

53/86

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

SUPERINDUSTRIA Y COMERCIO

Radicación : 01009443 00000003

Folios: 69

Fecha (RR): 2001-05-30 16:50:04

Trámite : 002 PATENTES D 1 REGISTRO/ 444 REPUESTA

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: **P1.-PHARMACIA & UPJOHN COMPANY.-Solicitud de Patente de Invención para "TIOAMIDAS DE OXAZOLIDINONA CON SUBSTITUYENTES DE PIPERAZIN-AMIDA".-Clase A. 61-Expediente número 01-009.443.-**

1. Me refiero a la solicitud de patente arriba nombrada de 8 de Febrero de 2001 y al requerimiento hecho por ese Despacho notificado por fijación en lista de fecha 5 de Abril del mismo año.

2. Anexos me permito presentar a usted:

(1) En original y dos copias, una de ellas de 6cm x 6cm, Artes finales (5) de las fórmulas químicas características de la invención para la publicación en la Gaceta de la Propiedad Industrial;

(2) Copia autentica, debidamente certificada de la solicitud de patente presentada para el invento arriba nombrado **respecto de la cual reclamo prioridad**, a saber la solicitud estadounidense número 60/181.640 de 10 de Febrero de 2000, junto con su traducción correspondiente a las legalizaciones y reivindicaciones de dicho documento; y

(3) Documento que acredita el traspaso que el autor del invento de la referencia hace a favor de mi representando, de sus derechos sobre el mismo, debidamente apostillado, junto con

51 57

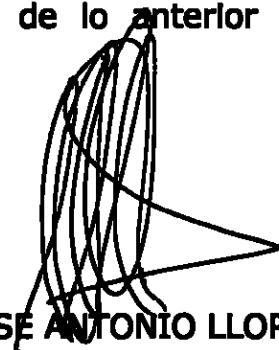
su traducción oficial número 8260, debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 131562 de 4 de Mayo de 2001 correspondiente a las legalizaciones y partes pertinentes de dicho documento de traspaso.

3. Copia debidamente autenticada por el Notario Sexto del Circulo de Bogotá, de los documentos que acreditan la calidad de Traductor Oficial de la señora María Mercedes Uricoechea quien elaboró la traducción de las legalizaciones y las reivindicaciones de la solicitud estadinense número 60/181.640 de 10 de Febrero 2000.

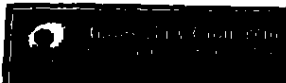
4. Llamo la atención de ese Despacho que el arte final no fue requerido pero va a ser presentado junto con este memorial.

5. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor SuperIntendente,



JOSE ANTONIO LLOREDA
T.P. 10.784
Código 231



FORMATO DE DIGITALIZACION
RELACION DE ANEXOS



Reyni
Technologies S.A.
Incorporated in the U.S.A.

Expediente No		No de Folio
Item	No de Unidades	
1	CD	
2	DVD	
3	REVISTA	
4	LIBRO	
5	PERIODICO	
6	DISQUETES	
7	SOBRE DE MANILA	
8	SOBRE BLANCO TAMAÑO CARTA	
9	SOBRE BLANCO TAMAÑO OFICIO	
10	OTROS:	
Observaciones: Ate Fum		

REPUBLICA DE COLOMBIA
MINISTERIO DE RELACIONES EXTERIORES

CERTIFICACION

Se hace constar que el Señor(a) MARIA MERCEDES URICOECHEA TORRES

se encuentra debidamente registrado(a) ante el Ministerio de Relaciones

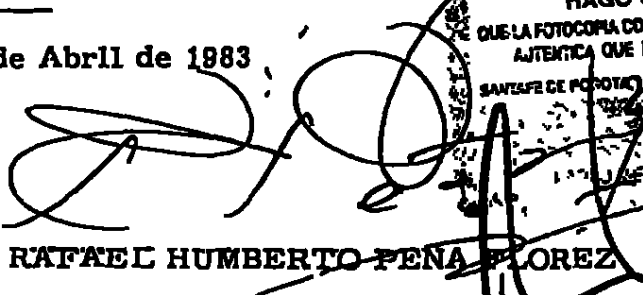
Exteriores, como traductor e interprete oficial para los idiomas

Inglés - Español - Inglés según resolución N° 10607

de fecha 31 de Diciembre de 1981 del Ministerio de Justicia.

Se expide a los 6 días del mes de Abril de 1983

Atentamente,


RAFAEL HUMBERTO PEÑA FLOREZ
JEFE DE NEGOCIOS GENERALES

COMO NOTARIO DEL DEPARTAMENTO
DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA

SANTAFE DE BOGOTA
24 AGO 1998

COMO NOTARIO DEL DEPARTAMENTO DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
16 JUN 1998

COMO NOTARIO DEL DEPARTAMENTO DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA
AUTENTICA QUE HE TENIDO A LA VISTA
24 NOV 1998

MINISTERIO DE RELACIONES EXTERIORES

Pharmaceutical
St. John Company
PUC 6296.1
01.009.443

ESTADOS UNIDOS DE AMERICA

A TODOS A QUIENES LLEGUE EL PRESENTE:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Marcas y Patentes

30 de enero de 2001

LA PRESENTE CERTIFICA QUE LA ADJUNTA ES UNA COPIA TOMADA DE LOS REGISTROS DE LA OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS, DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE ABAJO IDENTIFICADA Y LA CUAL CUMPLE CON LOS REQUISITOS PARA QUE LE SEA CONFERIDA UNA FECHA DE RADICACIÓN SEGÚN 35 USC 111.

NUMERO DE SOLICITUD 60/181,640

FECHA DE RADICACIÓN: 10 de febrero de 2000

Por Autoridad del

COMISIONADO DE MARCAS Y PATENTES

(FIRMA T. WALLACE

Oficial de Certificación)

(SELLO DORADO DE OBLEA)

Merla Mercedes Urcoechua
Lic. No. 10637 14. Justicia
Fideicomiso Judicial

50 61

CERTIFICADO DE CORREO (37 CFR 1.10)

Rótulo de correo "Expreso" No. EM 177639282 Fecha Depósito 10 de febrero de 2000

Certifico que este documento o comisión está siendo depositado en el Servicio Postal de los EE.UU. en la fecha arriba indicada y dirigido al Comisionado Asistente de Patentes, Washington D.C. 20231.

(FIRMA) JULIE K. LYONS, Asistente Legal.

OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS

Comisionado de Marcas y Patentes
Washington, DC 20231

**CARTA REMISORIA PARA UNA SOLICITUD DE PATENTE PROVISIONAL
BAJO 37 C.F.R. § 1.53 (c)**

La presente es una solicitud para radicar una solicitud provisional bajo 37 CFR 1.53(c).

La solicitud se titula **TIOAMIDAS DE OXAZOLIDINONA CON SUSTITUYENTES
DE AMIDA DE PIPERAZINA**, nuestro Expediente No. 6296 y consta de:

- [33] páginas de especificación
- [6] páginas de Reivindicaciones
- [1] página de Resumen

[x] El nombre y dirección del inventor se indican en la Hoja de Información del Inventor.

Esta solicitud es enviada por Correo Expreso bajo 37 CFR 1.10 y arriba aparece el respectivo certificado.

AUTORIZACIÓN ESPECIFICA PARA CUENTA DE DEPOSITO. Favor cargar a mi Cuenta de Depósito No. 21-0818 la suma de la comisión de Solicitud Provisional para una compañía (US\$150.00 o la suma que el Comisionado requiera). Se adjuntan 3 copias de esta hoja para tal fin.

Maria Mercedes M. ...
Pat. No. ...
Traducción de ...

UAE

54 12

La suscrita solicita que toda la correspondencia y comunicaciones telefónicas relacionadas con esta solicitud sean dirigidas a la suscrita a la dirección y número telefónico que se indican abajo.

(FIRMA) LUCY X. YANG. Apoderada

Fecha: 2-10-2000.

Registro No. 40,259

Pharmacia & Upjohn Company
Global Intellectual Property
301 Henrietta Street
Kalamazoo, Michigan 49001

Tel: (616)833-9536 o (616) 833-9500
Telefax No. (616) 833-8897 o (616) 833-2316

Se adjunta:

- ☒ Solicitud de Patente
- ☒ Hoja de Información del Inventor

Maria Mercedes Hinojosa
Rev. No. 14027
Traductora Jurada

Maria Mercedes Hinojosa

60. ~~63~~

1. Un compuesto de la fórmula (I):



A es una estructura i, ii o iii



- (a) H,
- (b) NH₂,
- (c) NH-alquilo C₁₋₄,

Udov - Hucsek

61 ~~61~~

- (d) alqueno C_{1-4} ,
- (e) O-alquilo C_{1-4} ,
- (f) S-alquilo C_{1-4} ,
- (g) $(CH_2)_n$ -cicloalquilo C_{3-6} , c
- (h) alquilo C_{1-4} , sustituido opcionalmente con 1-3 F, 1-2 Cl o CN;

R_2 y R_3 son independientemente H, F, Cl o alquilo C_{1-2} ;

R_4 es

- (a) $-C(=O)-CR_5R_6-O-R_7$,
- (b) $-C(=O)-CH_2S(O)_n-CH_3$,
- (c) $-C(=O)-CH_2-S(=O)(=NR_8)-CH_3$,
- (d) $-C(=S)-R_9$,
- (e) $-C(=O)-CH_2-O-R_{10}$,
- (f) $-C(=O)-(CH_2)_m-C(=O)-CH_3$,
- (g) $-C(=O)-(CH_2OH)_2-CH_3$,
- (h) $-C(=O)-CH_2-CH_2-OR_{14}$, o
- (i) $-CN$;

Maria Mercedes Lindochee
Reg. No. 10507 M. Uchier
Traductora Juramentada
Maria Mercedes Lindochee

62 65

R₅ es H

R₆ es fenilo, bencilo, CH₂OH o CH₂OCH₃; o

R₅ y R₆ tomados juntos forman cicloalquilo C₃₋₅;

R₇ es H, CH₃ o alcanoilo C₁₋₄;

R₈ es H, alquilo C₁₋₄, alcanoilo C₁₋₄, -C(=O)NH-alquilo C₁₋₄ o -CO₂alquilo C₁₋₄;

R₉ es alquilo C₁₋₄, CH₂OR₁₁, S-alquilo C₁₋₄, O-alquilo C₁₋₄ o NR₁₂R₁₂;

R₁₀ es fenilo, -CO₂-(CH₂)₂-OCH₃, -P(=O)(OH)₂, -C(=O)-NR₁₂R₁₂, o

-C(=O)-CH₂)₂-CO₂H;

R₁₁ es H, fenilo, bencilo, CH₃ o C(=O)CH₃;

R₁₂ y R₁₃ son independientemente H o alquilo C₁₋₃; o R₁₂ y R₁₃ tomados juntos forman un heterociclo saturado de 5 ó 6 miembros, en donde dicho heterociclo saturado puede contener además uno o dos heteroátomos adicionales seleccionados de un grupo compuesto por O, S(O)_n o NR₇;

R₁₄ es H, CH₃ o bencilo;

n es 0, 1 o 2; y m es 0 o 1.

2. Un compuesto de la fórmula I según Reivindicación 1, en donde R₁ es alquilo C₁₋₄.

Maria M. de los Angeles
not. 11. 1. 1977
Udaco - H. M. de los Angeles

63.68

3. Un compuesto de la fórmula I según la Reivindicación 1, en donde R_1 es etilo.

4. Un compuesto de la fórmula I según la Reivindicación 1, en donde R_2 y R_3 son independientemente H o F.

5. Un compuesto de la fórmula I según la Reivindicación 1, en donde al menos uno de R_2 o R_3 es H, y el otro es F.

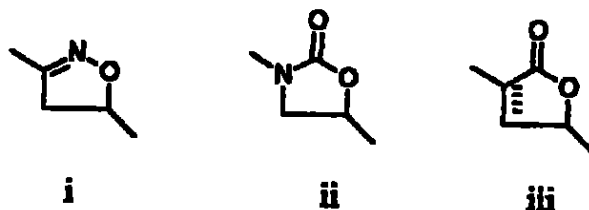
6. Un compuesto de la fórmula I según la Reivindicación 1, en donde R_4 es:

- (a) $C(=O)-CH(CH_2\text{-fenilo})(OH)$,
- (b) $C(=O)-CH_2-SO_2-CH_3$,
- (c) $C(=O)-CH(OH)(CH_2OH)$,
- (d) $C(=O)-C(=O)-CH_3$,
- (e) $C(=O)-CH(OH)(CH_2-O-CH_3)$,
- (f) $C(=O)-CH_2CH_2-OH$,
- (g) $C(=O)-CH_2-O-CO_2-(CH_2)_2-OCH_3$,
- (h) $C(=S)-CH_3$, o
- (i) CN.

