

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: P1.-PHARMACIA & UPJOHN COMPANY.-Solicitud de Patente de
Invención para "OXAZOLIDINONAS DERIVADAS DE SULTAMAS Y
SULTONAS".-Clase A.61.-Expediente número 00-083.532.-

1. Me refiero a mi solicitud de 2 de Noviembre de 2000 y al auto dictado por ese Despacho notificado por Estado el 30 de Noviembre del mismo año.
2. Anexas me permito presentar a usted:
 - (1) En original y dos copias, una de ellas de 6cm x 6cm, Arte Final de la fórmula química característica del invento, para la publicación en la Gaceta de la Propiedad Industrial; y
 - (2) Copia auténtica debidamente certificada de la solicitud de patente presentada para el invento arriba nombrado respecto de la cual reclamo prioridad, a saber la solicitud estadinense número 60/163,537, junto con su traducción oficial correspondiente a las legalizaciones y reivindicaciones.
3. Anexo también me permito acompañar 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 Uriceachea, quien elaboró la traducción de la solicitud estadinense número 60/163,537 de 4 de Noviembre de 1999, respecto de la cual se reivindica prioridad en el presente caso.
4. 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



Royal
Technologies S.A.
Bogotá, Colombia

30

Expediente No		00-083-532	No de Follo
Item		No de Unidades	
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA	1	
8	SOBRE BLANCO TAMAÑO CARTA		
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS:		

Observaciones: Arte Final

REPUBLICA DE COLOMBIA
MINISTERIO DE RELACIONES EXTERIORES

24
31

CERTIFICACION

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

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

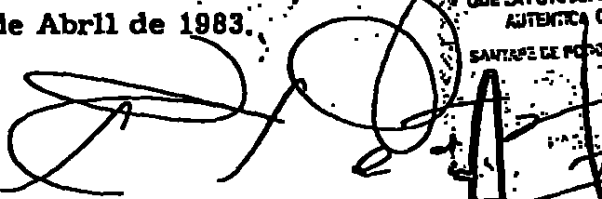
Exteriores, como traductor e interprete oficial para los idiomas _____

Ingles - Español - Ingles 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 PENA FLOREZ

JEFE DE NEGOCIOS GENERALES

COMO NOTARIO SEXTO ENCARGADO
DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCopia COINCIDE CON LA FOTOCopia
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 16 AGO. 1998

COMO NOTARIO SEXTO ENCARGADO
DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCopia COINCIDE CON LA FOTOCopia
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 25 ABR 2000

PABLO MENDEZ BARRAJA

COMO NOTARIO SEXTO DE
SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCopia COINCIDE CON LA FOTOCopia
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 29 JUL 1999
JUAN MANUEL BOTERO MEDINA
NOTARIO

COMO NOTARIO SEXTO ENCARGADO
DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCopia COINCIDE CON LA FOTOCopia
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 16 JUN 1998

COMO NOTARIO SEXTO ENCARGADO
DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCopia COINCIDE CON LA FOTOCopia
AUTENTICA QUE HE TENIDO A LA VISTA
SANTAFE DE BOGOTA 24 NOV 1998

ESTADOS UNIDOS DE AMERICA

A TODOS A QUIENES LLEGUE EL PRESENTE:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Marcas y Patentes

20 de octubre de 2000.

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 60/163,537

FECHA DE RADICACIÓN: 04 de noviembre de 1999

Por Autoridad del

COMISIONADO DE MARCAS Y PATENTES

(FIRMA L. EDELEN

Oficial de Certificaciones

(SELLO DORADO DE OBLEA)

Maria Mercedes Urtecho
Res. No. 10507 Minj. de la
Traductora Juramentada

Maria Mercedes

26
33

CERTIFICACION BAJO 37 CFR § 1.10

CERTIFICADO DE CORREO No. EM177639000 US 4 de noviembre de 1999

Certifico que esta Remisión de Nueva Solicitud y los documentos que en ella se refieren como adjuntos son depositados en el Servicio Postal de lo EE.UU. el 4 de noviembre de 1999 en un sobre como "Oficina Postal al Destinatario" bajo el rótulo de correo No. EM177639000 US y dirigido al Comisionado Asistente de Patentes, Washington, D.C. 20231.

(FIRMA) DEBORAH A. TUCKER – Asistente Legal

CUBIERTA SOLICITUD PROVISIONAL

La presente es una solicitud para la radicación de UNA SOLICITUD PROVISIONAL bajo 37 CFR § 1.53 (c). La Solicitud se titula Oxazolidinonas Derivadas de Sultam y Sultona. Nuestro Caso No. 6234 y consta de:

13 páginas de Especificación
3 páginas de Reivindicaciones
1 página de Resumen

☒ El/los nombre(s) y residencia(s) del(os) inventor(es) se indican en la Hoja de Información del Inventor adjunta.

