propanethioamide (**6**)

PNU-255889

Step 1

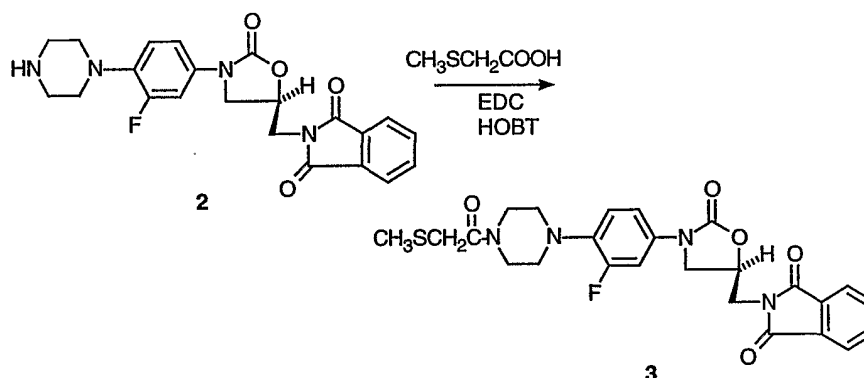


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A mixture of **1** (may be prepared according to US Patent No. 5,547,950) (5.00 g, 8.95 mmol), EtOH (150 ml), THF (150 ml), concentrated hydrochloric acid (1.5 ml) and 10% palladium on carbon catalyst (2 g) is hydrogenated at an initial pressure of 32 p.s.i. for 18 hours. The mixture is filtered and the solid is washed with MeOH/CH₂Cl₂.

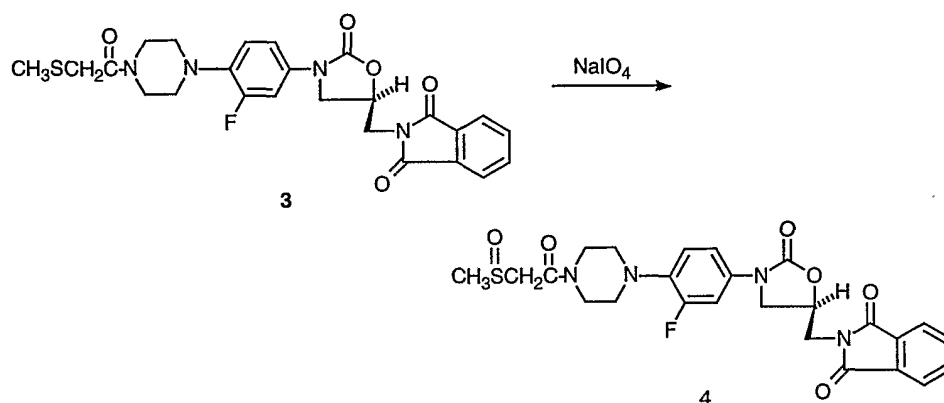
Concentration of the combined filtrate gave a solid which is stirred for 18 hours with a mixture of saturated aqueous NaHCO₃ (100 ml) and EtOAc (100 ml), collected by filtration washed with water and dried. It is dissolved in 20% MeOH/CH₂Cl₂, dried (MgSO₄) and concentrated to give 1.94 g of compound **2**.

15 **Step 2**



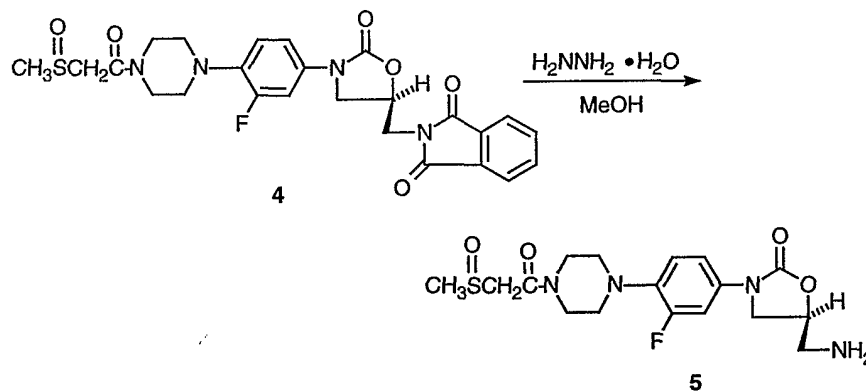
A stirred mixture of **2** (1.70 g, 4.01 mmol), 1-hydroxybenzotriazole hydrate (HOBT, 650 mg, 4.81 mmol), (methylthio)acetic acid (419 μL, 4.81 mmol) and DMF (38 ml) is cooled to 0°C and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 1.54 g, 8.02 mmol). It is kept at 0°C for two days and concentrated *in vacuo* at 50°C. The residue is mixed with water and extracted with EtOAc. The extract is dried (MgSO₄) and concentrated. Chromatography of the residue on silica gel with mixtures of MeOH/CH₂Cl₂ containing 1-2% MeOH gave 1.75 g of compound **3**.

Step 3



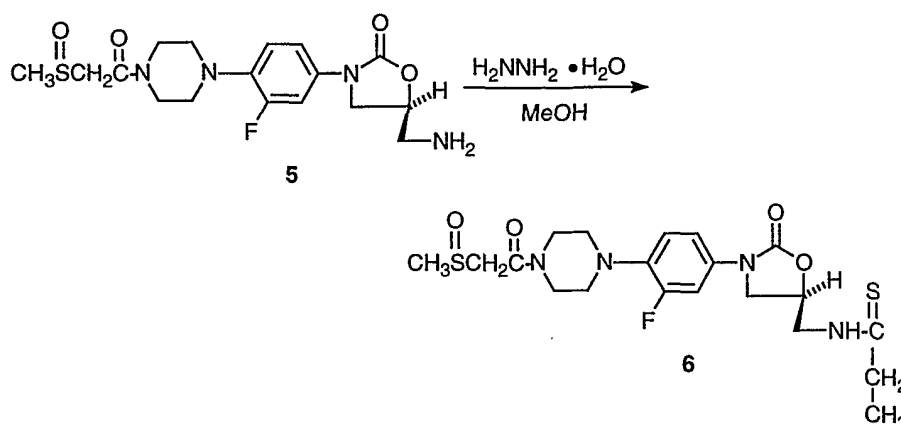
A stirred, ice cold mixture of **3** (1.70 g, 3.32 mmol) in MeOH (17 ml) and water (8.5 ml) is treated with sodium periodate (1.06 g, 4.98 mmol) and kept in the ice bath for 4 hours and at ambient temperature (24°C) for 4 days. It is concentrated *in vacuo*, mixed with water and extracted with CH₂Cl₂. The extract is dried (MgSO₄) and concentrated. Chromatography of the residue on silica gel with 5% MeOH-CH₂Cl₂ gave 1.22 g of compound **4**.

10 Step 4



A stirred mixture of **4** (964 mg, 1.82 mmol), hydrazine hydrate (177 μL, 3.64 mmol) and MeOH (16 ml) is warmed at 80°C for 6 hours and kept at ambient temperature for 4 days. It is concentrated *in vacuo*. Chromatography of the residue on silica gel with 10% MeOH-1% NH₄OH-CH₂Cl₂ gave 630 mg of compound **5**.

Step 5

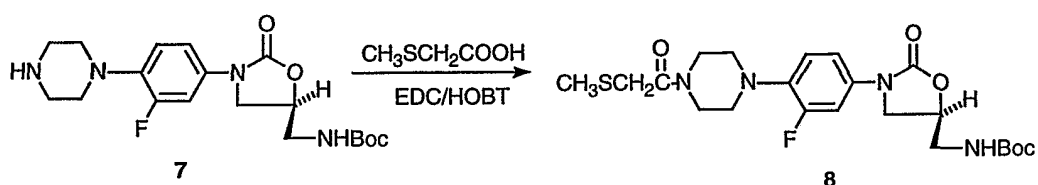


A stirred mixture of **5** (326 mg, 0.815 mmol), triethylamine (0.91 mL, 6.55 mmol), and methyl dithiopropionate (393 mg, 3.27 mmol) in CH_2Cl_2 (8.0 ml) and THF (8 ml) is kept at ambient temperature (24°C) for 18 hours, mixed with water and extracted with CH_2Cl_2 . The extract is dried (MgSO_4) and concentrated. Chromatography of the residue on silica gel with mixtures of MeOH/ CH_2Cl_2 containing 2.5-5% MeOH gave the product which is recrystallized from MeOH to give 257 mg of compound **6**. Anal. calcd for $\text{C}_{10}\text{H}_{27}\text{FN}_4\text{O}_4\text{S}_2$: C, 51.05; H, 5.78; N, 11.91. Found: C, 50.82; H, 5.85; N, 11.80.

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Example 2 Preparation of N-[[[(5S)-3-(3-fluoro-4-{4-[2-(methylsulfonyl)acetyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl]propanethioamide (**10**) (PNU-247827).