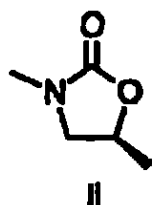
María Mercedes Uricoechea
Res. No. 10.077 - Antigua
Traductora Juramentada
María Mercedes Uricoechea

64 87

7. Un compuesto de la fórmula I según la Reivindicación 1, en donde A es una configuración óptica de la estructura i, ii o iii:



8. Un compuesto de la fórmula (II) según la Reivindicación 1, en donde A es una configuración óptica de la estructura ii:



9. Un compuesto según la Reivindicación 1, que es:

- (1) N-(((5S)-3-(3-fluoro-4-{4-[2-metilsulfinil]acetil}-1-piperazinil)fenilo)-2-oxo-1,3-oxazolidin-5-ilo]metilo} propantioamida,
- (2) N-(((5S)-3-(3-fluoro-4-{4-[2-metilsulfanil]acetil}-1-piperazinil)fenilo)-2-oxo-1,3-oxazolidin-5-ilo]metilo} propantioamida,

María Mercedes Llanos Sánchez
 Abogada
 Legales y Litigios

María Mercedes Llanos Sánchez

5 60

- (3) N-(((5S)-3-(3-fluoro-4-(4-[2-metilsulfonyl]acetil)-1-piperazinil)fenilo)-2-oxo-1,3-oxazolidin-5-ilo)metilo)propantioamida,
- (4) N-(((5S)-3-(4-(4-etantioil-1-piperazinil)-3-fluorofenil)-2-oxo-1,3-oxazolidin-5-ilo)metilo)propantioamida,
- (5) N-(((5S)-3-(4-(4-ciano-1-piperazinil)-3-fluorofenil)-2-oxo-1,3-oxazolidin-5-ilo)metilo)propantioamida,
- (6) N-(((5S)-3-(3-fluoro-4-(4-[2-metilaminocarboniloxi]acetil)-1-piperazinil)fenilo)-2-oxo-1,3-oxazolidin-5-ilo)metilo)propantioamida,
- (7) N-(((5S)-3-(3-fluoro-4-(4-[2-[(2-metoxietoxi)carboniloxi]acetil)-1-piperazinil]fenilo)-2-oxo-1,3-oxazolidin-5-ilo)metilo)propantioamida,
- (8) N-(((5S)-3-(3-fluoro-4-[4-((2S)-2-hidroxi-3-metoxipropanoil)-1-piperazinil]fenilo)-2-oxo-1,3-oxazolidin-5-ilo)metilo)propantioamida,
- (9) N-(((5S)-3-(3-fluoro-4-[4-((2S)-2,3-dimetioxipropanoil)-1-piperazinil]fenilo)-2-oxo-1,3-oxazolidin-5-ilo)metilo)propantioamida,

Maria Mercedes Unzueta
de No. 123456789
Firma Juremanada

66/89

- (10) N-(((5S)-3-{3-fluoro-4-[4-((2S)-3-hidroxi-3-metoxipropanoil)-1-piperazinil]fenilo}-2-oxo-1,3-oxazolidin-5-ilo)metilo) propantioamida,
- (11) N-(((5S)-3-{3-fluoro-4-(4-acetoacetil-1-piperazinil]fenilo)-2-oxo-1,3-oxazolidin-5-ilo)metilo) propantioamida,
- (12) N-(((5S)-3-{3-fluoro-4-(4-piruvoilo-1-piperazinil]fenilo)-2-oxo-1,3-oxazolidin-5-ilo)metilo) propantioamida,
- (13) N-(((5S)-3-{3-fluoro-4[4-(3-hidroxiopropanoil)-1-piperazinil]fenilo]-2-oxo-1,3-oxazolidin-5-ilo)metilo) propantioamida,
- (14) N-(((5S)-3-{3-fluoro-4-(4-acetoacetil-1-piperazinil]fenilo)-2-oxo-1,3-oxazolidin-5-ilo)metilo) propantioamida,
- (15) N-(((5S)-3-{3-fluoro-4-[4-(2-fenoxiacetil)-1-piperazinil]fenilo)-2-oxo-1,3-oxazolidin-5-ilo)metilo) propantioamida,
- (16) N-(((5S)-3-{3-fluoro-4-[4-[4-(2S)-2,3-dihidroxiopropanoil)-1-piperazinil]fenil]-2-oxo-1,3-oxazolidin-5-ilo)metilo) propantioamida,
- (17) N-(((5S)-3-{3-fluoro-4-[4-((2R)-2,3-dihidroxiopropanoil)-1-piperazinil]fenilo]-2-oxo-1,3-oxazolidin-5-ilo)metilo) propantioamida,

Maria Mercedes Utrachea
Traductora Juramentada
Utrachea Mercedes

(2) N-(((5S)-3-[4-(4-etanoliol-1-piperazinil)-3-fluorofenil]-2-oxo-1,3-oxazolidin-5-il)metilo)propantioamida,

11. Un compuesto según la Reivindicación 1, que es:

N-(((5S)-3-[4-(4-ciano-1-piperazinil)-3-fluorofenil]-2-oxo-1,3-oxazolidin-5-ilo)metilo)propantioamida,

12. Un compuesto según la Reivindicación 1, que es:

(1) N-(((5S)-3-(3-fluoro-4-{4-[2-[(2-metoxietoxi)carboniloxi]acetil]-1-piperazinil}fenilo)-2-oxo-1,3-oxazolidin-5-ilo)metilo)propantioamida,

(2) N-[[[(5S)-3-{3-fluoro-4-[4-(2S)-2-hidroxi-3-metoxipropanoil)-1-piperazinil]fenilo}-2-oxo-1,3-oxazolidin-5-ilo)metilo]propantioamida,

(3) N-(((5S)-3-[3-fluoro-4-[4-(3-hidroxiopropanoil)-1-piperazinil]fenilo]-2-oxo-1,3-oxazolidin-5-ilo)metilo]propantioamida,

(4) N-(((5S)-3-[3-fluoro-4-[4-(2S)-2,3-dihidroxiopropanoil)-1-piperazinil]fenilo]-2-oxo-1,3-oxazolidin-5-ilo)metilo)propantioamida,

[illegible]

89 27

(5) N-(((5S)-3-[3-fluoro-4-[4-(2R)-2,3-dihidroxiopropanoil)-1-piperazinil]fenilo]-2-oxo-1,3-oxazolidin-5-ilo)metilo)propantioamida,

(6) N-(((5S)-3-[3-fluoro-4-[4-((2R)-2-hidroxi-3-fenilpropanoil)-1-piperazinil]fenilo]-2-oxo-1,3-oxazolidin-5-ilo)metilo)propantioamida.

13. Un compuesto según la Reivindicación 1 que es:

N-(((5S)-3-[3-fluoro-4-(4-piruvil-1-piperazinil)fenilo]-2-oxo-1,3-oxazolidin-5-ilo)metilo)propantioamida.

14. Un método para el tratamiento de infecciones microbianas que consiste en administrar a un mamífero que lo requiera, una cantidad efectiva de un compuesto de la fórmula I según la Reivindicación 1.

15. El método según la Reivindicación 14, en donde dicho compuesto de la fórmula I es administrado pro vía oral, parenteral, transdermal o tópicamente en una composición farmacéutica.

16. El método según la Reivindicación 14, en donde dicho compuesto es administrado en una cantidad entre aproximadamente 0,1 a aproximadamente 100 mg/kg de peso corporal por día.

Usted utiliza

P 23

17. El método según la Reivindicación 14, en donde dicho compuesto es administrado en una cantidad entre aproximadamente 1 a aproximadamente 50 mg/kg de peso corporal por día.

18. Un método para el tratamiento de infecciones microbianas según la Reivindicación 14, en donde la infección es una infección cutánea

19. Un método para el tratamiento de infecciones microbianas según la Reivindicación 14, en donde la infección es una infección de los ojos.

o

20. Una composición farmacéutica que comprende un compuesto según la Reivindicación 1 y un vehículo farmacéuticamente aceptable.

Ward University

PA 357070

THE UNITED STATES OF AMERICA**TO ALL TO WHOM THESE PRESENTS SHALL COME:****UNITED STATES DEPARTMENT OF COMMERCE****United States Patent and Trademark Office****January 30, 2001**

**THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM
THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK
OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT
APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A
FILING DATE UNDER 35 USC 111.**

APPLICATION NUMBER: 60/181,640**FILING DATE: February 10, 2000**

**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

T. Wallace
T. WALLACE
Certifying Officer

02-11-00

Docket No.: 6296

PROVISIONAL APPLICATION COVER SHEET

CERTIFICATE OF MAILING (37 CFR 1.10)

"Express Mail" No: EM177639282Date of Deposit: February 10, 2000

I hereby certify that this transmittal together with the patent application referred to below is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, DC 20231.

Julie K. Lyons, Legal Assistant

Name of Person Mailing Paper

Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner of Patents and Trademarks
Washington, DC 20231

TRANSMITTAL OF A PROVISIONAL APPLICATION
UNDER 37 CFR 1.53(c)

Sir:

This is a request for filing a provisional application under 37 CFR 1.53(c). The application is entitled OXAZOLIDINONE THIOAMIDES WITH PIPERAZINE AMIDE SUBSTITUENTS, our Docket No. 6296, and consists of:

- [33] page(s) of Specification
- [6] page(s) of Claims
- [] page(s) of Drawings
- [] page(s) of Sequence Listings
- [1] page(s) of Abstract

- ☐ A disk containing nucleotide and/or amino acid sequences in a computer readable format is attached. The contents of the sequence listing in the application is the same as the document on the disk. (37 CFR 1.821(f) and MPEP 2422.06)
- ☒ The name(s) and residence address(es) of the inventor(s) are set forth on the attached Inventor Information Sheet.
- ☐ As provided in 37 CFR 1.41(a)(3), instead of providing the names of the inventors at this time, the applicant identifier is: PNU.

This application is being sent by Express Mail under 37 CFR 1.10 and the required certificate appears above.

23
26

SPECIFIC DEPOSIT ACCOUNT AUTHORIZATION. Please charge my Deposit Account No. 21-0718 in the amount of the total Provisional Application filing fee for a large entity (\$150.00 or such greater or lesser amount as the Commissioner may require). Triplicate copies of this sheet are enclosed for this purpose.

The undersigned hereby requests that all correspondence and telephone communications in connection with this application be directed to the undersigned person at the mailing address and telephone number shown below.

Respectfully submitted,

Lucy X. Yang

Lucy X. Yang, Attorney
Registration No. 40,259

Date: 2-10-2000

Pharmacia & Upjohn Company
Global Intellectual Property
301 Henrietta Street
Kalamazoo, Michigan 49001

Telephone No. (616) 833-9536 or (616) 833-9500
Telefax No. (616) 833-8897 or (616) 833-2316

Enclosures:

- ☒ Patent Application
- ☐ Disk containing Nucleotide and/or Amino Acid Sequence Listing
- ☒ Inventor Information Sheet

60181640-021000

INVENTOR INFORMATION SHEET

Full name of sole or first inventor: Jackson B. Hester, Jr.
Address: 9219 East ML Avenue
Galesburg, Michigan 49053
Citizenship: USA

50181640.021000

25

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.

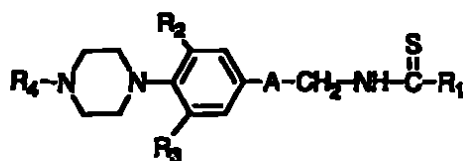
30 PCT International Publication WO 99/12914 discloses antimicrobial thiourea
derivatives.