AUTORIZACION DE CUENTA DE DEPÓSITO. Sírvanse cargar a mi Cuenta de depósito No. 21-0718 el monto total de la comisión de radicación de la Solicitud Provisional para una compañía grande (US\$150.00) o la suma mayor o menor que el Comisionado requiera.

Por la presente, la compañía suscrita solicita que toda la correspondencia y comunicaciones telefónicas relacionadas con esta solicitud sean dirigidas a la

María Mercedes I. Infante
Res. No. 10027
Tratado de París
Nueva York

persona que firma este documento a la dirección y teléfono que se indican a continuación.

Respetuosamente,

Lucy X. Yang, Abogada
Registro No. 40,259

Fecha: 11-03-99

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

Tel: (616) 833-9536 o (616) 833-9500
Fax: (616) 833-8897 o (616) 833-2316

Documentos adjuntos:

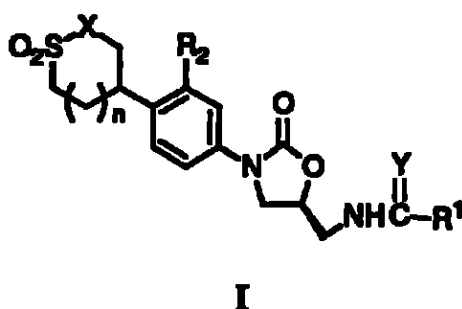
- ☒ Solicitud de patente
- ☒ Hoja de Información del Inventor

Maria Mercedes Uricuechea
Ros. No. 10037 August 1998
Traductora Juramentada
Maria Mercedes Uricuechea

OXAZOLIDINONAS DERIVADAS DE SULTAM Y SULTONA

REIVINDICACIONES:

1. Un compuesto de la fórmula I:



o una sal farmacéuticamente aceptable de lo mismo, donde

R¹ es

- (a) H,
- (b) cicloalquil C₁₋₈, sustituido opcionalmente por uno a tres F, Cl, OH OC(=O)alquil C₁₋₄ o alquilOC₁₋₄,
- (c) cicloalquil C₃₋₆,
- (d) amino
- (e) alquilamino C₁₋₈
- (f) dialquilamino C₁₋₈, o
- (g) alquilOC₁₋₈

R² es H o F;

X es O o NR^3 ;

R^3 es

- (a) H,
- (b) alquil C_{1-8} , sustituido por uno a tres F, Cl, OH, CN , NH_2 , $\text{OC}(=\text{O})\text{alquilC}_{1-4}$, o alquilOC_{1-4} ,
- (c) alqueno C_{3-8} , o
- (d) $\text{C}(=\text{O})\text{NR}^4\text{R}^5$;

R^4 y R^5 son independientemente,

- (a) H, o
- (b) alquil C_{1-8} sustituido opcionalmente por uno a tres F, Cl, OH, CN o NH_2 ;

Y es O o S; y

n es 0 o 1.

2. Un compuesto según la Relvindicación 1, en donde R^1 es metilo.

3. Un compuesto según la Relvindicación 1, en donde Y es un átomo de oxígeno.

4. Un compuesto según la Relvindicación 1, en donde Y es un átomo de azufre.

40
37

5. Un compuesto según la Reivindicación 1, en donde R² es un átomo de fluoro.

6. Un compuesto según la Reivindicación 1, en donde X es un átomo de oxígeno.

7. Un compuesto según la Reivindicación 1, en donde X es NH.

8. Un compuesto según la Reivindicación 1, en donde n es 1.

9. Un compuesto que es:

a) N-[[[(5S)-3-[3-fluoro-4-[tetrahidro-1,1-dióxido-2-(2-propenil)-2H-1,2-tiazin-4-il]fenil]-2-oxo-5-oxazolidinil]metil]acetamida.

b) N-[[[(5S)-3-[3-fluoro-4-[tetrahidro-1,1-dióxido-2H-1,2-tiazin-4-il]fenil]-2-oxo-5-oxazolidinil]metil]acetamida,

c) N-[[[(5S)-3-[3-fluoro-4-[tetrahidro-1,1-dióxido-2-(2-propenil)-2H-1,2-tiazin-4-il]fenil]-2-oxo-5-oxazolidinil]metil]acetamida.

d) N-[[[(5S)-3-[3-fluoro-4-(tetrahidro-2-metil-1,1-dióxido-2H-1,2-tiazin-4-il]fenil]-2-oxo-5-oxazolidinil]metil]etanotioamida,

e) N-[[[(5S)-3-[4-(2,2-dióxido-1,2-oxatiazin-5-il)-3-fluorofenil]-2-oxo-5-oxazolidinil]metil]etanotioamida, o

f) N-[[[(5S)-3-[4-(1,1-dióxido-4-isotiazolidinil)-3-fluorofenil]-2-oxo-5-oxazolidinil]metil]etanotioamida.