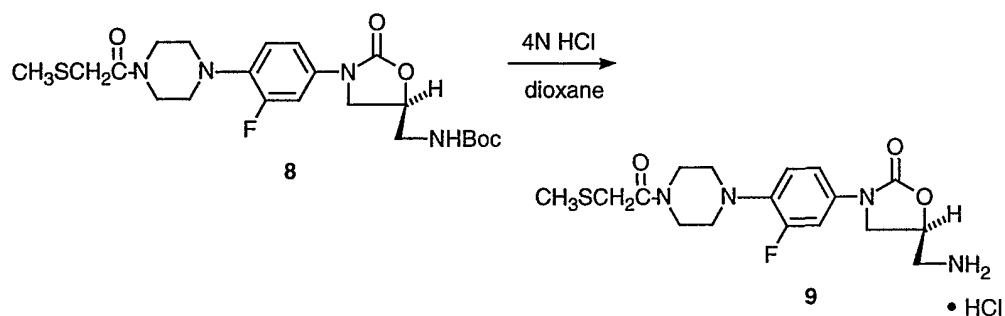
Step 1



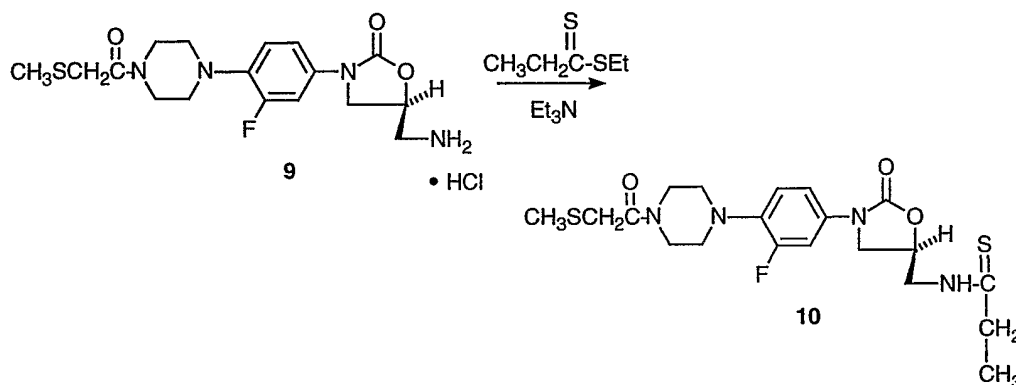
15

A stirred, ice cold, solution of **7** (may be prepared according to PCT International Publication WO 98/54161) (3.00 g, 7.61 mmol), HOBT (1.13 g, 2.79 mmol) and methylthioacetic acid (0.66 mL, 2.54 mmol) in DMF (69 ml) are treated with EDC (3.21 g, 5.58 mmol) and allowed to warm slowly to ambient temperature (24°C) during about 18 hours. It is concentrated *in vacuo* at 50°C and the residue is mixed with water and extracted with EtOAc. The extract is washed with water and brine, dried (MgSO_4) and concentrated. Crystallization of the residue from MeOH/EtOAc/heptane gave 2.36 g of compound **8**.

20

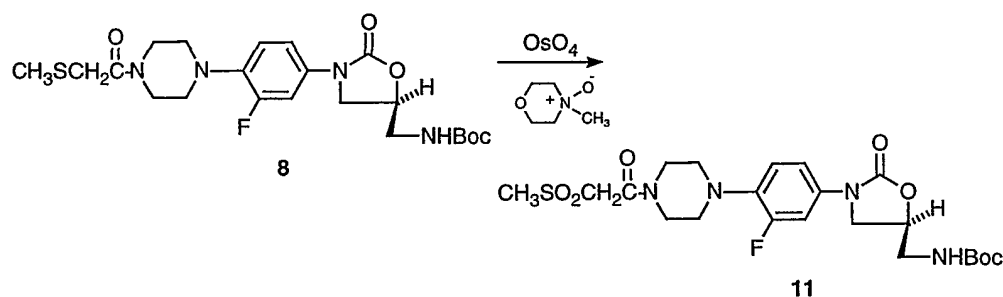
Step 2

A sample of **8** (1.00 g, 2.07 mmol) is cooled in an ice bath, treated with 4N HCl in dioxane (10 ml) and stirred in the bath for 1.5 hours and at ambient temperature (24°C) for 1 hour. The mixture is concentrated and the residue is mixed with three portions of CH₂Cl₂ with concentration after each addition to give **9**.

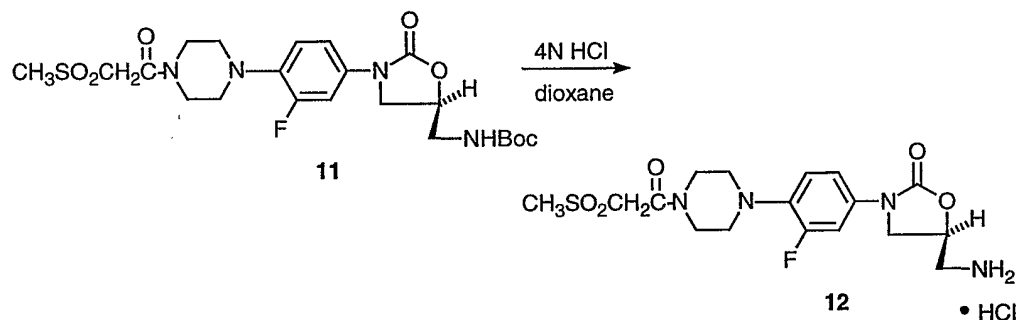
Step 3

A stirred mixture of compound **9** (578 mg, 1.38 mmol), triethylamine (1.5 mL, 11.0 mmol), ethyl dithiopropionate (0.76 mL, 5.52 mmol), CH₂Cl₂ (15.5 ml) and THF (15.5 ml) is kept at ambient temperature (24°C) for 18 hours and concentrated *in vacuo*. The residue is stirred with a mixture of water (30 ml) and 10% EtOAc-heptane (30 ml) for 2 hours and the solid is collected by filtration, washed with water, dried and crystallized from EtOAc-MeOH-heptane. The resulting solid is chromatographed on silica gel with 2% MeOH-CH₂Cl₂ and the product is crystallized from MeOH/EtOAc to give 465 mg of compound **10**: MS (EI) *m/z* 454 (M⁺). Anal. Calcd for C₂₀H₂₇FN₄O₃S₂: C, 52.84; H, 5.99; N, 12.32. Found: C, 52.83; H, 6.02; N, 12.23.

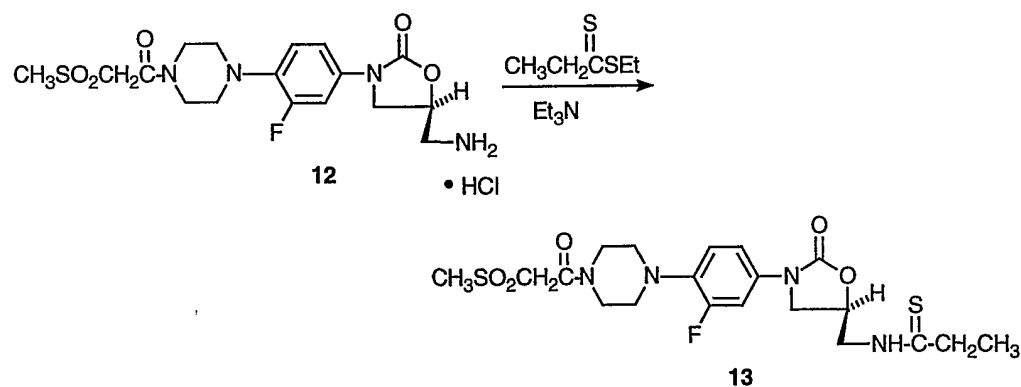
Example 3 Preparation of N-[[[(5*S*)-3-(3-fluoro-4-{4-[2-(methylsulfonyl)acetyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl]propanethioamide (**13**) (PNU-248337)

Step 1

A stirred mixture of compound **8** (100 mg, 0.207 mmol), 4-methylmorpholine, N-oxide (73 mg, 0.621 mmol), acetone (1.5 ml) and water (0.5 ml) is treated with a 2.5% solution of osmium tetroxide in 2-methyl-2-propanol (17 μL) and kept at ambient temperature (24°C) for 18 hours. It is then treated with 10% aqueous NaHSO_3 (60 ml) and extracted with CH_2Cl_2 . The extracts are washed with 10% NaHSO_3 , dried (MgSO_4) and concentrated. Crystallization of the residue from EtOAc-heptane gave 96 mg of **11**: MS (EI) m/z 514 (M^+).

10 **Step 2**

As described in Example 2, Step 2 compound **11** is treated with 4N HCl in dioxane to give **12**: HRMS (FAB) calcd for $\text{C}_{17}\text{H}_{24}\text{FN}_4\text{O}_5\text{S}$ ($\text{M}+\text{H}^+$) 415.1451, found 415.1445.

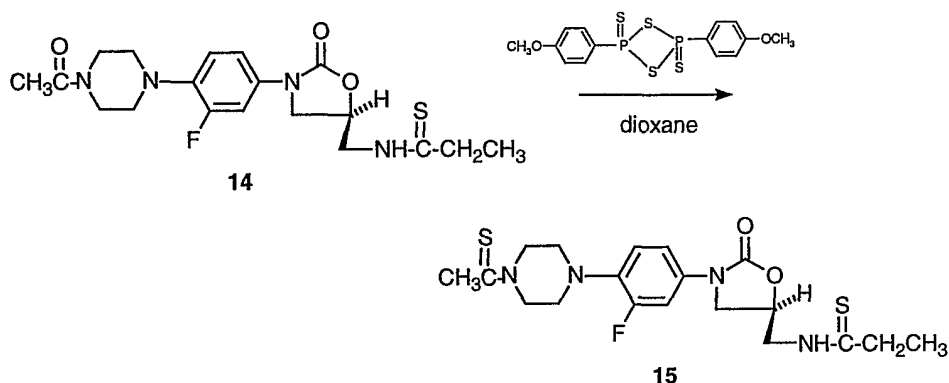
Step 3

15

As described in Example 2, Step 3 compound **12** is allowed to react with ethyl dithiopropionate and triethylamine to give **13** which is purified by chromatography on silica

gel with 1% MeOH-CH₂Cl₂ and crystallization from MeOH-EtOAc: MS(EI) *m/z* 486 (M⁺); HRMS (FAB) calcd for C₂₀H₂₈FN₄O₅S₂ (M+H⁺) 487.1485, found 487.1494. Anal. Calcd for C₂₀H₂₇FN₄O₅S₂: C, 49.37; H, 5.59; N, 11.51. Found: C, 49.25; H, 5.63; N, 11.47.