E0181640.021000

76. 78

SUMMARY OF THE INVENTION

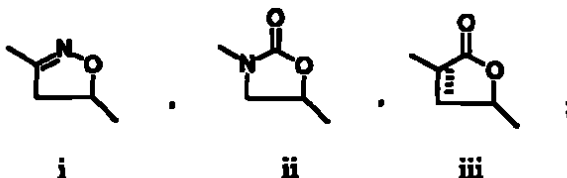
The present invention provides a compound of formula I



I

5 or a pharmaceutically acceptable salt thereof wherein:

A is a structure i, ii, or iii



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

10 $(CH_2)_n-C_{3-6}$ 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

- (a) $-C(=O)-CR_5R_6-O-R_7$,
- (b) $-C(=O)-CH_2S(O)_n-CH_3$,
- 15 (c) $-C(=O)-CH_2S(=O)(=NR_8)CH_3$,
- (d) $-C(=S)-R_9$,
- (e) $-C(=O)-CH_2-O-R_{10}$,
- (f) $-C(=O)-(CH_2)_m-C(=O)-CH_3$,
- (g) $-C(=O)-(CH_2OH)_2-CH_3$,
- 20 (h) $-C(=O)-CH_2-CH_2-OR_{14}$, or
- (i) $-CN$;

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;

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

R_8 is H, C_{1-4} alkyl, C_{1-4} alkanoyl, $-C(=O)NH-C_{1-4}$ alkyl or $-CO_2C_{1-4}$ alkyl;

R_9 is C_{1-4} alkyl, CH_2OR_{11} , $S-C_{1-4}$ alkyl, OC_{1-4} alkyl, or $NR_{12}R_{13}$;

77

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-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.

In another aspect, the present invention also provides:

- 10 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
- 15 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 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.

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,

25 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,

30 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

50181640.021000

7B. 2A

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.

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

A specific value for R₁ is C₁₋₄ alkyl.

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).

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).

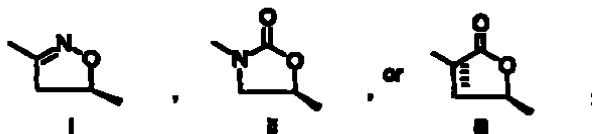
A specific value for R₄ is C(=O)-CH₂CH₂-OH.

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:



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.

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:

298

- (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-(methylsulfonyl)acetyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- 5 (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-ethanethiolyl-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,
- 10 (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,
- 15 (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,
- 20 (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,
- 25 (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,
- 30 (16) N-(((5S)-3-(3-fluoro-4-{4-[(2S)-2,3-dihydroxypropanoyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,

80-81

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

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

15 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 alternatively by resolution from a racemic mixture.

In step 1 of Scheme I, a suitably protected piperazine (II) is allowed to react with an

20 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 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

25 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 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

30 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

60181640.021000

81 82

5). Protecting groups (P) are chosen for their compatibility with other functional groups on the molecule. Benzyloxycarbonyl (Cbz) and *tert*-butoxycarbonyl (Boc) are generally 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.

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. 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 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 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 formula I (R₄ is -C(=O)-CH₂-S(=O)(=NR₃)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

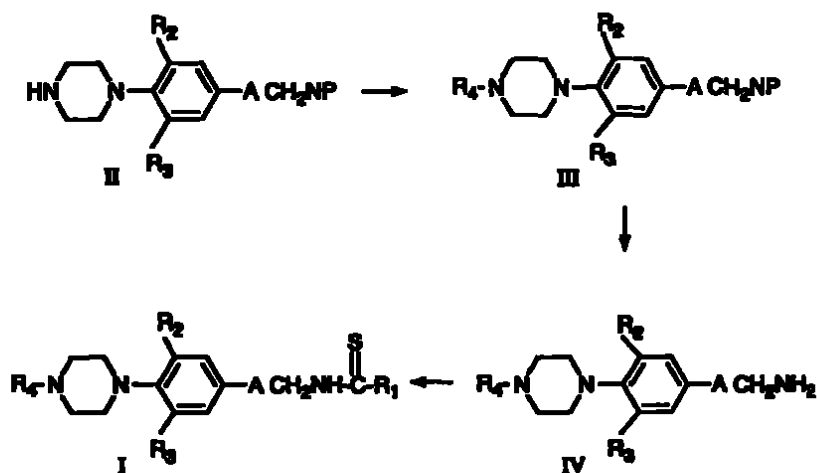
60181640-021000

82 83

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 R_4 substituents of compounds I or III of Scheme I can be modified to give additional compounds of formula I.

5

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
- 15 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
- 20 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.

60181640-021000

83.84

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

E0181640-021000

34/05

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.

60181640-021000

85 88

TABLE 1

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

	SAUR 9213 MIC	SEPI 30593 MIC	EPAB 12712 MIC	SPNE 9912 MIC	HINF 30063 MIC	HINF 30063 MIC	EPAB 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

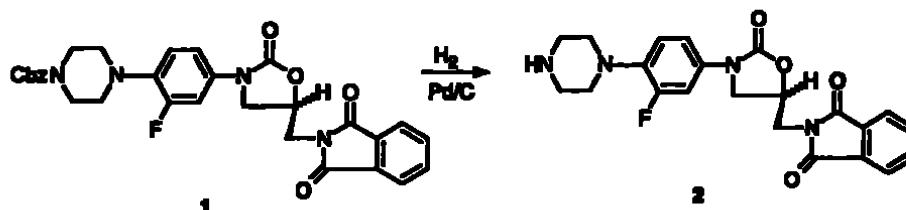
50181640-021000

86.87

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

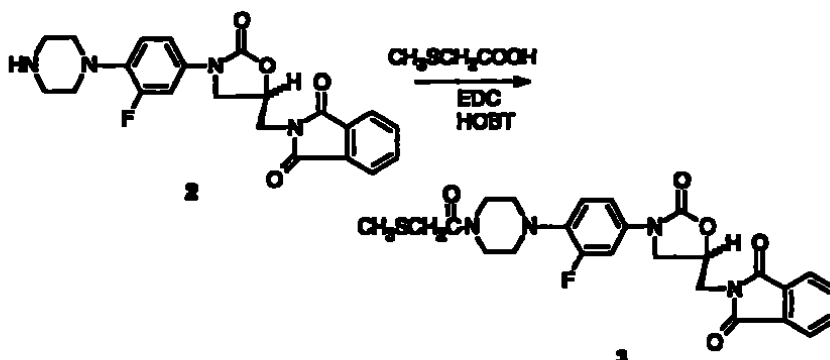
Step 1



5

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.

Step 2

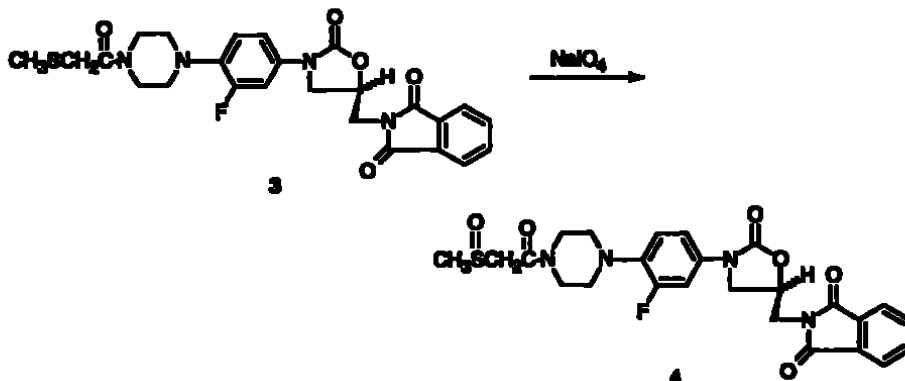


A stirred mixture of 2 (1.70 g, 4.01 mmol), 1-hydroxybenzotriazole hydrate (HOBT, 650 mg, 4.81 mmol), (methylthio)acetic acid (419 μ L, 4.81 mmol) and DMF (38 ml) is cooled to 0°C and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 1.54 g, 8.02 mmol). It is kept at 0°C 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.

60181640-021000

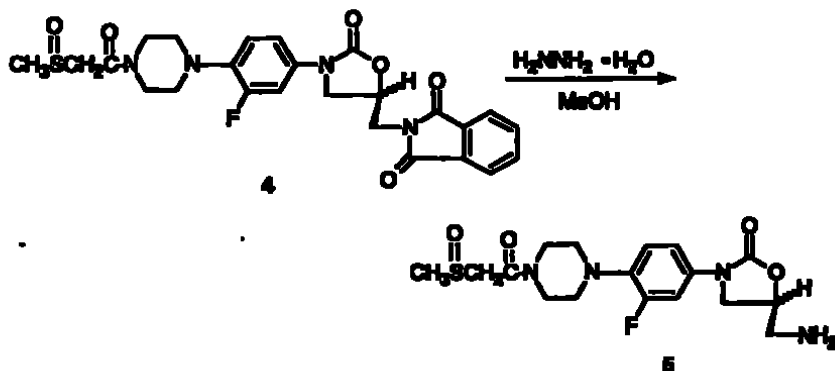
37. 88

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.

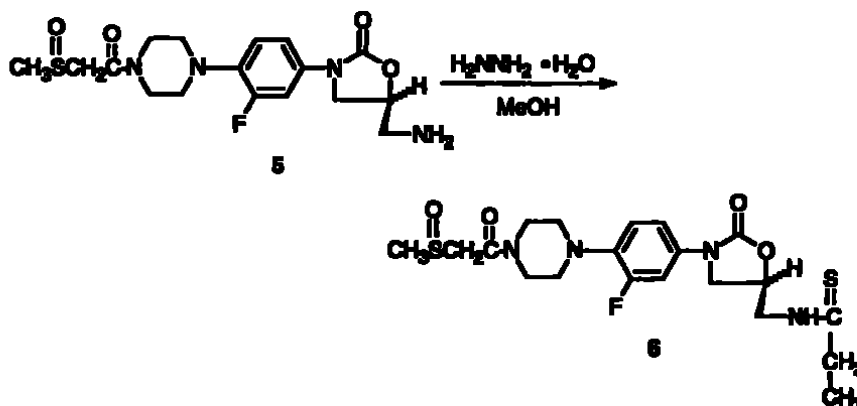
Step 4



A stirred mixture of 4 (964 mg, 1.82 mmol), hydrazine hydrate (177 μ L, 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.

000120-04918709

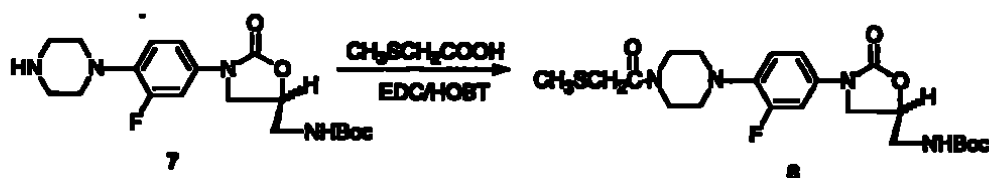
Step 5



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 $\text{C}_{19}\text{H}_{27}\text{FN}_4\text{O}_4\text{S}_2$: C, 51.05; H, 5.78; N, 11.91. Found: C, 50.82; H, 5.85; N, 11.80.

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

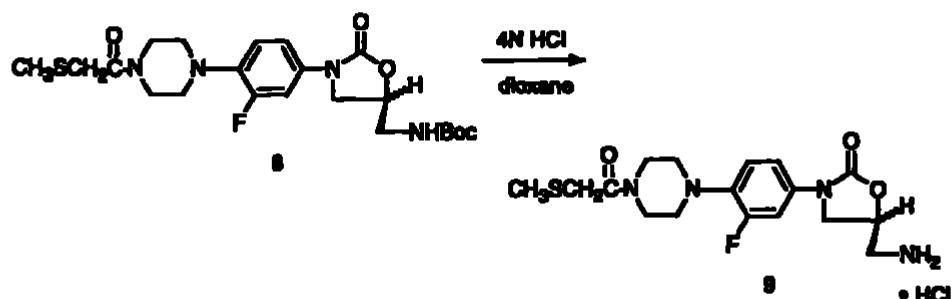
Step 1



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**.