10. Un método para el tratamiento de infecciones microbianas en un mamífero que consiste en administrar a dicho mamífero que lo requiera,

Maria Mercedes Hernandez
Escriba el nombre y apellido del titular
Vale para el uso exclusivo del titular

una cantidad efectiva de un compuesto de la fórmula I según se muestra en la Reivindicación 1.

11. El método según la Reivindicación 10, en donde dicho compuesto de la fórmula I es administrado por vía oral, parenteral, transdermal o tópica en una composición farmacéutica.

12. El método según la Reivindicación 10, en donde dicho compuesto es administrado en una cantidad entre 0,1 y 100 mg/kg aproximadamente de peso corporal por día.

13. Un método para el tratamiento de infecciones microbianas según la Reivindicación 10, en donde la infección es una infección de la piel.

14. Un método para el tratamiento de infecciones microbianas según la Reivindicación 10, en donde la infección es una infección en los ojos.

15. Una composición farmacéutica que comprende un compuesto de la fórmula I según la Reivindicación 1, y un excipiente farmacéuticamente aceptable.



United States Patent and Trademark Office

FILING DATE: *November 04, 1999*



PROVISIONAL APPLICATION COVER SHEET

CERTIFICATE OF MAILING (37 CFR 1.10)

"Express Mail" No: EM177639000USDate of Deposit: 4 November 1999

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.

Deborah A. TuckerName of Person Mailing Lead Legal AssistantSignature Deborah A. Tucker

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 Sultam and Sultone Derived Oxazolidinones, our Docket No. 6234, and consists of:

[13] page(s) of Specification
[3] page(s) of Claims
[0] page(s) of Drawings
[0] 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.

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: 11-3-99

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

664011-455537-110499

45
42

INVENTOR INFORMATION SHEET

Full name of sole or first inventor:

David John Anderson

Address:

3809 Middlebury Drive

Kalamazoo, Michigan 49006

Citizenship:

Great Britain

Full name of second inventor:

Jackson B. Hester, Jr.

Address:

9219 East ML Avenue

Galesburg, Michigan 49053

Citizenship:

USA

664011-7E5E9T09

SULTAM AND SULTONE DERIVED OXAZOLIDINONES

BACKGROUND OF THE INVENTION

The present invention provides sultam and sultone derived oxazolidinones, and more specifically, provides compounds of formula (I) described herein below. These compounds are useful as antibiotic agents.

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

INFORMATION DISCLOSURE

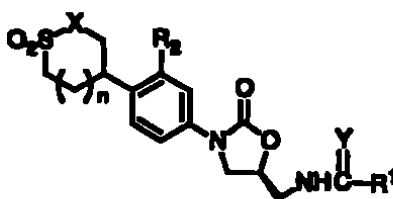
International Publication No. WO 97/09328 discloses phenyloxazolidinones having a C-C bond to 4-8 membered heterocyclic rings useful as antimicrobial agents.

US Patent Number 4,709,026 discloses ketosultams useful as sensitizers or dyes.

J. Org. Chem. 1991, 56, 3549-3556 discloses vinyl sulfonyl esters and amides in the synthesis of substituted δ -sultams and δ -sultones.

SUMMARY OF THE INVENTION

The present invention provides a compound of formula I:



I

or a pharmaceutically acceptable salt thereof wherein R^1 is

- (a) H,
- (b) C_{1-8} alkyl, optionally substituted with one to three F, Cl, OH, $OC(=O)C_{1-4}$ alkyl, or OC_{1-4} alkyl,
- (c) C_{3-6} cycloalkyl,

47
44

- (d) amino,
- (e) C₁₋₈ alkylamino,
- (f) C₁₋₈ dialkylamino, or
- (g) OC₁₋₈ alkyl;

5 R² is H or F;

X is O or NR³;

R³ is

- (a) H,
- (b) C₁₋₈ alkyl, optionally substituted with one to three F, Cl, OH, CN, NH₂,
10 OC(=O)C₁₋₈ alkyl, or OC₁₋₈ alkyl,
- (c) C₃₋₈ alkene, or
- (d) C(=O)NR⁴R⁵;

R⁴ and R⁵ are independently

- (a) H, or
- 15 (b) C₁₋₈ alkyl, optionally substituted with one to three F, Cl, OH, CN, or NH₂;

Y is O or S; and n is 0 or 1.