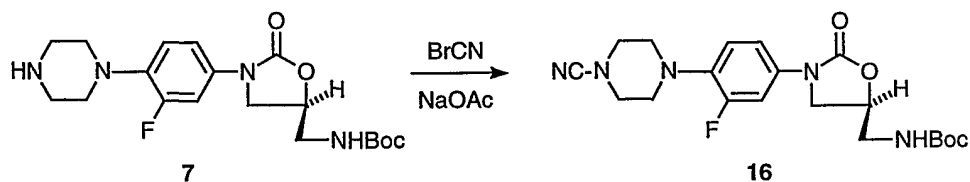
- 5 **Example 4** Preparation of N-((5*S*)-3-[4-(4-ethanethioly-1-piperazinyl)-3-fluorophenyl]2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide (**15**) (PNU-276575).



A stirred mixture of **14** ((*S*)-N-[[3-[3-fluoro-4-(4-acetyl-1-piperazinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propanethioamide (may be prepared according to the procedure disclosed in PCT International Publication WO 98/54161) (0.53 g, 1.3 mmol), Lawesson's Reagent (0.53 g) and dioxane (27 ml) is refluxed, under nitrogen for 90 min, cooled and concentrated *in vacuo*. Chromatography of the residue on silica gel with 2% MeOH-CH₂Cl₂ gave the product which is decolorized with activated carbon and crystallized from acetonitrile to give 0.303 g of **15**: mp 209-210°C. Anal. Calcd for C₁₉H₂₅FN₄O₂S₂: C, 53.75; H, 5.93; N, 13.20. Found: C, 53.69; H, 6.00; N, 13.25.

- Example 5** Preparation of N-((5*S*)-3-[4-(4-cyano-1-piperazinyl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide (**18**) (PNU-278605)

20 **Step 1**



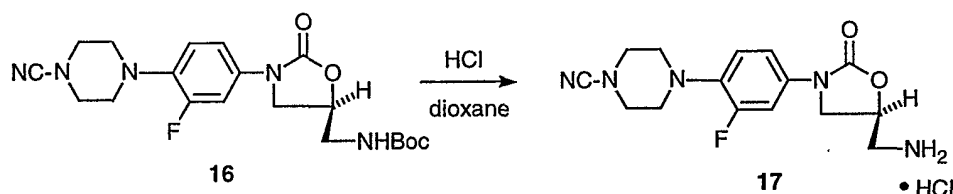
A stirred, ice cold mixture of **7** (0.488 g, 1.24 mmol) and sodium acetate (0.55 g, 6.7 mmol) in MeOH (40 ml) is treated during 1 minute, with a MeOH (10 ml) solution of

5M cyanogen bromide in CH_2Cl_2 (0.35 ml, 1.48 mmol) and kept in the ice bath for 2 hours. It is then concentrated *in vacuo* and the residue is mixed with dilute NaHCO_3 and extracted with CH_2Cl_2 . The extract is washed with water, dried (Na_2SO_4) and concentrated.

Chromatography of the residue on silica gel with 2% $\text{MeOH}-\text{CH}_2\text{Cl}_2$ gave 0.42 g of **16**:

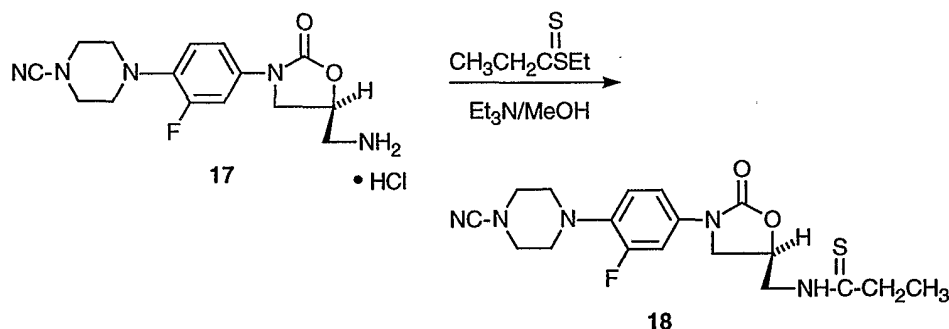
5 MS(ES) m/z 420 ($\text{M}+\text{H}^+$).

Step 2



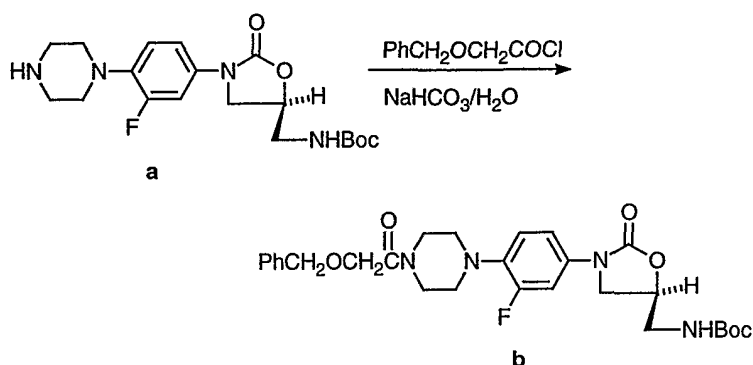
A stirred ice cold suspension of **16** (0.42 g, 1.0 mmol) in dioxane (10 ml), under nitrogen is treated dropwise with ice cold 4N HCl in dioxane (10 ml), kept in the ice bath
 10 for 2 hours and concentrated *in vacuo*. The residue is dried *in vacuo* for 18 hours to give **17**: MS(ES) m/z 320 ($\text{M}+\text{H}^+$).

Step 3

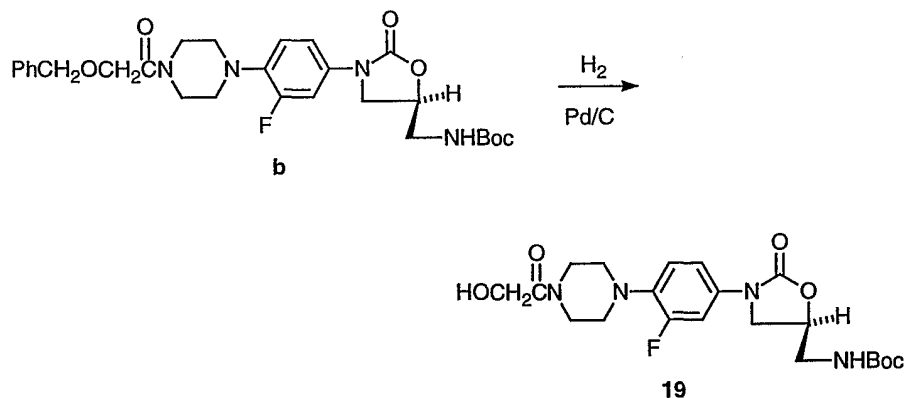


A stirred mixture of **17** (0.25 g, 0.64 mmol), and triethylamine (0.178 ml) in MeOH
 15 (5 ml), under nitrogen is warmed to 50°C during 30 minutes, kept at 50°C for 30 minutes and cooled in an ice bath. The solid is collected by filtration and crystallized from EtOH to give **18**: mp 182-184°C; HRMS (FAB) calcd for $\text{C}_{18}\text{H}_{23}\text{FN}_5\text{O}_2\text{S}$ ($\text{M}+\text{H}^+$) 392.1556, found 392.1550.

20 **Example 6** Preparation of N-((5S)-3-(3-fluoro-4-(4-[2-(methylaminocarbonyloxy)acetyl]-1-piperazinyl)phenyl)-2-oxo-1,3-oxazolidin-5-yl)methylpropanethioamide (**22**) (PNU-281328)

Step 1

A stirred, ice cold mixture of **a** (PCT International Publication WO 98/54161) (20.0 g, 50.7 mmol), acetone (1500 mL) and saturated aqueous sodium bicarbonate (500 ml) is treated, during 20 min, with a solution of benzyloxycarbonyl chloride (9.5 ml, 60.8 mmol) in acetone (150 ml). The mixture is allowed to warm slowly to ambient temperature (24°C) and stand for 18 hours. It is extracted with Et₂O and the extract is washed with water and brine, dried (MgSO₄), and concentrated to give 25.4 g of the product **b**.