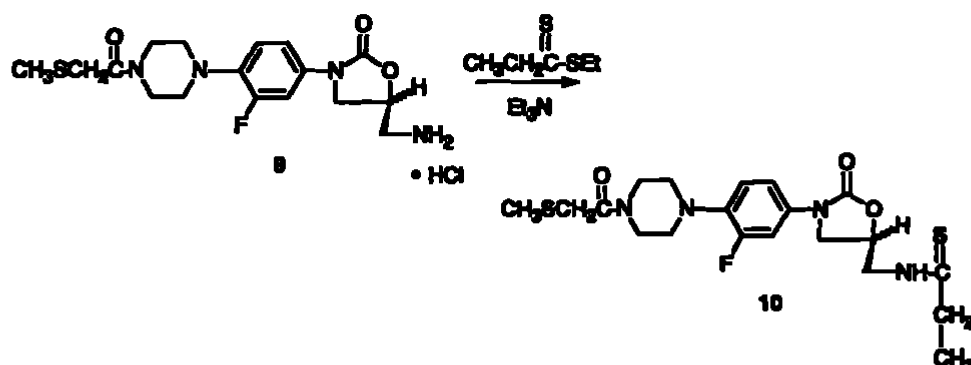
89

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

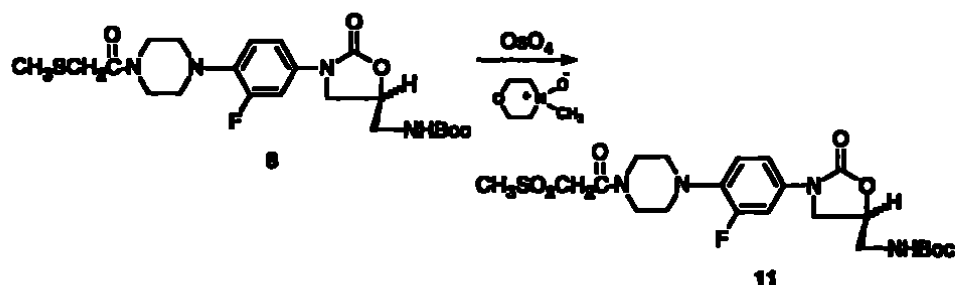


A stirred mixture of compound 9 (578 mg, 1.38 mmol), triethylamine (1.5 mL, 11.0 mmol), ethyl dithiopropanoate (0.76 mL, 5.52 mmol), CH₂Cl₂ (15.5 ml) and THF (15.5 ml) is kept at ambient temperature (24°C) for 18 hours and concentrated *in vacuo*. The residue is stirred with a mixture of water (30 ml) 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-(((5S)-3-(3-fluoro-4-{4-[2-(methylsulfonyl)acetyl]-1-piperazinyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide (13) (PNU-248337)

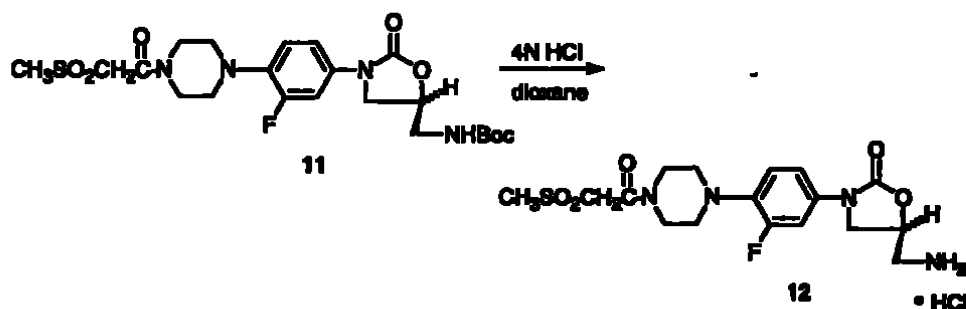
90.0%

Step 1



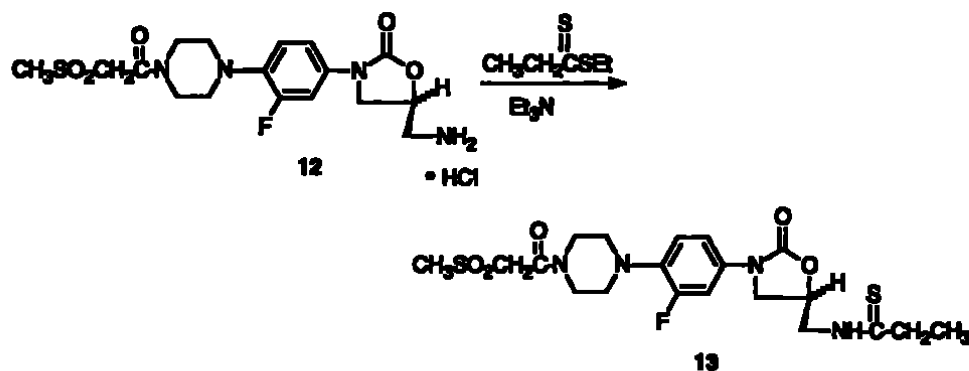
A stirred mixture of compound 8 (100 mg, 0.207 mmol), 4-methylmorpholine, N-oxide (73 mg, 0.621 mmol), acetone (1.5 ml) and water (0.5 ml) is treated with a 2.5% solution of osmium tetroxide in 2-methyl-2-propanol (17 μL) and kept at ambient temperature (24°C) for 18 hours. It is then treated with 10% 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^+).

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

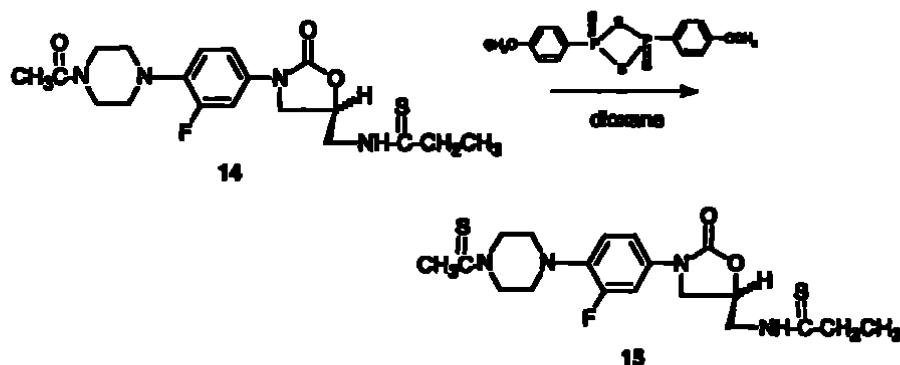
As described in Example 2, Step 3 compound 12 is allowed to react with ethyl dithiopropionate and triethylamine to give 13 which is purified by chromatography on silica

50181640-021000

91 92

gel with 1% MeOH-CH₂Cl₂ and crystallization from MeOH-EtOAc: MS(ESI) *m/z* 486 (M⁺); HRMS (FAB) calcd for C₂₀H₂₃FN₄O₃S₂ (M+H⁺) 487.1485, found 487.1494. Anal. Calcd for C₂₀H₂₃FN₄O₃S₂: C, 49.37; H, 5.59; N, 11.51. Found: C, 49.25; H, 5.63; N, 11.47.

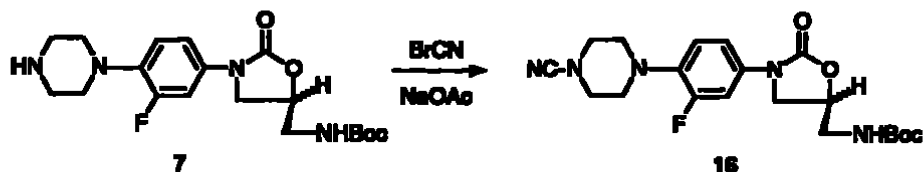
- 5 **Example 4** Preparation of N-(((5*S*)-3-[4-(4-ethanethioly-1-piperazinyl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide (15) (PNU-276575).



- 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 C₁₉H₂₃FN₄O₃S₂: C, 53.75; H, 5.93; N, 13.20. Found: C, 53.69; H, 6.00; N, 13.25.
- 10
- 15

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**

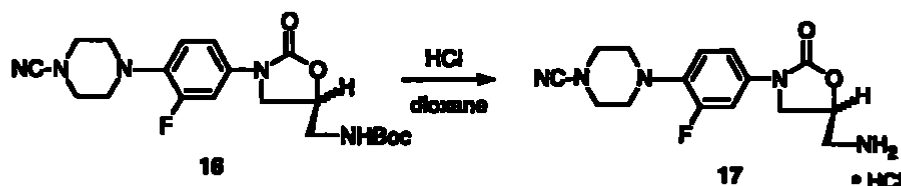


A stirred, ice cold mixture of 7 (0.488 g, 1.24 mmol) and sodium acetate (0.55 g, 6.7 mmol) in MeOH (40 ml) is treated during 1 minute, with a MeOH (10 ml) solution of

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:

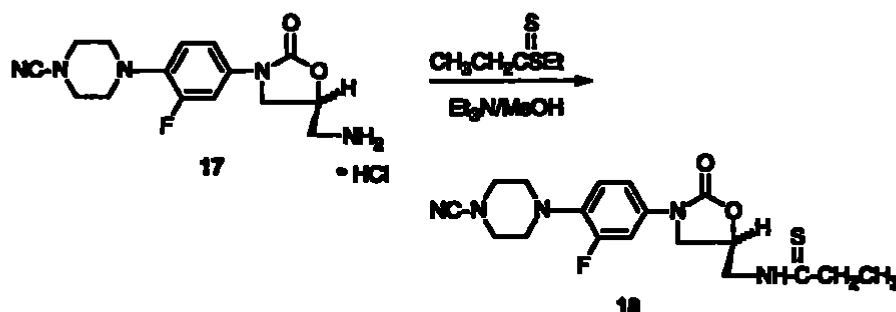
5 MS(ES) m/z 420 ($M+H^+$).

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 for 2 hours and concentrated *in vacuo*. The residue is dried *in vacuo* for 18 hours to give 17: MS(ES) m/z 320 ($M+H^+$).

Step 3

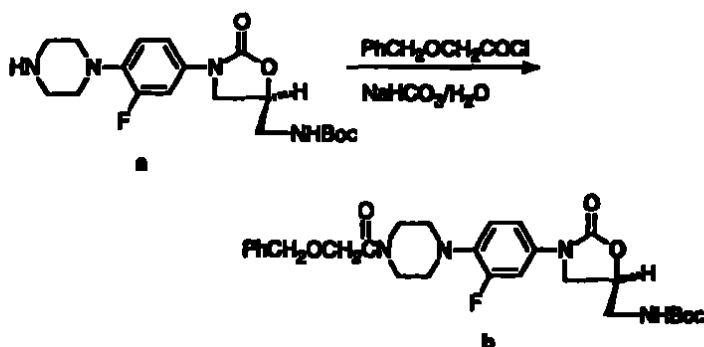


A stirred mixture of 17 (0.25 g, 0.64 mmol), and triethylamine (0.178 ml) in MeOH (5 ml), under nitrogen is warmed to 50°C during 30 minutes, kept at 50°C for 30 minutes and cooled in an ice bath. The solid is collected by filtration and crystallized from EtOH to give 18: mp 182-184°C; HRMS (FAB) calcd for $\text{C}_{18}\text{H}_{23}\text{FN}_5\text{O}_2\text{S}$ ($M+H^+$) 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)methyl)propanethioamide (22) (PNU-281328)

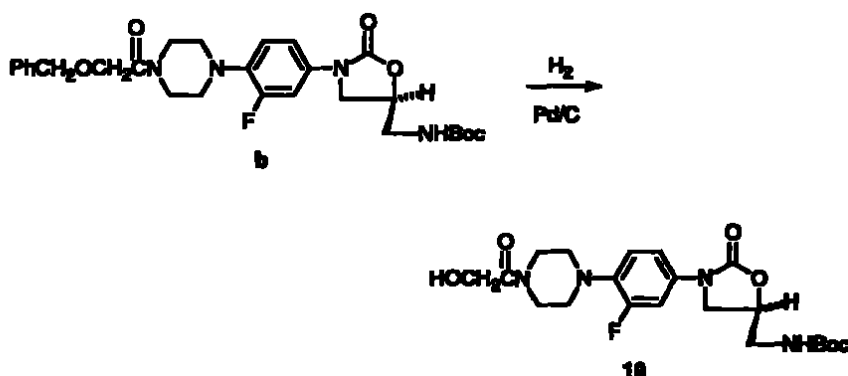
a3 g

Step 1



A stirred, ice cold mixture of 2 (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 benzoyloxycarbonyl 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 2b.

Step 2



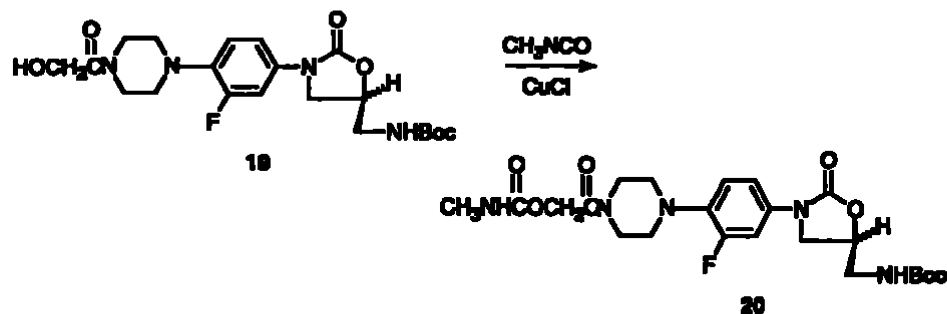
10

A mixture of 2c (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.

20

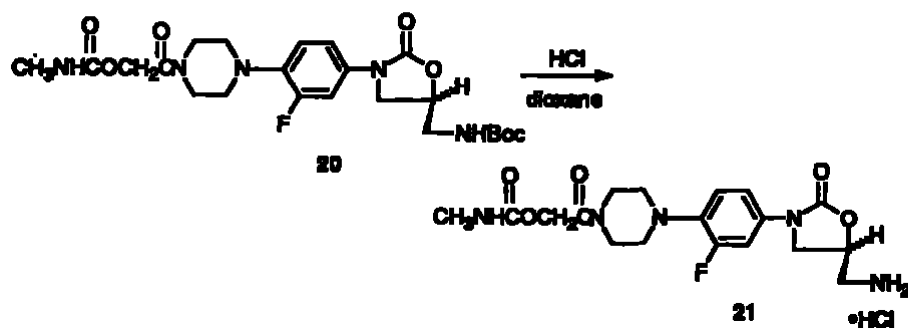
Step 3

94



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

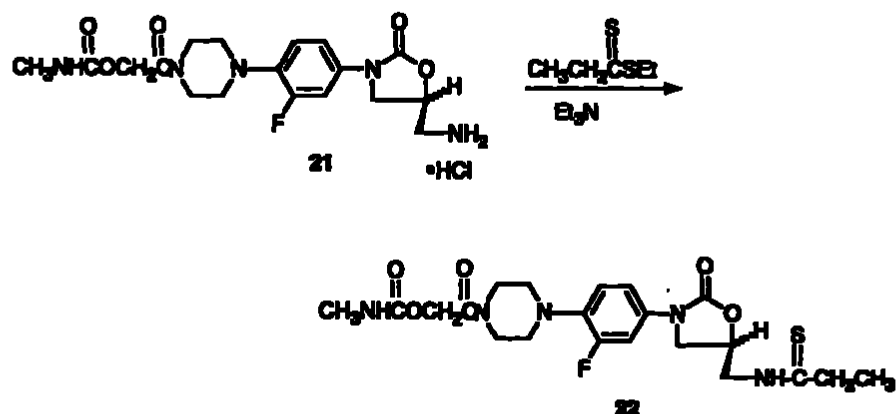


An ice cold, stirred mixture of 20 (0.37 g, 0.726 mmol) in dioxane (10 ml), under nitrogen is treated, drop-wise with ice cold 4N hydrogen chloride in dioxane (8 ml). The mixture is kept in the ice bath for 1 hour 15 minutes and at ambient temperature (24°C) for 1 hour. It is diluted with additional 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⁺).

50181640-021000

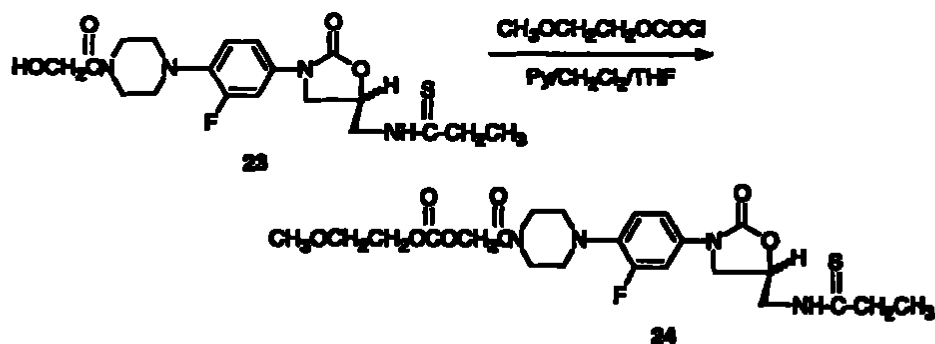
as
96

Step 5



A stirred mixture of 21 (0.20 g, 0.416 mmol), ethyl dithiopropanoate (0.17 ml) and triethylamine (0.5 ml) in CH_2Cl_2 (20 ml) and MeOH (5 ml) is kept, under nitrogen at ambient temperature (24°C) for 21 hours and concentrated under a stream of nitrogen. Chromatography of the residue on silica gel with 2% MeOH- CH_2Cl_2 gave 22: HRMS (FAB) calcd for $\text{C}_{21}\text{H}_{29}\text{FN}_5\text{O}_5\text{S}$ ($\text{M}+\text{H}^+$) 482.1873, found 482.1873.

Example 7 Preparation of N-((5S)-3-(3-fluoro-4-((2-methoxyethoxy)carbonyloxy)acetyl)-1-piperazinyl)phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide (24) (PNU-276528)



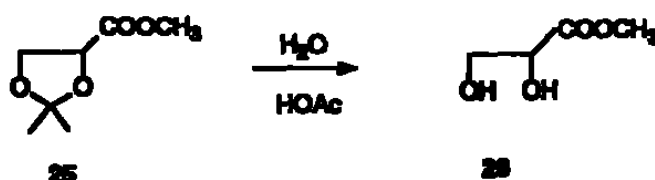
A stirred, ice cold mixture of 23 (may be prepared according to the procedure disclosed in PCT International Publication WO 98/54161) (0.212 g, 0.496 mmol) and pyridine (0.2 ml, 2.5 mmol) in CH_2Cl_2 (5 ml) and THF (5 ml) is treated, dropwise with 2-methoxyethyl chloroformate (0.069 g, 0.5 mmol) and kept in the ice bath for 1 hour and at ambient temperature (24°C) for 2 hours. Additional 2-methoxyethyl chloroformate (0.07 ml) is added; the mixture is kept at ambient temperature for 3 hours and again treated with additional 2-methoxyethyl chloroformate (0.1 ml). This mixture is kept at ambient temperature for 18 hours. It is mixed with saturated aqueous NaHCO_3 and extracted with

CH_2Cl_2 . The extract is washed with water and brine, dried (Na_2SO_4) and concentrated. Chromatography of the residue on silica gel with 2.5% $\text{MeOH}-\text{CH}_2\text{Cl}_2$ gave the product which is crystallized from EtOAc to give 0.185 g of 24: mp 150-151°C. Anal. Calcd for $\text{C}_{23}\text{H}_{31}\text{FN}_4\text{O}_7\text{S}$: C, 52.46; H, 5.93; N, 10.64. Found: C, 52.45, H, 6.05; N, 10.61.

5

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

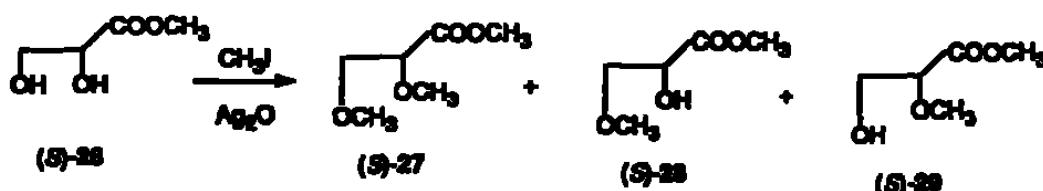
Step 1



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

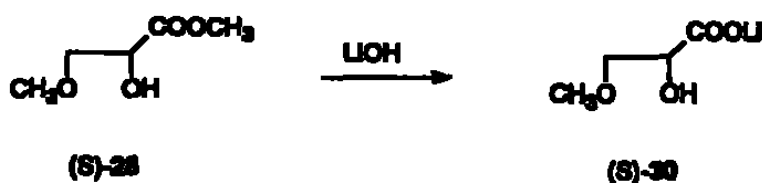


15

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 $\text{MeOH}-\text{CH}_2\text{Cl}_2$ 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).

Step 3

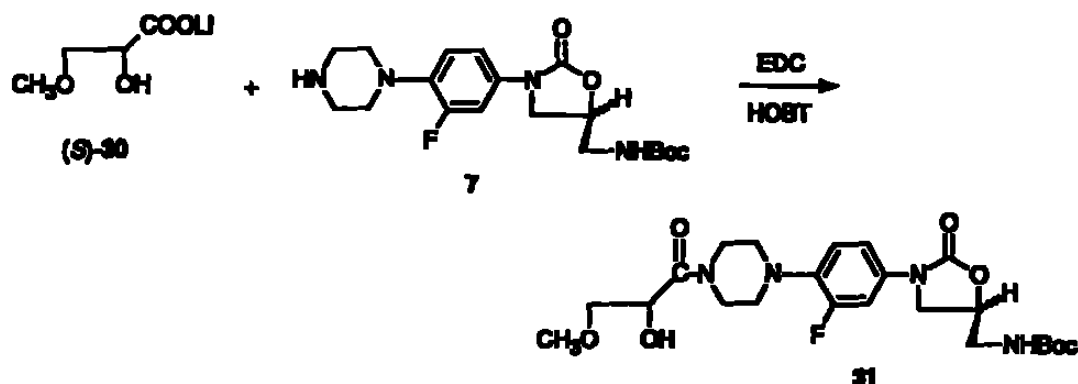


A stirred mixture of (*S*)-28 (0.08 g, 0.6 mmol) and MeOH (3.0 ml) under nitrogen, is treated with 1M lithium hydroxide (0.57 ml) and kept at ambient temperature (24°C) for

25

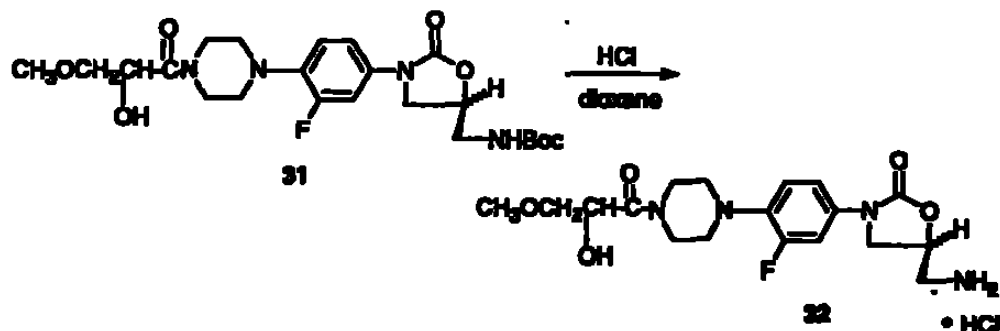
3 hours and under a stream of nitrogen for 18 hours. It is then concentrated *in vacuo* to give (S)-30.