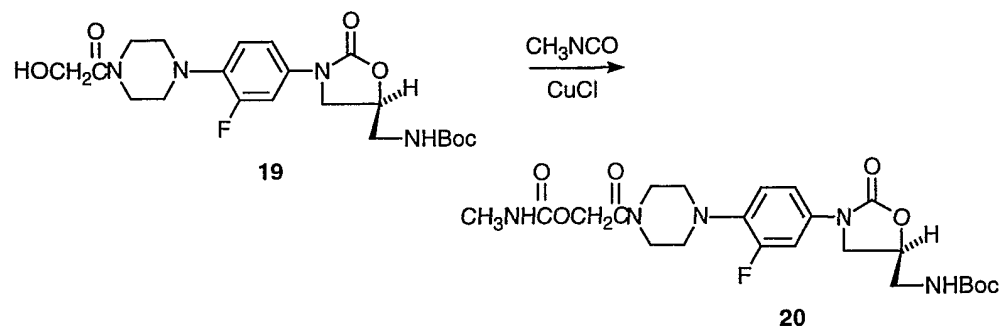
Step 2

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A mixture of **2** (25.0 g, 46.1 mmol), MeOH (1700 ml) and 10% palladium - on - carbon catalyst (6.25 g) is hydrogenated at an initial pressure of 35 p.s.i. for 4 days. Additional catalyst (6.25 g) is added and the hydrogenation is continued for 1 day. The mixture is filtered and the filtrate is concentrated. Chromatography of the residue on silica gel with 2.5% MeOH-CH₂Cl₂ gave the product which is crystallized from acetone - CH₂Cl₂ to give 13.7 g of **3**.

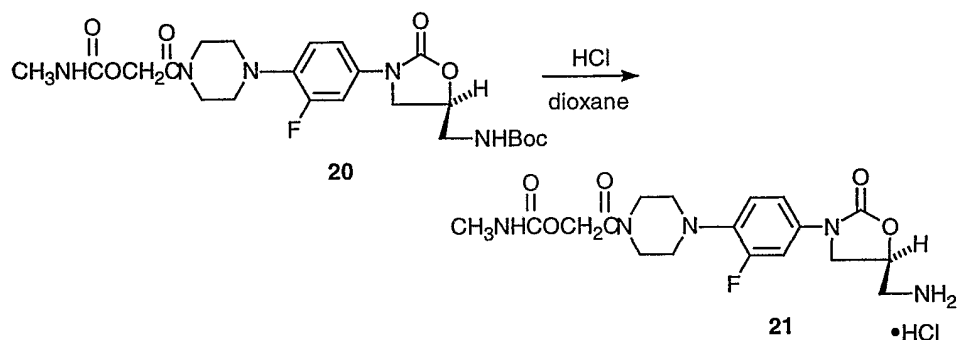
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Step 3



A stirred mixture of **19** and cuprous chloride (0.075 g) in DMF (4 ml) is treated with methyl isocyanate (0.081 ml), kept at ambient temperature (24°C) for 60 minutes and concentrated *in vacuo*. The residue is mixed with water and Et₂O to give a solid which is collected by filtration and chromatographed on silica gel with 2.5% MeOH-CH₂Cl₂ to give 0.28 g of **20**.

Step 4



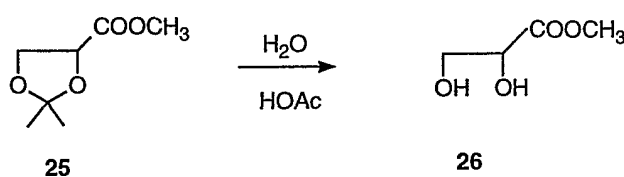
An ice cold, stirred mixture of **20** (0.37 g, 0.726 mmol) in dioxane (10 ml), under nitrogen is treated, drop-wise with ice cold 4N hydrogen chloride in dioxane (8 ml). The mixture is kept in the ice bath for 1 hour 15 minutes and at ambient temperature (24°C) for 1 hour. It is diluted with additional dioxane (10 ml), kept at ambient temperature for 30 minutes, at 0°C for 18 hours and at ambient temperature for 6 hours. It is concentrated *in vacuo* to give **21**: MS(ES) *m/z* 410 (M+H⁺).

CH₂Cl₂. The extract is washed with water and brine, dried (Na₂SO₄) and concentrated. Chromatography of the residue on silica gel with 2.5% MeOH-CH₂Cl₂ gave the product which is crystallized from EtOAc to give 0.185 g of **24**: mp 150-151°C. Anal. Calcd for C₂₃H₃₁FN₄O₇S: C, 52.46; H, 5.93; N, 10.64. Found: C, 52.45, H, 6.05; N, 10.61.

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Example 8 Preparation of N-[(*S*)-3-{3-fluoro-4-[4-((*S*)-2-hydroxy-3-methoxypropanoyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide (**33**) (PNU-272200).

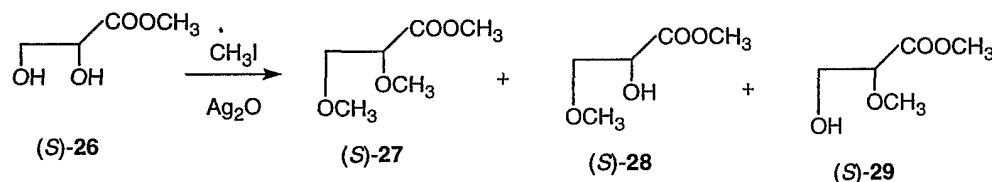
Step 1



10

A stirred solution of methyl (*S*)-(-)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (**25**) (5.0 g, 0.031 mol) in acetic acid (10 ml) and water (2.5 ml) is kept at ambient temperature for 72 hours and concentrated *in vacuo* to give (*S*)- **26**.

Step 2

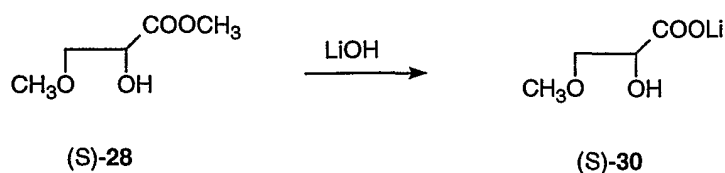


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A stirred mixture of (*S*)-**26** (1.0 g) from Step 1 and methyl iodide (20 ml), under nitrogen is treated with silver oxide (1.3 g) and 3A molecular sieves (2 g) and warmed at 43°C for 90 minutes. It is cooled and filtered. The filtrate is concentrated and the residue is chromatographed on silica gel with mixtures of MeOH-CH₂Cl₂ containing 2-4% MeOH. The products eluted from the column are (*S*)-**27** (0.15 g), (*S*)-**28** (0.08 g), and (*S*)-**29** (0.28 g).

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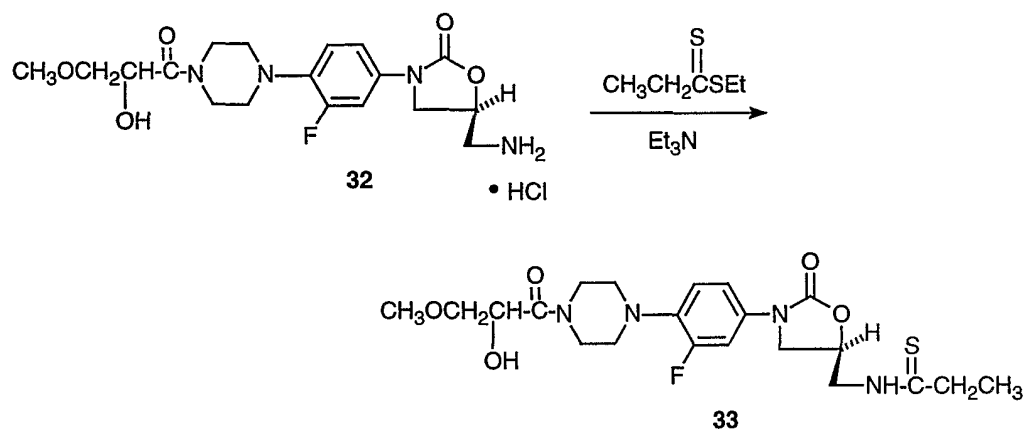
Step 3



A stirred mixture of (*S*)-**28** (0.08 g, 0.6 mmol) and MeOH (3.0 ml) under nitrogen, is treated with 1M lithium hydroxide (0.57 ml) and kept at ambient temperature (24°C) for

25

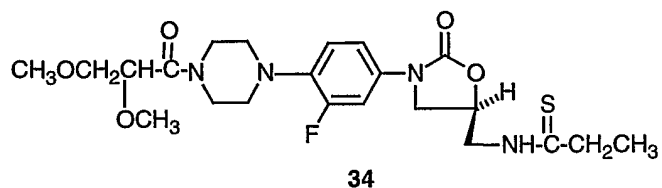
Step 6



A stirred mixture of **32** from Step 5, triethylamine (0.5 ml, 3.5 mmol), CH_2Cl_2 (10 ml and THF (7 ml), under nitrogen is treated, dropwise with ethyl dithiopropionate (0.22 ml, 1.71 mmol) and kept at ambient temperature (24°C) for 72 hours. Additional ethyl dithiopropionate (0.22 ml) is added and the mixture is kept at ambient temperature for 24 hours and concentrated. The residue which still contain **32** is mixed with CH_2Cl_2 (10 ml), THF (7 ml), triethylamine (0.75 ml) and ethyl dithiopropionate (0.35 ml), kept at ambient temperature for 24 hours and concentrated. Chromatography of the residue on silica gel with 2.5% MeOH- CH_2Cl_2 gave 0.0457 g of **33**: mp 190-191°C (dec). Anal. Calcd for $\text{C}_{21}\text{H}_{29}\text{FN}_4\text{O}_5\text{S}$: C, 53.83; H, 6.24; N, 11.96. Found: C, 53.59; H, 6.35; N, 11.83.