Step 4



- 5 A stirred mixture of 7 (0.237 g, 0.60 mmol), the product ((S)-30) from Step 3, HOBT 0.095 g (0.703 mmol) and DMF (4 ml), under nitrogen, is treated with EDC (0.26 g, 1.36 mmol), kept at ambient temperature (24°C) for 2.5 hours and concentrated *in vacuo*. The residue is chromatographed on silica gel with 2.5% MeOH-CH₂Cl₂ to give 0.18 g of 31: MS(ES) *m/z* 497 (M+H⁺).

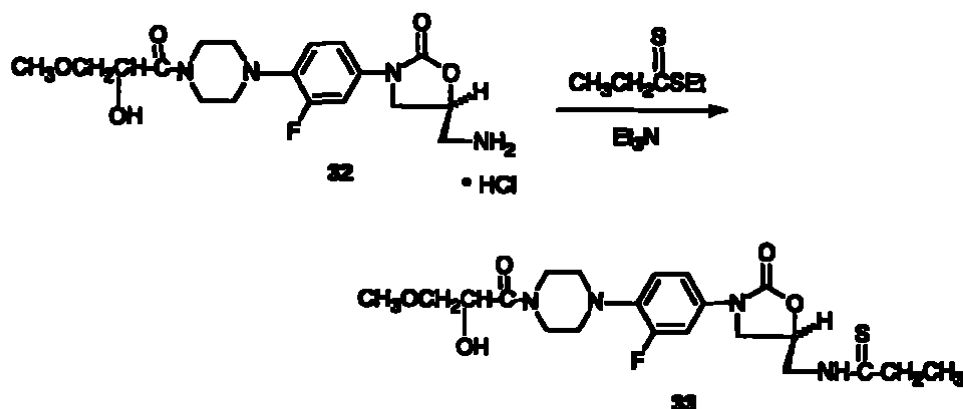
10 Step 5



- 15 An ice cold stirred mixture of 31 (0.17 g, 0.342 mmol) in dioxane (10 ml), under nitrogen, is treated, dropwise during 3 minutes with cold 4N HCl in dioxane (10 ml) and kept in the ice bath for 50 minutes, at ambient temperature (24°C) for 90 minutes and at 0°C for 18 hours. It is then concentrated *in vacuo* to give 32: MS(ES) *m/z* 397 (M+H⁺).

08 29

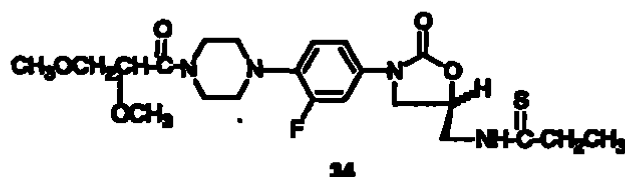
Step 6



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 dithiopropanoate (0.22 ml, 1.71 mmol) and kept at ambient temperature (24°C) for 72 hours. Additional ethyl dithiopropanoate (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 dithiopropanoate (0.35 ml), kept at ambient temperature for 24 hours and concentrated. Chromatography of the residue on silica gel with 2.5% $\text{MeOH}-\text{CH}_2\text{Cl}_2$ gave 0.0457 g of 33: mp $190-191^\circ\text{C}$ (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-(((5S)-3-((3-fluoro-4-((2S)-2,3-dimethoxypropionyl)-1-piperazinyl)phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl]propanethioamide (34)

(PNU-272199)

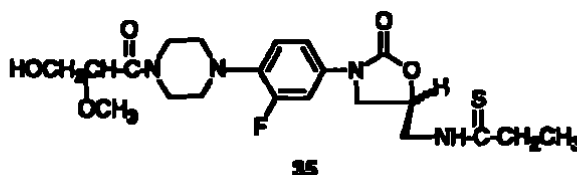


As described in Example 8 the ester ((S)-27, prepared in Step 2) is hydrolyzed with lithium hydroxide and coupled with 7. The resulting amide is deprotected and allowed to react with ethyl dithiopropanoate and triethylamine. The product is purified by silica gel chromatography with 2.5% $\text{MeOH}-\text{CH}_2\text{Cl}_2$ and crystallized from EtOAc -hexane to give 34: mp $140-142^\circ\text{C}$ (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.

000120-04918109

99
100

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)

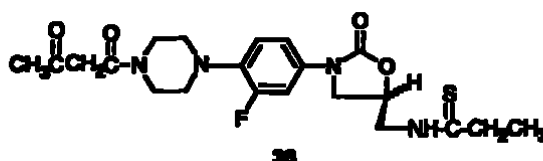


5

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 dithiopropionate. The product is purified by silica gel chromatography with 2.5% MeOH-CH₂Cl₂ to give 35. Anal. calcd for C₂₁H₂₈FN₄O₃S: 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)

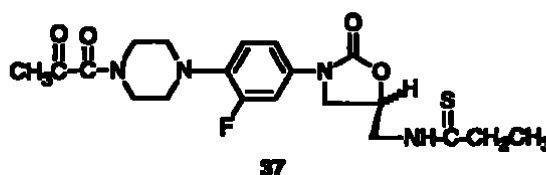


15

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 dithiopropionate 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 dithiopropionate and

25

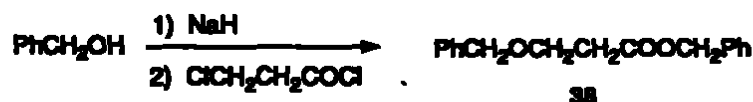
100
10/10

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

5

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

Step 1

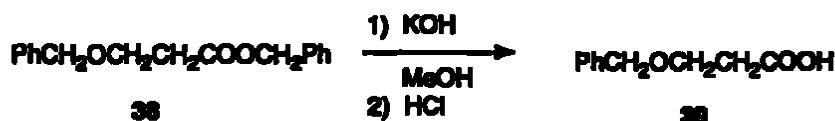


10

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⁺).

15

Step 2



20

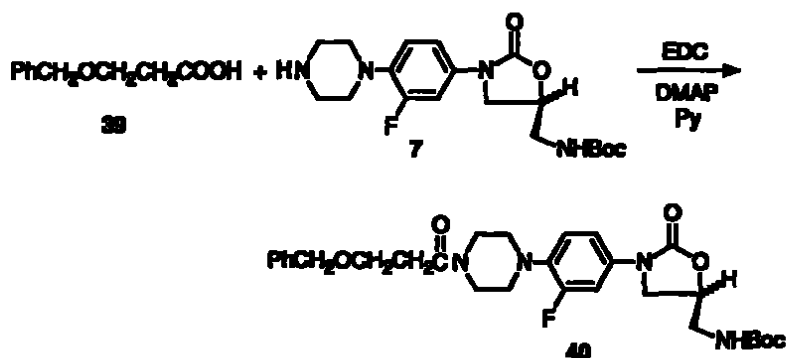
An ice cold, stirred solution of 38 from Step 1 in MeOH (50 mL), under nitrogen, is treated with potassium hydroxide (0.94 g, 0.0168 mol) and kept in the ice bath for 10 minutes, at ambient temperature for 1 hour and at -20 °C for 18 hours. It is treated with additional potassium hydroxide (0.98 g), 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

000181640-021000

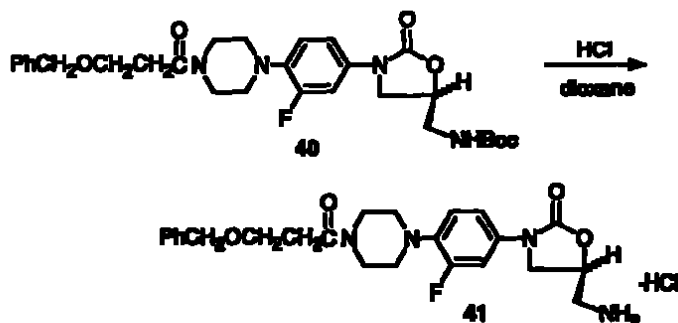
101
102

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 (2 mL) 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⁺).

Step 4

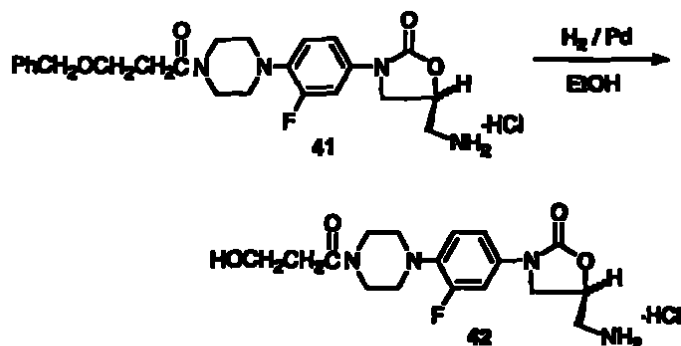


A stirred, ice cold solution of 40 (0.43 g, 0.772 mmol) in dioxane (12 mL), under nitrogen is treated with 4N hydrogen chloride in dioxane (10 mL), dropwise during 3 minutes. It is warmed to ambient temperature (24 °C) during 90 minutes, kept for 3 hours 30 minutes and concentrated to give 0.43 g of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

000181640-021000

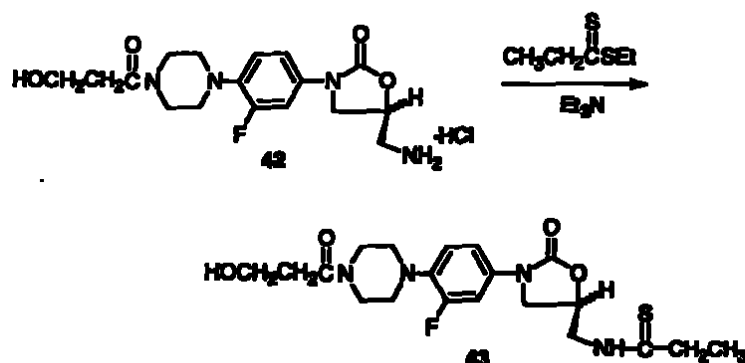
152 103

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

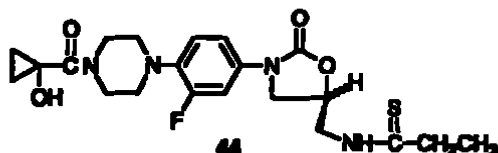
A stirred mixture of 42 (0.07 g, 0.19 mmol), CH₂Cl₂ (8 mL) and THF (8 mL) is treated with triethylamine (0.20 mL) and ethyl dithiopropanoate (0.08 mL) and kept at ambient temperature (24 °C) for 24 hours, at 45 °C for 7.5 hours and at ambient temperature for 16 hours. It is then concentrated and the 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 C₂₀H₂₃FN₄O₄S (M+H⁺) 439.1815, found 439.1812.

15

60181640-021000

103
104

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)

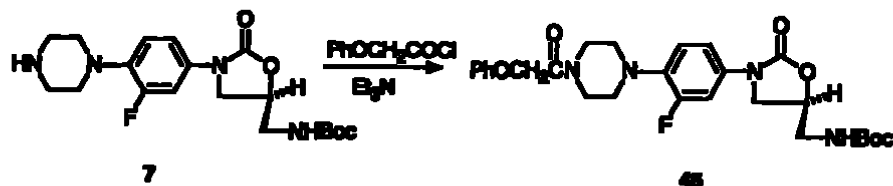


5

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⁺). 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)

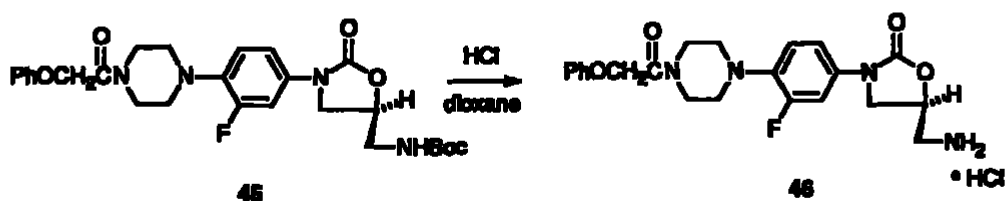
Step 1



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⁺).

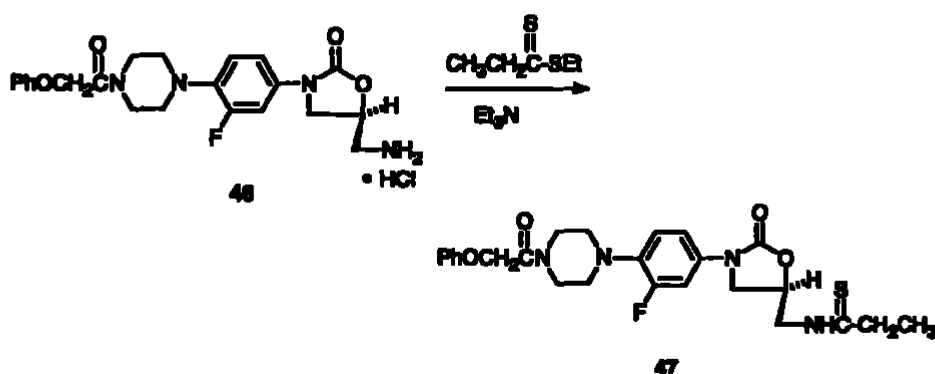
000720-04918109

Step 2



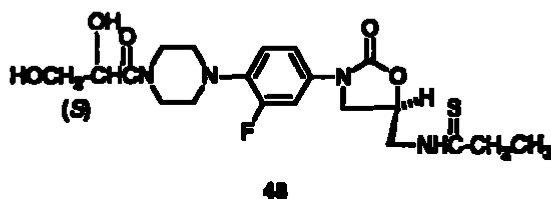
As described in Example 8 (Step 5) compound 45 is deprotected with hydrogen chloride in dioxane to give 46: MS(ES) m/z 429 ($M+H^+$).

Step 3



As described in Example 8 (Step 6) the amine hydrochloride (46) is allowed to react with ethyl dithiopropanoate and triethylamine in CH_2Cl_2 -THF. The product is chromatographed on silica gel with 2.5% $\text{MeOH}-\text{CH}_2\text{Cl}_2$ and crystallized from EtOAc to give 47: mp 171-172°C; MS(ES) m/z 501 ($M+H^+$), 523 ($M+\text{Na}^+$). Anal. Calcd for $\text{C}_{25}\text{H}_{29}\text{FN}_4\text{O}_4\text{S}$: C, 59.98; H, 5.84; N, 11.19. Found: C, 59.59; H, 5.89; N, 11.03.

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



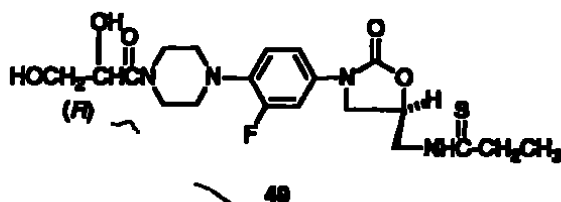
As described in Example 8 (Steps 4-6) L-glyceric acid, calcium salt dihydrate is coupled with 7 and the resulting amide is deprotected and allowed to react with ethyl

105
106

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

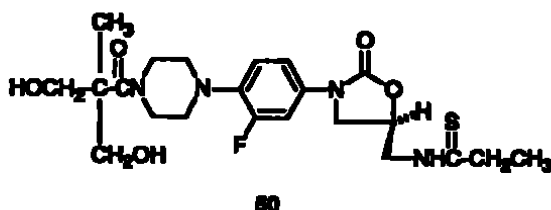
Example 17 Preparation of N-(((5S)-3-[3-fluoro-4-[4-((2R)-2,3-dihydroxypropanoyl)-1-piperazinyl]phenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide (49) (PNU-248438)



10 As described in Example 8 (Steps 4-6) D-glycemic 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-(((5S)-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

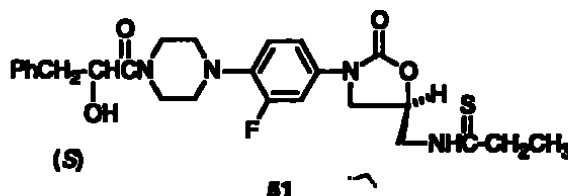


As described in Example 8 (Steps 4-6) 2,2-bis(hydroxymethyl)propionic acid is coupled with 7 and the resulting amide is deprotected and allowed to react with ethyl dithiopropionate and triethylamine. The product is purified by silica gel chromatography
25 with 5% MeOH- CH_2Cl_2 and crystallized from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

106
102

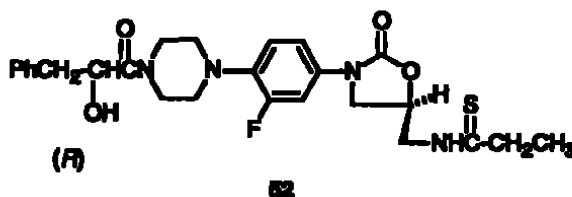
203°C (dec); MS(ES) m/z 483 ($M+H^+$), 502 ($M+Na^+$). Anal. Calcd for $C_{22}H_{31}FN_4O_5S$: C, 54.76; H, 6.47; N, 11.61. Found: C, 54.38; H, 6.54; N, 11.43.

- Example 19** Preparation of N-(((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 (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-CH₂Cl₂ and crystallized from EtOAc-hexane to give 51: mp 174-175°C. Anal calcd for $C_{22}H_{31}FN_4O_5S$: C, 60.68; H, 6.07; N, 10.89. Found: C, 60.56; H, 6.17; N, 10.68.

- Example 20** Preparation of 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 (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-CH₂Cl₂ and crystallized from EtOAc-hexane to give 52: mp 128-130°C (dec). Anal. Calcd for $C_{22}H_{31}FN_4O_5S$: C, 60.68; H, 6.07; N, 10.98. Found: C, 60.50; H, 6.17; N, 10.80.

ED181540-021000



10

10



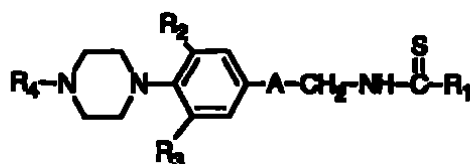
15

- 33 -

CLAIMS

What is claimed is:

1. A compound of formula I

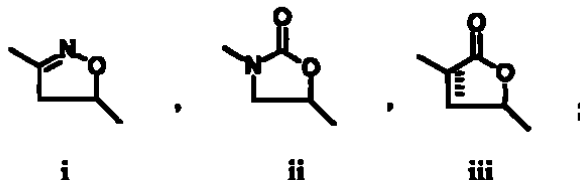


5

I

or a pharmaceutically acceptable salt thereof wherein:

A is a structure i, ii, or iii



10

R¹ is

- (a) H,
- (b) NH₂,
- (c) NHC₁₋₄ alkyl,
- (d) C₁₋₄ alkenyl,
- (e) OC₁₋₄ alkyl,
- (f) SC₁₋₄ alkyl,
- (g) (CH₂)_n-C₃₋₆ cycloalkyl, or
- (h) C₁₋₄ alkyl, optionally substituted with 1-3 F, 1-2 Cl or CN;

15

R₂ and R₃ are independently H, F, Cl or C₁₋₂ alkyl;

20

R₄ is

- (a) -C(=O)-CR₃R₆-O-R₇,
- (b) -C(=O)-CH₂S(O)_n-CH₃,
- (c) -C(=O)-CH₂-S(=O)(=NR₈)CH₃,
- (d) -C(=S)-R₉,
- (e) -C(=O)-CH₂-O-R₁₀,
- (f) -C(=O)-(CH₂)_m-C(=O)-CH₃,
- (g) -C(=O)-(CH₂OH)₇-CH₃,

25

(h) $-\text{C}(=\text{O})-\text{CH}_2-\text{CH}_2-\text{OR}_{14}$, or

(i) $-\text{CN}$;

R_5 is H;

R_6 is phenyl, benzyl, CH_2OH or CH_2OCH_3 ; or

5 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;

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

10 $-\text{C}(=\text{O})-(\text{CH}_2)_2-\text{CO}_2\text{H}$;

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-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 ;

15 R_{14} is H, CH_3 or benzyl;

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

2. A compound of formula I according to claim 1 wherein R_1 is C_{1-4} alkyl.

20 3. A compound of formula I according to claim 1 wherein R_1 is ethyl.

4. A compound of formula I according to claim 1 wherein R_2 and R_3 are independently H or F.

25 5. A compound of formula I according to claim 1 wherein at least one of R_2 or R_3 is H, the other one is F.

6. A compound of formula I according to claim 1 wherein R_4 is

(a) $\text{C}(=\text{O})-\text{CH}(\text{CH}_2\text{-phenyl})(\text{OH})$,

30 (b) $\text{C}(=\text{O})-\text{CH}_2-\text{SO}_2-\text{CH}_3$,

(c) $\text{C}(=\text{O})-\text{CH}(\text{OH})(\text{CH}_2\text{OH})$,

(d) $\text{C}(=\text{O})-\text{C}(=\text{O})-\text{CH}_3$,

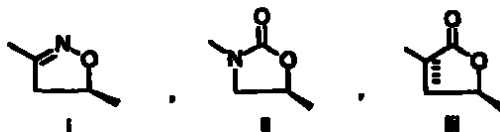
(e) $\text{C}(=\text{O})-\text{CH}(\text{OH})(\text{CH}_2-\text{O}-\text{CH}_3)$,

110
14

- (f) $C(=O)-CH_2CH_2-OH$,
 (g) $C(=O)-CH_2-O-CO_2-(CH_2)_2-OCH_3$,
 (h) $C(=S)-CH_3$ or
 (i) CN .

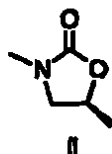
5

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



10

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



15

9. A compound of claim 1 which is

- (1) $N\{[(5S)-3-(3-fluoro-4-[2-(methylsulfinyl)acetyl]-1-piperazinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl\}methyl\}propanethioamide$,
 (2) $N\{[(5S)-3-(3-fluoro-4-[2-(methylsulfonyl)acetyl]-1-piperazinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl\}methyl\}propanethioamide$,
 (3) $N\{[(5S)-3-(3-fluoro-4-[2-(methylsulfonyl)acetyl]-1-piperazinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl\}methyl\}propanethioamide$,
 (4) $N\{[(5S)-3-(4-(4-ethanethiolyl-1-piperazinyl)-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl\}methyl\}propanethioamide$,
 (5) $N\{[(5S)-3-(4-(4-cyano-1-piperazinyl)-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl\}methyl\}propanethioamide$,
 (6) $N\{[(5S)-3-(3-fluoro-4-[2-(methylaminocarbonyloxy)acetyl]-1-piperazinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl\}methyl\}propanethioamide$,
 (7) $N\{[(5S)-3-(3-fluoro-4-[2-[(2-methoxyethoxy)carbonyloxy]acetyl]-1-piperazinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl\}methyl\}propanethioamide$,

25

11
42

- (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,
- 5 (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,
- 10 (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 (15) N-(((5S)-3-(3-fluoro-4-[4-(2-phenoxyacetyl)-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- (16) N-(((5S)-3-(3-fluoro-4-[4-((2S)-2,3-dihydroxypropanoyl)-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- (17) N-(((5S)-3-(3-fluoro-4-[4-((2R)-2,3-dihydroxypropanoyl)-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- 20 (18) N-(((5S)-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-(((5S)-3-(3-fluoro-4-[4-((2S)-2-hydroxy-3-phenylpropanoyl)-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- 25 (20) N-(((5S)-3-(3-fluoro-4-[4-((2R)-2-hydroxy-3-phenylpropanoyl)-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,
- (21) N-(((5S)-3-(3-fluoro-4-[4-((2R)-2-hydroxy-2-phenylacetyl)-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide, or
- (22) N-(((5S)-3-(3-fluoro-4-[4-((2S)-2-acetoxy-2-phenylacetyl)-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide.
- 30

50181640-021000

112
43

10. A compound of claim 1 which is

(1) N-(((5S)-3-(3-fluoro-4-[4-(2-(methylsulfonyl)acetyl)-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide, or

(2) N-(((5S)-3-[4-(4-ethanethiolyl-1-piperazinyl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide.