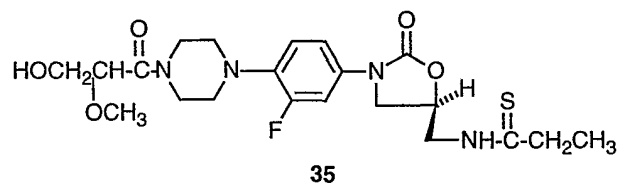
Example 9 Preparation of N-[(*S*)-3-{3-fluoro-4-[4-((*S*)-2,3-dimethoxypropanoyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide (**34**)

(PNU-272199)



As described in Example 8 the ester (*S*)-**27**, prepared in Step 2) is hydrolyzed with lithium hydroxide and coupled with **7**. The resulting amide is deprotected and allowed to react with ethyl dithiopropionate and triethylamine. The product is purified by silica gel chromatography with 2.5% MeOH- CH_2Cl_2 and crystallized from EtOAc-hexane to give **34**: mp 140-142 °C (dec). Anal. calcd for $\text{C}_{22}\text{H}_{31}\text{FN}_4\text{O}_5\text{S}$: C, 54.76; H, 6.47; N, 11.61. Found: C, 54.53; H, 6.54; N, 11.50.

Example 10 Preparation of N-[(*(5S)*-3-{3-fluoro-4-[4-((*(2S)*-3-hydroxy-2-methoxypropanoyl)-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide (**35**) (PNU-272198)

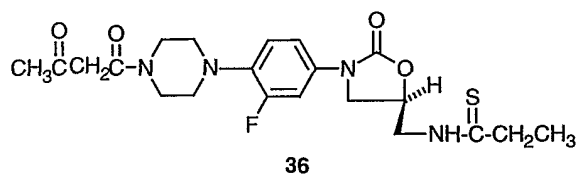


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As described in Example 8 the ester (*(S)*-29, prepared in Step 2) is hydrolyzed with lithium hydroxide and coupled with **7**. The resulting amide is deprotected and condensed with ethyl dithiopropanoate. The product is purified by silica gel chromatography with 2.5% MeOH-CH₂Cl₂ to give **35**. Anal. calcd for C₂₁H₂₉FN₄O₅S: C, 53.83; H, 6.24; N, 11.96. Found: C, 53.71; H, 6.32; N, 11.85.

10

Example 11 Preparation of N-[(*(5S)*-3-[3-fluoro-4-(4-acetoacetyl-1-piperazinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide (**36**)

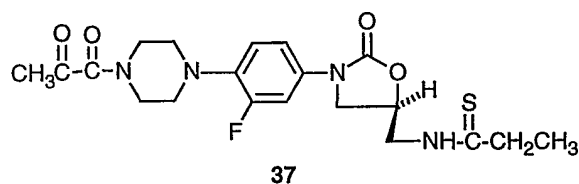


15

As described in Example 8 (Steps 4-6) the lithium salt of acetylacetic acid is coupled with **7** and the resulting amide is deprotected and allowed to react with ethyl dithiopropanoate and triethylamine. The product is purified by silica gel chromatography to give **36**: MS(ES) *m/z* 451 (M+H⁺), 473 (M+Na⁺).

20

Example 12 Preparation of N-[(*(5S)*-3-[3-fluoro-4-(4-pyruvoyl-1-piperazinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide (**37**) PNU-264886



As described in Example 8 (Steps 4-6) pyruvic acid is coupled with **7** and the resulting amide is deprotected and allowed to react with ethyl dithiopropanoate and

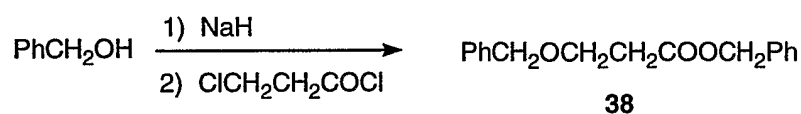
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triethylamine. The product is purified by silica gel chromatography with 2% MeOH-CH₂Cl₂ and crystallized from EtOAc-hexane to give **37**: mp 173-175 °C (dec); MS(ES) *m/z* 437 (M+H⁺), 459 (M+Na⁺). Anal. calcd for C₂₀H₂₅FN₄O₄S·0.1 EtOAc; C, 54.97; H, 5.84; N, 12.57. Found: C, 55.05; H, 6.15; N, 12.12

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Example 13 Preparation of N-((5*S*)-3-[3-fluoro-4-[4-(3-hydroxypropanoyl)-1-piperazinyl]phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide (**43**) (PNU-272690)

Step 1

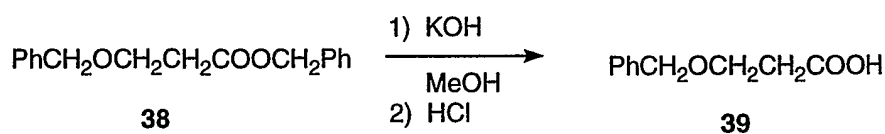


10

An ice cold, stirred solution of benzyl alcohol (4.0 mL, 0.0386 mol) in THF (20 mL), under nitrogen is treated, portionwise during 40 minutes with a 60% oil dispersion of sodium hydride (1.6 g, 0.04 mol), kept in the ice bath for 20 minutes and treated during 5 minutes with a solution of 3-chloropropionyl chloride (1.50 mL, 0.0157 mol) in THF (3 mL). The mixture is warmed slowly to ambient temperature (24 °C), kept for 23 hours, mixed with saturated ammonium chloride (15 mL) and ice water and extracted with EtOAc. The extract is washed with water and brine, dried (Na₂SO₄) and concentrated to give **38**: MS(ES) *m/z* 293 (M+Na⁺).

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Step 2

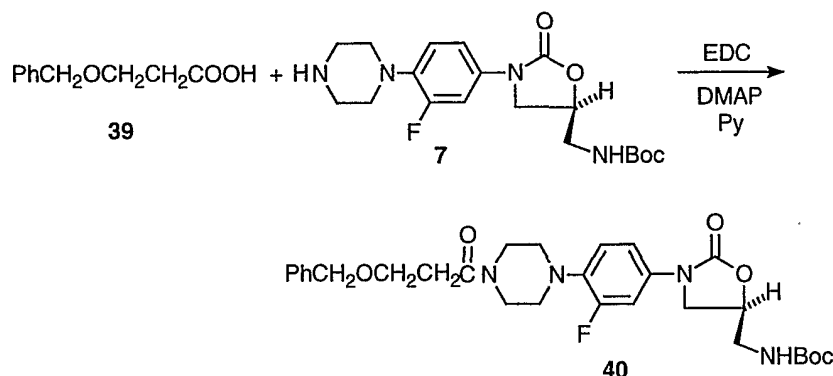


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An ice cold, stirred solution of **38** from Step 1 in MeOH (50 mL), under nitrogen, is treated with potassium hydroxide (0.94 g, 0.0168 mol) and kept in the ice bath for 10 minutes, at ambient temperature for 1 hour and at -20 °C for 18 hours. It is treated with additional potassium hydroxide (0.98 g), kept at ambient temperature for 8.5 hours and at -20 °C for 18 hours and concentrated *in vacuo*. The residue is mixed with ice water, cooled in an ice bath and treated with 2N HCl to pH 3. It is extracted with EtOAc. The extract is washed with 2N NaOH and water and the wash is reacidified with 2N HCl and extracted with EtOAc. The extract is concentrated to give 1.48 g of **39**: MS(ES) *m/z* 181 (M+H⁺), 203 (M+Na⁺).

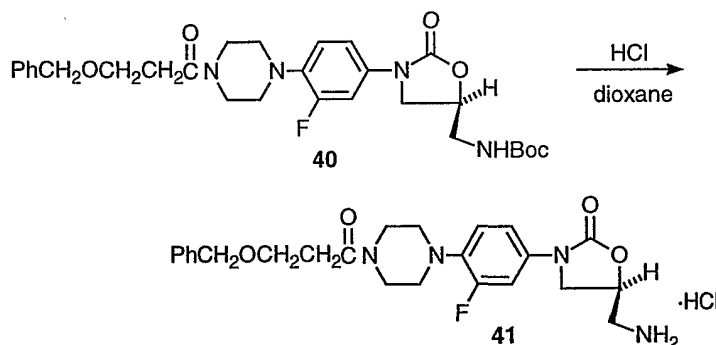
25

Step 3



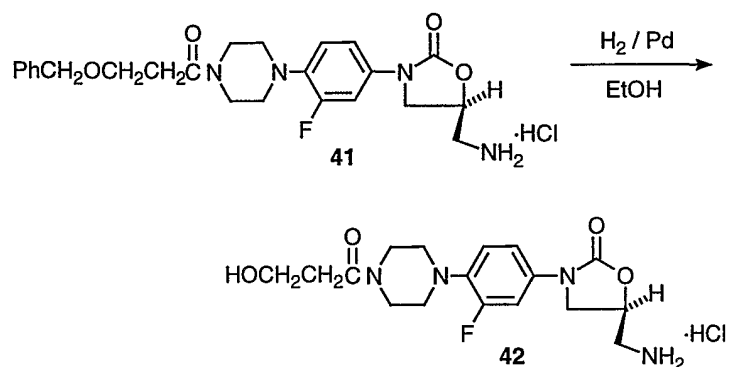
A stirred mixture of **7** (0.5 g, 1.26 mmol) and pyridine (6 mL), under nitrogen, is treated with 4-(dimethylamino)pyridine (DMAP, 8 mg), EDC (0.243 g, 1.26 mmol) and a solution of **39** (0.228 g, 1.26 mmol) in CH₂Cl₂ (2mL) and kept at ambient temperature (24 °C) for 2 hours 20 minutes. It is concentrated *in vacuo* and the residue is mixed with CH₂Cl₂, washed with saturated NaHCO₃, water and brine, dried (Na₂SO₄) and concentrated. Chromatography of the residue on silica gel with 2.5% MeOH-CH₂Cl₂ gave 0.43 g of **40**: MS(ES) *m/z* 557 (M+H⁺), 579 (M+Na⁺).

10 Step 4



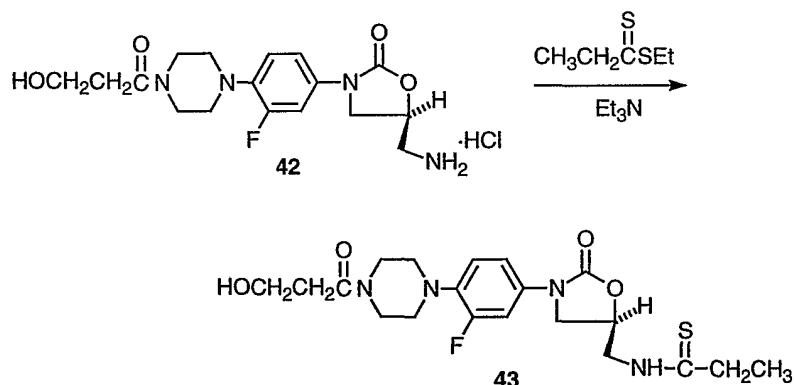
A stirred, ice cold solution of **40** (0.43 g, 0.772 mmol) in dioxane (12 mL), under nitrogen is treated with 4N hydrogen chloride in dioxane (10 mL), dropwise during 3 minutes. It is warmed to ambient temperature (24 °C) during 90 minutes, kept for 3 hours 15 30 minutes and concentrated to give 0.43 g of **41**.

Step 5



A mixture of **41** (0.21 g), 10% palladium on carbon catalyst (0.17 g) and EtOH (50 mL) is hydrogenated at an initial pressure of 44 p.s.i. for 90 minutes, treated with additional catalyst (0.1 g) and hydrogenated at an initial pressure of 40 p.s.i. for 22 hours. It is filtered and the solid is washed with MeOH. The filtrates are concentrated and the residue is chromatographed on silica gel with mixtures of MeOH-NH₄OH-CH₂Cl₂ that contained 5-7.5% MeOH and 0.25-0.5% NH₄OH to give 0.07 g of **42**: MS(ES) *m/z* 367 (M+H⁺).

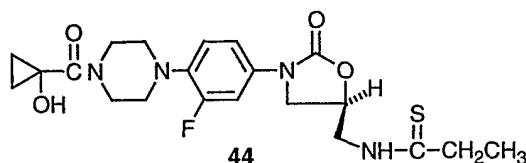
Step 6



10

A stirred mixture of **42** (0.07 g, 0.19 mmol), CH₂Cl₂ (8 mL) and THF (8 mL) is treated with triethylamine (0.20 mL) and ethyl dithiopropanoate (0.08 mL) and kept at ambient temperature (24 °C) for 24 hours, at 45 °C for 7.5 hours and at ambient temperature for 16 hours. It is then concentrated and the residue is chromatographed on silica gel with mixtures of MeOH-CH₂Cl₂ that contained 2-3.5% MeOH. The product (**43**) amounted to 0.057 g: HRMS (FAB) calcd for C₂₀H₂₈FN₄O₄S (M+H⁺) 439.1815, found 439.1812.

Example 14 Preparation of N-[[[(5S)-3-(3-fluoro-4-{4-[(1-hydroxycyclopropyl)carbonyl]-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl]propanethioamide (**44**) (PNU-251110)

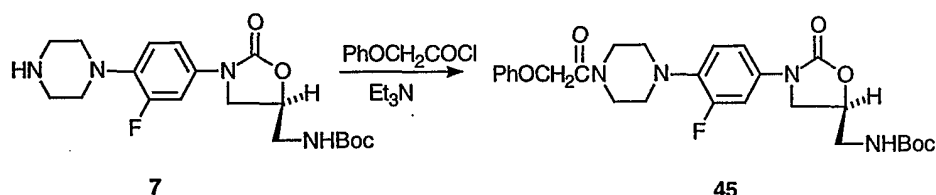


5

As described in Example 8 (Steps 4-6) 1-hydroxy-1-cyclopropanecarboxylic acid is coupled with **7** and the resulting amide is deprotected and allowed to react with ethyl dithiopropionate and triethylamine. The product is purified by silica gel chromatography with mixtures of MeOH-CH₂Cl₂ that contained 2-12% MeOH and by crystallization from MeOH-EtOAc to give **44**: mp 185-186 °C (dec); MS(ES) *m/z* 451 (M+H⁺), 473 (M+Na⁺).
 10 Anal. calcd for C₂₁H₂₇FN₄O₄S: C, 55.99; H, 6.04; N, 12.44. Found: C, 55.78; H, 6.09; N, 12.18.

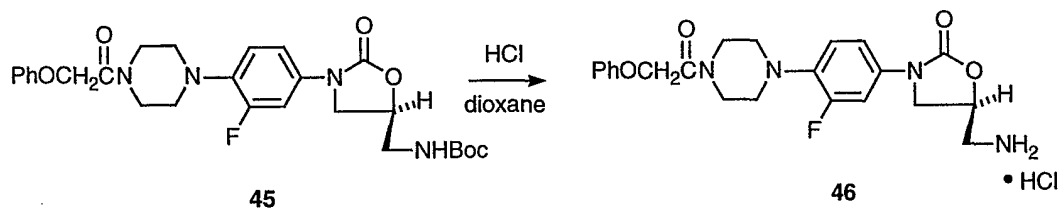
Example 15 Preparation of N-[[[(5S)-3-{3-fluoro-4-[4-(2-phenoxyacetyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl]methyl]propanethioamide (**47**) (PNU-251037)

Step 1



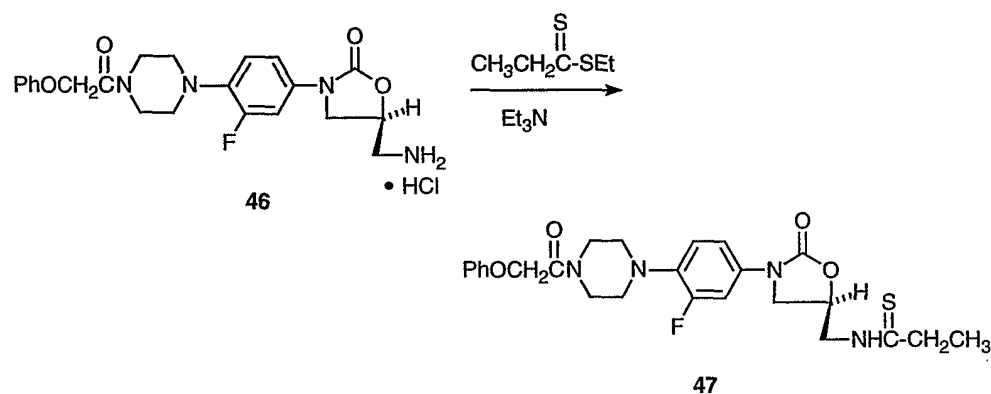
An ice cold, stirred solution of **7** (0.5 g, 1.26 mmol) and triethylamine (0.385 ml, 2.76 mmol) in CH₂Cl₂ (25 ml), under nitrogen, is treated dropwise with a solution of phenoxyacetyl chloride (0.35 ml, 2.52 mmol) in CH₂Cl₂ (3 ml) and kept in the ice bath for 2 hours and at ambient temperature for 30 minutes. It is diluted with CH₂Cl₂, washed with saturated NaHCO₃, water and brine, dried (Na₂SO₄) and concentrated. Crystallization of the residue from MeOH-EtOAc gave 0.53 g of **45**: MS(ES) *m/z* 529 (M+H⁺), 551 (M+Na⁺).
 20
 25

Step 2



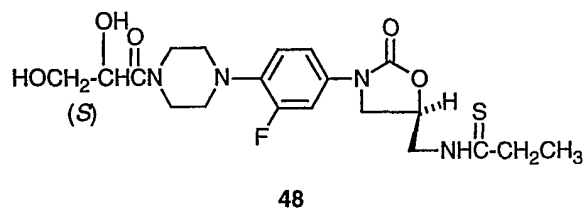
As described in Example 8 (Step 5) compound **45** is deprotected with hydrogen chloride in dioxane to give **46**: MS(ES) m/z 429 ($M+H^+$).

Step 3



As described in Example 8 (Step 6) the amine hydrochloride (**46**) is allowed to react with ethyl dithiopropionate and triethylamine in CH_2Cl_2 -THF. The product is chromatographed on silica gel with 2.5% MeOH- CH_2Cl_2 and crystallized from EtOAc to give **47**: mp 171-172°C; MS(ES) m/z 501 ($M+H^+$), 523 ($M+Na^+$). Anal. Calcd for $C_{25}H_{29}FN_4O_4S$: C, 59.98; H, 5.84; N, 11.19. Found: C, 59.59; H, 5.89; N, 11.03.