11. A compound of claim 1 which is

N-(((5S)-3-[4-(4-cyano-1-piperazinyl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide.

12. A compound of claim 1 which is

(1) N-(((5S)-3-(3-fluoro-4-[4-(2-[(2-methoxyethoxy)carbonyloxy]acetyl)-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,

(2) N-(((5S)-3-(3-fluoro-4-[4-((2S)-2-hydroxy-3-methoxypropanoyl)-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,

(3) N-(((5S)-3-(3-fluoro-4-[4-(3-hydroxypropanoyl)-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,

(4) N-(((5S)-3-(3-fluoro-4-[4-((2S)-2,3-dihydroxypropanoyl)-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide,

(5) N-(((5S)-3-(3-fluoro-4-[4-((2R)-2,3-dihydroxypropanoyl)-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide, or

(6) N-(((5S)-3-(3-fluoro-4-[4-((2R)-2-hydroxy-3-phenylpropanoyl)-1-piperazinyl]phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide.

13. A compound of claim 1 which is

N-(((5S)-3-(3-fluoro-4-(4-pyruvoyl-1-piperazinyl)phenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl)propanethioamide.

14. A method for treating microbial infections comprising: administering to a mammal

in need thereof an effective amount of a compound of formula I as shown in claim 1.

15. The method of claim 14 wherein said compound of formula I is administered orally, parenterally, transdermally, or topically in a pharmaceutical composition.

60181640-021000

113
44

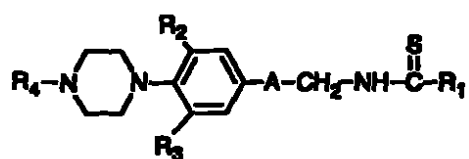
16. The method of claim 14 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.
- 5 17. The method of claim 14 wherein said compound is administered in an amount of from about 1 to about 50 mg/kg of body weight/day.
18. A method for treating microbial infections of claim 14 wherein the infection is skin infection.
- 10 19. A method 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
15 pharmaceutically acceptable carrier.

50181540-021000

114

ABSTRACT

The present invention provides a compound of formula I



I

5 which have potent activities against gram positive and gram-negative bacteria.

000120-04918709

116

ante quien se hizo el juramento del instrumento adjunto, en la fecha especificada en el presente era un Notario Público en y para el Condado mencionado, debidamente comisionado y calificado y debidamente autorizado por las leyes de este Estado para administrar juramentos y para tomar y certificar testimonios y declaraciones jurídicas. Certifico además que la autenticación anterior está hecha de acuerdo con lo establecido por la ley, y que conozco bien la escritura manuscrita de dicho Notario Público y creo verdaderamente que el nombre suscrito en ella es la firma auténtica del Notario Público mencionado.

En testimonio de ello he puesto mi firma y estampado el sello del Tribunal del Circuito mencionado, en la ciudad de Kalamazoo el día 16 de Abril del año 2001..

Firmado: Timothy A. Snow, Escribano del Condado

Sello en relieve: Tribunal del Circuito del Condado de Kalamazoo - Michigan - Sello.

=====

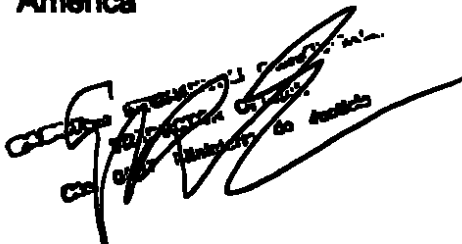
APOSTILLA

(Convención de La Haya de octubre 5 de 1961)

1. País: Estados Unidos de América

Este Documento Público

2. ha sido firmado por Timothy A. Snow



117

- 3. actuando en su condición de Escribano del Condado de Kalamazoo
- 4. tiene el sello/estampilla del Tribunal del Circuito del Condado de Kalamazoo

CERTIFICADO

- 5. en Lansing, Michigan
- 6. el 18 de Abril de 2001
- 7. por el Secretario de Estado, Estado de Michigan
- 8. No. 4330C-01
- 9. Sello/estampilla: El Gran Sello del Estado de Michigan – Año 1835 -.con escudo en el centro.

Este mismo sello en relieve está estampado en el borde superior izquierdo sobre lámina de papel metalizado ligando los documentos entre sí:

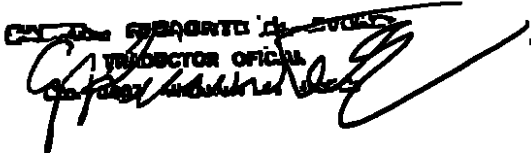
- 10. Firma: Firmado: Candice S. Miller

=====

Es traducción fiel y competa, de la cual queda copia en el archivo de esta oficina de traducciones para su confrontación, a la cual me remito.

Derechos de traducción: \$24.000

Santafé de Bogotá, 3 de mayo de 2001


Candice S. Miller
Traductor Oficial
Código de Traducción: 117

=====

APOSTILLE

(Convention de La Haye du 5 Octobre 1961)

1. Country: **UNITED STATES OF AMERICA**

This public document

2. has been signed by: **Timothy A. Snow**

3. acting in the capacity of: **Kalamazoo County Clerk**

4. bears the seal/stamp of: **Kalamazoo County Circuit Court**

CERTIFIED:

5. at **Lansing, Michigan**

6. the **18th** of April, 2001

7. by **Secretary of State, State of Michigan**

8. NO. **4330C-01**

9. Seal/Stamp:

10. Signature:

Candice S. Miller

Candice S. Miller

STATE OF MICHIGAN }
 } ss.
COUNTY OF KALAMAZOO }

I, TIMOTHY A. SNOW, Clerk of the County of Kalamazoo, and of the Circuit Court for said County, the same being a Court of Record having a Seal, do hereby certify that

121
119

Debra J. Marquette
before whom oath to the annexed instrument appears to have been made was, at the date hereon stated, a Notary Public in and for said County, duly commissioned and qualified, and duly authorized by the laws of this State to administer oaths, and to take and certify affidavits and depositions. I further certify that the foregoing authentication is in due form of law, and that I am well acquainted with the handwriting of the said Notary Public, and verily believe the name subscribed thereto to be the genuine signature of said Notary Public.

In Witness Whereof, I have hereunto set my hand and affixed the seal of said Circuit Court, at the City of Kalamazoo, this 16th day of April A.D. 2001

Timothy A. Snow County Clerk
TIMOTHY A. SNOW

MINISTERIO DE RELACIONES
EXTERIORES

131562
Gabriel Escobar
Cuya firma aparece en el
documento desempeña
las funciones indicadas

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2001 MAY -4 F 12-31
JEF DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

26

120 122

CERTIFICADO NOTARIAL (INDIVIDUO)

A los días del mes de
de 2 , comparecí personalmente ante mí,

a quien doy fé de conocer y me consta que
la persona descrita y firmante
del documento que precede, declarando ante mí que otor-
ga el mismo para los fines y propósitos que en él se
expresan.

NOTARY PUBLIC (Notario Público)

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this 13th day of April, 2001
2000 personally appeared before me, a Notary Public,
in Kalamazoo County, Michigan,

Jackson B. Hester, Jr.

to me known and known to me to be the person
described in and who executed the foregoing document,
and duly acknowledged to me that
he executed the same for the uses and purposes
therein expressed.



DEBRA J. MARQUETTE
Notary Public, Kalamazoo County, MI
My Commission Expires 9/25/2004

CERTIFICADO NOTARIAL (INDIVIDUO)

A los días del mes de
de 2 , comparecí personalmente ante mí,

a quien doy fé de conocer y me consta que
la persona descrita y firmante
del documento que precede, declarando ante mí que otor-
ga el mismo para los fines y propósitos que en él se
expresan.

NOTARY PUBLIC (Notario Público)

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this day of
2000 personally appeared before me, a Notary Public,

to me known and known to me to be the person
described in and who executed the foregoing document,
and duly acknowledged to me that
executed the same for the uses and purposes
therein expressed.

69



6296.1 Colombia

ASSIGNMENT

The undersign, Jackson B. Hester, Jr.

domiciled in 9219 East ML Avenue, Galesburg, Michigan
49053

hereby state under oath to be sole and true inventor
of OXAZOLIDINONE THIOAMIDES WITH
PIPERAZINE AMIDE SUBSTITUENTS

state as well that they assign, without reserva-
tions or limitation, in favor of
Pharmacia & Upjohn Company

a corporation organized and existing under the laws of
the State of Delaware

domiciled in
301 Henrietta Street
Kalamazoo, Michigan 49001

all rights inherent to said invention, and that the above
mentioned corporation hereby is enabled to apply, in its
name, for the corresponding patent in the Republic of
Colombia.

Jackson B. Hester, Jr.
Jackson B. Hester, Jr.

Legalization up to Colombian Consulate

TRASPASO

abajo firmado

Jackson B. Hester, Jr.

domiciliado en

9219 East ML Avenue, Galesburg,
Michigan 49053

decla^o bajo juramento ser único y verda-
dero inventor de
TIOAMIDAS DE OXAZOLIDINONA CON SUBSTITUYENTES
DE PIPERAZIN-AMIDA

Declaro aismismo que ced^o y
transfiero sin reserva ni limitación, a favor de la
sociedad

Pharmacia & Upjohn Company
organizada y existente de conformidad con las leyes de
Estado de Delaware

domiciliada en
301 Henrietta Street
Kalamazoo, Michigan 49001

todos los derechos inherentes a dicha invención y que la
citada sociedad queda facultada para solicitar en su nombre
la patente correspondiente en la República de Colombia.

4/13/01
Date

2do. EXAMEN DE FORMA PATENTE DE INVENCION

Folio 123

Radicación no 01- 9443

Concepto Técnico no 1702

Clasificación Internacional de Patentes A 61 K 31/ 498/31/422

Practicado el examen de acuerdo a lo establecido en el Art. 38 de la Decisión 486 se determinó que esta solicitud de Patente de Invención:

- SI ☒ NO ☐ Contiene un resumen de la invención (Art.26-e).
- SI ☒ NO ☐ Contiene el título o nombre de la invención (Art.27-d).
- SI ☒ NO ☐ Contiene la descripción de la invención (Art.26-b).
- SI ☒ NO ☐ NO ES APLICABLE ☐ Contiene los dibujos necesarios para comprender la invención (Art.26-d)
- SI ☒ NO ☐ Contiene una o más reivindicaciones. (Art.26-c).
- SI ☐ NO ☐ NO ES APLICABLE ☒ Han sido desarrollados los productos y/o procedimientos a partir de recursos genéticos o de sus productos derivados de los que cualquiera de los Países Miembros es país de origen. (Art. 26- h).
- SI ☐ NO ☐ NO ES APLICABLE ☒ Los productos y/o procedimientos han sido obtenidos o desarrollados a partir de los conocimientos tradicionales de las comunidades indígenas, afroamericanas, o locales de los países miembros, de acuerdo a lo establecido en la Decisión 391 y sus modificaciones y reglamentaciones vigentes.(Art.26-i).
- SI ☐ NO ☒ La invención se refiere a un producto relativo a un material biológico. (Art.26-J).
- SI ☒ NO ☐ La prioridad coincide con la materia reivindicada.
- SI ☒ NO ☐ **CUMPLE LOS REQUISITOS TÉCNICOS**

OBSERVACIONES Y OTROS: SI ☐ NO ☒ ver hoja(s) anexa(s)

EXAMINADOR TÉCNICO
202050

Bogotá D. C., DICIEMBRE 6 DE 2002

Folio 124

2020
Bogotá DC

Doctor
JOSE ANTONIO LLOREDA
Apoderado

REFERENCIA:	Radicación No.	01-8443
	Trámite	002
	Evento	001
	Actuación	416
	Oficio No.	2258
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486 de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la misma Decisión.

Cúmplase
Dado en Bogotá DC, a los

56 DIC. 2002

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

527

202050