Example 16 Preparation of N-((5*S*)-3-[3-fluoro-4-[4-((2*S*)-2,3-dihydroxypropanoyl)-1-piperazinyl]phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide (**48**) (PNU-248440)

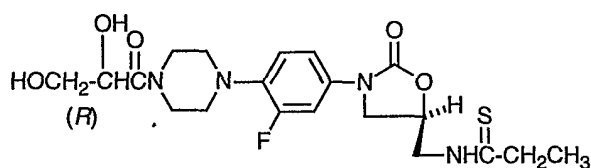


As described in Example 8 (Steps 4-6) L-glyceric acid, calcium salt dihydrate is coupled with **7** and the resulting amide is deprotected and allowed to react with ethyl

dithiopropionate and triethylamine. The product is purified by silica gel chromatography with 7.5% MeOH-EtOAc to give **48**: mp 142°C (dec); MS(ES) m/z 455 ($M+H^+$), 477 ($M+Na^+$). Anal. Calcd for $C_{20}H_{27}FN_4O_5S \cdot 0.3$ EtOAc: C, 52.94; H, 6.15; N, 11.65, Found: C, 52.75; H, 6.02; N, 11.53.

5

Example 17 Preparation of N-({(5*S*)-3-[3-fluoro-4-[4-((2*R*)-2,3-dihydroxypropanoyl)-1-piperazinyl]phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanethioamide (**49**) (PNU-248438)

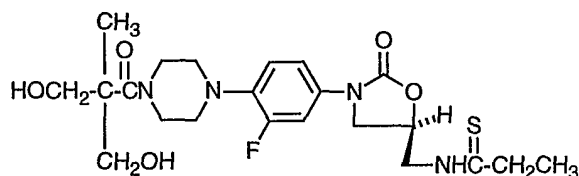


49

10 As described in Example 8 (Steps 4-6) D-glyceric acid, calcium salt dihydrate is coupled with **7** and the resulting amide is deprotected and allowed to react with ethyl dithiopropionate and triethylamine. The product is purified by silica gel chromatography with 7.5% MeOH- CH_2Cl_2 and crystallized from EtOAc-hexane to give **49**: mp 132°C (dec); MS(ES) m/z 455 ($M+H^+$), 477 ($M+Na^+$). Anal. Calcd for $C_{20}H_{27}FN_4O_5S \cdot 0.5$ H_2O :
15 C, 51.88; H, 6.09; N, 12.09; H_2O , 3.88. Found: C, 51.77; H, 6.09; N, 11.96; H_2O , 3.85.

Example 18 Preparation of N-{{(5*S*)-3-(3-fluoro-4-{4-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl}methyl}propanethioamide (**50**) (PNU-248437)

20

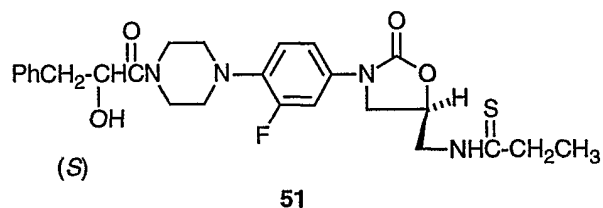


50

As described in Example 8 (Steps 4-6) 2,2-bis(hydroxymethyl)propionic acid is coupled with **7** and the resulting amide is deprotected and allowed to react with ethyl dithiopropionate and triethylamine. The product is purified by silica gel chromatography
25 with 5% MeOH- CH_2Cl_2 and crystallized from MeOH-EtOAc-hexane to give **50**: mp 202-

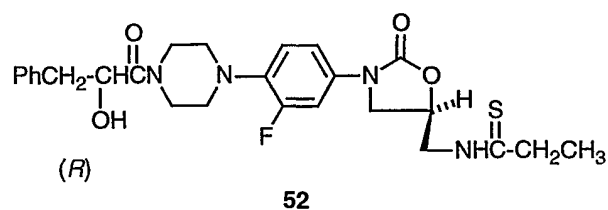
203°C (dec); MS(ES) m/z 483 ($M+H^+$), 502 ($M+Na^+$). Anal. Calcd for $C_{22}H_{31}FN_4O_5S$: C, 54.76; H, 6.47; N, 11.61. Found: C, 54.38; H, 6.54; N, 11.43.

Example 19 Preparation of N-[(*(5S)*-3-{3-fluoro-4-[4-((*(2S)*-2-hydroxy-3-phenylpropanoyl)-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide (**51**) (PNU-246967)



As described in Example 8 (Steps 4-6) L-3-phenyllactic acid is coupled with **7** and the resulting amide is deprotected and allowed to react with ethyl dithiopropionate and triethylamine. The product is purified by silica gel chromatography with 2.5% MeOH- CH_2Cl_2 and crystallized from EtOAc-hexane to give **51**: mp 174-175°C. Anal calcd for $C_{26}H_{31}FN_4O_4S$: C, 60.68; H, 6.07; N, 10.89. Found: C, 60.56; H, 6.17; N, 10.68.

Example 20 Preparation of N-[(*(5S)*-3-{3-fluoro-4-[4-((*(2R)*-2-hydroxy-3-phenylpropanoyl)-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide (**52**) (PNU-246966)

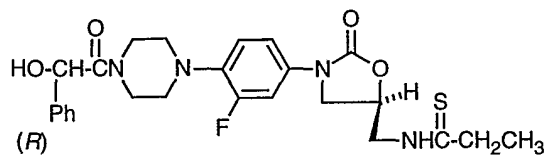


As described in Example 8 (Steps 4-6) D-3-phenyllactic acid is coupled with **7** and the resulting amide is deprotected and allowed to react with ethyl dithiopropionate and triethylamine. The product is purified by silica gel chromatography with 2.5 % MeOH- CH_2Cl_2 and crystallized from EtOAc-hexane to give **52**: mp 128-130°C (dec). Anal. Calcd for $C_{26}H_{31}FN_4O_4S$: C, 60.68; H, 6.07; N, 10.98. Found: C, 60.50; H, 6.17; N, 10.80.

25

Example 21 Preparation of N-[(*(5S)*-3-{3-fluoro-4-[4-((*(2R)*-2-hydroxy-2-phenylacetyl)-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide (**53**)

(PNU-245689)



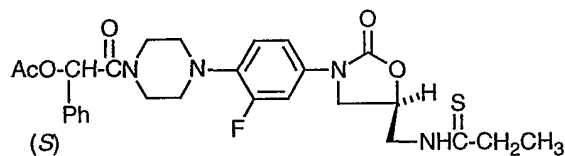
53

5 As described in Example 8 (Steps 4-6) (*(R)*-(-)-mandelic acid is coupled with **7** and the resulting amide is deprotected and allowed to react with ethyl dithiopropionate and triethylamine. The product is purified by silica gel chromatography with mixtures of MeOH-CH₂Cl₂ containing 2-3.5 % MeOH to give **53**: HRMS (FAB) calcd for C₂₅H₃₀FN₄O₄S (M+H⁺) 501.1971, found: 501.1980.

10

Example 22 Preparation of N-[(*(5S)*-3-{3-fluoro-4-[4-((*(2S)*-2-acetoxy-2-phenylacetyl)-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide (**54**)

(PNU-245878)



54

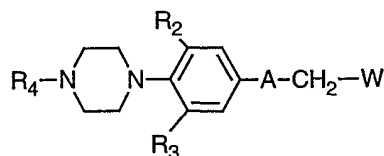
15 As described in Example 8 (Steps 4-6) (*(S)*-(+)-O-acetylmandelic acid is coupled with **7** and the resulting amide is deprotected and allowed to react with ethyl dithiopropionate and triethylamine. The product is purified by silica gel chromatography with 2% MeOH-CH₂Cl₂ to give **54**: HRMS (FAB) calcd for C₂₇H₃₂FN₄O₅S (M+H⁺) 543.2077, found: 543.2063.

20

CLAIMS

What is claimed is:

1. A compound of formula I

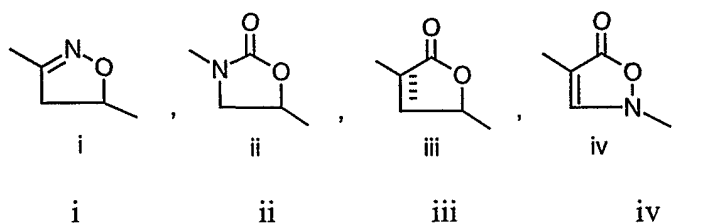


5

I

or a pharmaceutically acceptable salt thereof wherein:

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



- 10 W is NHC(=S)R_1 , or $-\text{Y-het}$; provided that when A is a structure iv, W is not $-\text{Y-het}$;
Y is NH, O, or S;

R^1 is

- (a) H,
(b) NH_2 ,
15 (c) NHC_{1-4} alkyl,
(d) C_{1-4} alkenyl,
(e) OC_{1-4} alkyl,
(f) SC_{1-4} alkyl,
(g) $(\text{CH}_2)_n\text{-C}_{3-6}$ cycloalkyl, or
20 (h) C_{1-4} alkyl, optionally substituted with 1-3 F, 1-2 Cl or CN;

R_2 and R_3 are independently H, F, Cl or C_{1-2} alkyl;

R_4 is

- (a) $-\text{C(=O)-CR}_5\text{R}_6\text{-O-R}_7$,
(b) $-\text{C(=O)-CH}_2\text{S(O)}_n\text{-CH}_3$,
25 (c) $-\text{C(=O)-CH}_2\text{-S(=O)(=NR}_8\text{)CH}_3$,
(d) $-\text{C(=S)-R}_9$,
(e) $-\text{C(=O)-CH}_2\text{-O-R}_{10}$,

- (f) $-\text{C}(=\text{O})-(\text{CH}_2)_m-\text{C}(=\text{O})-\text{CH}_3$,
 (g) $-\text{C}(=\text{O})-(\text{CH}_2\text{OH})_2-\text{CH}_3$,
 (h) $-\text{C}(=\text{O})-\text{CH}_2-\text{CH}_2-\text{OR}_{14}$, or
 (i) $-\text{CN}$;

5 R_5 is H;

R_6 is phenyl, benzyl, CH_2OH or CH_2OCH_3 ; or

R_5 and R_6 taken together form C_{3-5} cycloalkyl;

R_7 is H, CH_3 or C_{1-4} alkanoyl;

R_8 is H, C_{1-4} alkyl, C_{1-4} alkanoyl, $-\text{C}(=\text{O})\text{NH}-\text{C}_{1-4}$ alkyl or $-\text{CO}_2\text{C}_{1-4}$ alkyl;

10 R_9 is C_{1-4} alkyl, $\text{CH}_2\text{OR}_{11}$, $\text{S}-\text{C}_{1-4}$ alkyl, OC_{1-4} alkyl, or $\text{NR}_{12}\text{R}_{13}$;

R_{10} is phenyl, $-\text{CO}_2-(\text{CH}_2)_2-\text{OCH}_3$, $-\text{P}(=\text{O})(\text{OH})_2$, $-\text{C}(=\text{O})-\text{NR}_{12}\text{R}_{13}$, or
 $-\text{C}(=\text{O})-(\text{CH}_2)_2-\text{CO}_2\text{H}$;

R_{11} is H, phenyl, benzyl, CH_3 or $\text{C}(=\text{O})\text{CH}_3$;

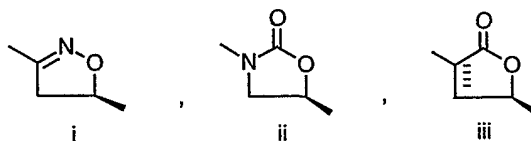
R_{12} and R_{13} are independently H or C_{1-3} alkyl; or R_{12} and R_{13} taken together form a 5- or 6-

15 membered saturated heterocycle, wherein said saturated heterocycle may further contain one or two additional hetero-atoms selected from a group consisting of O, $\text{S}(\text{O})_n$ or NR_7 ;

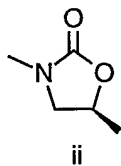
R_{14} is H, CH_3 or benzyl;

n is 0, 1 or 2; and m is 0 or 1.

20 2. A compound of formula I according to claim 1 wherein A is an optical configuration of structure i, ii or iii:



25 3. A compound of formula I according to claim 1 wherein A is an optical configuration of structure ii:



4. A compound of formula I according to claim 3 wherein R₁ is C₁₋₄ alkyl.
5. A compound of formula I according to claim 3 wherein R₁ is ethyl.
- 5 6. A compound of formula I according to claim 3 wherein R₂ and R₃ are independently H or F.
7. A compound of formula I according to claim 3 wherein at least one of R₂ or R₃ is H, the other one is F.
- 10 8. A compound of formula I according to claim 3 wherein R₄ is
- (a) C(=O)-CH(CH₂-phenyl)(OH),
- (b) C(=O)-CH₂-SO₂-CH₃,
- (c) C(=O)-CH(OH)(CH₂OH),
- 15 (d) C(=O)-C(=O)-CH₃,
- (e) C(=O)-CH(OH)(CH₂-O-CH₃),
- (f) C(=O)-CH₂CH₂-OH,
- (g) C(=O)-CH₂-O-CO₂-(CH₂)₂-OCH₃,
- (h) C(=S)-CH₃ or
- 20 (i) CN.
9. A compound of claim 3 which is
- (a) N{[(5*S*)-3-(3-fluoro-4-{4-[2-(methylsulfinyl)acetyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}propanethioamide,
- 25 (b) N-[(5*S*)-3-(3-fluoro-4-{4-[2-(methylsulfanyl)acetyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}propanethioamide,
- (c) N-[(5*S*)-3-(3-fluoro-4-{4-[2-(methylsulfonyl)acetyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}propanethioamide,
- (d) N-[(5*S*)-3-[4-(4-ethanethiolyl-1-piperazinyl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl]methyl}propanethioamide,
- 30 (e) N-[(5*S*)-3-[4-(4-cyano-1-piperazinyl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl]methyl}propanethioamide,

- (f) N-((5*S*)-3-(3-fluoro-4-{4-[2-(methylaminocarbonyloxy)acetyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- (g) N-((5*S*)-3-(3-fluoro-4-{4-[2-[(2-methoxyethoxy)carbonyloxy]acetyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- 5 (h) N-(((5*S*)-3-{3-fluoro-4-[4-((2*S*)-2-hydroxy-3-methoxypropanoyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- (i) N-(((5*S*)-3-{3-fluoro-4-[4-((2*S*)-2,3-dimethoxypropanoyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- (j) N-(((5*S*)-3-{3-fluoro-4-[4-((2*S*)-3-hydroxy-2-methoxypropanoyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- 10 (k) N-((5*S*)-3-[3-fluoro-4-(4-acetoacetyl-1-piperazinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- (l) N-((5*S*)-3-[3-fluoro-4-(4-pyruvoyl-1-piperazinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- 15 (m) N-((5*S*)-3-[3-fluoro-4-[4-(3-hydroxypropanoyl)-1-piperazinyl]phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- (n) N-(((5*S*)-3-(3-fluoro-4-{4-[(1-hydroxycyclopropyl)carbonyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- (o) N-(((5*S*)-3-{3-fluoro-4-[4-(2-phenoxyacetyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- 20 (p) N-((5*S*)-3-[3-fluoro-4-[4-((2*S*)-2,3-dihydroxypropanoyl)-1-piperazinyl]phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- (q) N-((5*S*)-3-[3-fluoro-4-[4-((2*R*)-2,3-dihydroxypropanoyl)-1-piperazinyl]phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- 25 (r) N-(((5*S*)-3-(3-fluoro-4-{4-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- (s) N-(((5*S*)-3-{3-fluoro-4-[4-((2*S*)-2-hydroxy-3-phenylpropanoyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- (t) N-(((5*S*)-3-{3-fluoro-4-[4-((2*R*)-2-hydroxy-3-phenylpropanoyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- 30 (u) N-(((5*S*)-3-{3-fluoro-4-[4-((2*R*)-2-hydroxy-2-phenylacetyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide, or

- (v) N-(((5*S*)-3-{3-fluoro-4-[4-((2*S*)-2-acetoxy-2-phenylacetyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide.
10. A compound of claim 3 which is
- 5 (a) N-(((5*S*)-3-(3-fluoro-4-{4-[2-(methylsulfonyl)acetyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide, or
- (b) N-(((5*S*)-3-[4-(4-ethanethiolyl-1-piperazinyl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide.
- 10 11. A compound of claim 3 which is
- N-(((5*S*)-3-[4-(4-cyano-1-piperazinyl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide.
12. A compound of claim 3 which is
- 15 (a) N-(((5*S*)-3-(3-fluoro-4-{4-[2-[(2-methoxyethoxy)carbonyloxy]acetyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- (b) N-(((5*S*)-3-{3-fluoro-4-[4-((2*S*)-2-hydroxy-3-methoxypropanoyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- (c) N-(((5*S*)-3-[3-fluoro-4-[4-(3-hydroxypropanoyl)-1-piperazinyl]phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- 20 (d) N-(((5*S*)-3-[3-fluoro-4-[4-((2*S*)-2,3-dihydroxypropanoyl)-1-piperazinyl]phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- (e) N-(((5*S*)-3-[3-fluoro-4-[4-((2*R*)-2,3-dihydroxypropanoyl)-1-piperazinyl]phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide, or
- 25 (f) N-(((5*S*)-3-{3-fluoro-4-[4-((2*R*)-2-hydroxy-3-phenylpropanoyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide.
13. A compound of claim 3 which is
- N-(((5*S*)-3-[3-fluoro-4-(4-pyruvoyl-1-piperazinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- 30
14. Use of a compound of formula I as shown in claim 1 to 13 for manufacturing of medicinals for the treatment of microbial infections in a mammal.

15. The use of claim 14 wherein said compound of formula I is administered to the mammal orally, parenterally, transdermally, or topically in a pharmaceutical composition.
- 5 16. The use of claim 15 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.
17. The use of claim 15 wherein said compound is administered in an amount of from about 1 to about 50 mg/kg of body weight/day.
- 10 18. A use for treating microbial infections of claim 14 wherein the infection is skin infection.
- 15 19. A use for treating microbial infections of claim 14 wherein the infection is eye infection.
20. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D263/22 A61K31/42 A61P31/00		
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, PAJ, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
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X	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 cpds.30,32,38,45 page 1, line 11 - line 20; examples 1,7,11,25,26,31	1-20
-/--		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> 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 *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family		
Date of the actual completion of the international search	Date of mailing of the international search report	
1 June 2001	12/06/2001	
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	Fritz, M	

INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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