In another aspect, the present invention also provides:

- a pharmaceutical composition comprising a compound of formula I, or a
pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient (the
20 composition preferably comprises an effective amount of the compound or salt),
- a method of treating or preventing microbial infections in a mammal including skin
and eye infections, comprising administering to said mammal in need of such treatment, a
compound of formula (I) or a pharmaceutically acceptable salt thereof, and
- a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in
25 medical treatment (e.g. the treatment or prevention of a microbial infection), and

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

DETAILED DESCRIPTION OF THE INVENTION

- 30 The compounds of the present invention are generally named according to the
IUPAC or CAS nomenclature system. Abbreviations which are well known to one of
ordinary skill in the art may be used (e.g. "Ph" for phenyl, "Me" for methyl, "Et" for ethyl,
"h" for hour or hours and "rt" for room temperature).

664011-110499

48
45

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, C₁₋₇alkyl refers to alkyl of one to seven carbon atoms, inclusive.

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.

The following definitions are used, unless otherwise described.

Alkyl denotes both straight and branched groups; but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to. Specifically, C₁₋₈ alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, hexyl, heptyl, octyl and their isomeric forms thereof. Specifically, C₁₋₄ alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, and their isomeric forms thereof.

Alkene denotes both straight and branched groups having at least one double bond. Specifically, C₃₋₈ alkene can be allyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl and their isomeric forms thereof.

C₃₋₆ cycloalkyl denotes a cycloalkyl having three to six carbon atoms. Specifically, C₃₋₆ cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

Mammal denotes human and other warm blooded animals.

Pharmaceutically acceptable salts denotes those salts useful for administering the compounds of this invention and include hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, mesylate, malate, succinate, tartrate, citric acid, 2-hydroxyethyl sulfonate, fumarate, methanesulfonic acid salt and etc.

Compounds of the present invention may be in a form of pharmaceutically acceptable salts.

It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, tautomeric, or stereoisomeric form, or mixture thereof.

A specific value for R¹ is H.

A specific value for R¹ is C₁₋₈ alkyl, optionally substituted with one to three F, Cl, OH, OC(=O)C₁₋₄ alkyl, or OC₁₋₄ alkyl.

A specific value for R¹ is C₃₋₆ cycloalkyl.

4
16

A specific value for R^1 is amino, C_{1-2} alkylamino, C_{1-2} dialkylamino.

A specific value for R^1 is OC_{1-2} alkyl.

A preferred value for R^1 is methyl.

A specific value for R^2 is F.

5 A specific value for X is O.

A specific value for X is NR^3 ; wherein R^3 is H.

A specific value for X is NR^3 ; wherein R^3 is C_{1-3} alkyl, optionally substituted with one to three F, Cl, OH, CN, NH_2 , $OC(=O)C_{1-4}$ alkyl, or OC_{1-4} alkyl.

A specific value for X is NR^3 ; wherein R^3 is C_{3-8} alkene.

10 A specific value for X is NR^3 ; wherein R^3 is $C(=O)NR^4R^5$; wherein R^4 and R^5 are independently H or C_{1-3} alkyl, optionally substituted with one to three F, Cl, OH, CN, or NH_2 ;

A preferred value for X is O.

Another preferred value for X is NH.

15 A specific value for Y is O.

A specific value for Y is S.

A specific value for n is 0 or 1.

A preferred value for n is 1.

Examples of the present invention includes:

- 20 a) N-[[[(5S)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2-(2-propenyl)-2H-1,2-thiazin-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamida,
- b) N-[[[(5S)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamida,
- c) N-[[[(5S)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide,
- 25 d) N-[[[(5S)-3-[3-fluoro-4-(tetrahydro-2-methyl-1,1-dioxido-2H-1,2-thiazin-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide,
- e) N-[[[(5S)-3-[4-(2,2-dioxido-1,2-oxathian-5-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide, or
- 30 f) N-[[[(5S)-3-[4-(1,1-dioxido-4-isothiazolidinyl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide.

The following Schemes describe the preparation of compounds of the present invention. All of the starting materials are commercially available or prepared by

41

procedures described in these schemes or by procedures that would be well known to one of ordinary skill in organic chemistry. The variables used in the Schemes are as defined above or as in the claims.

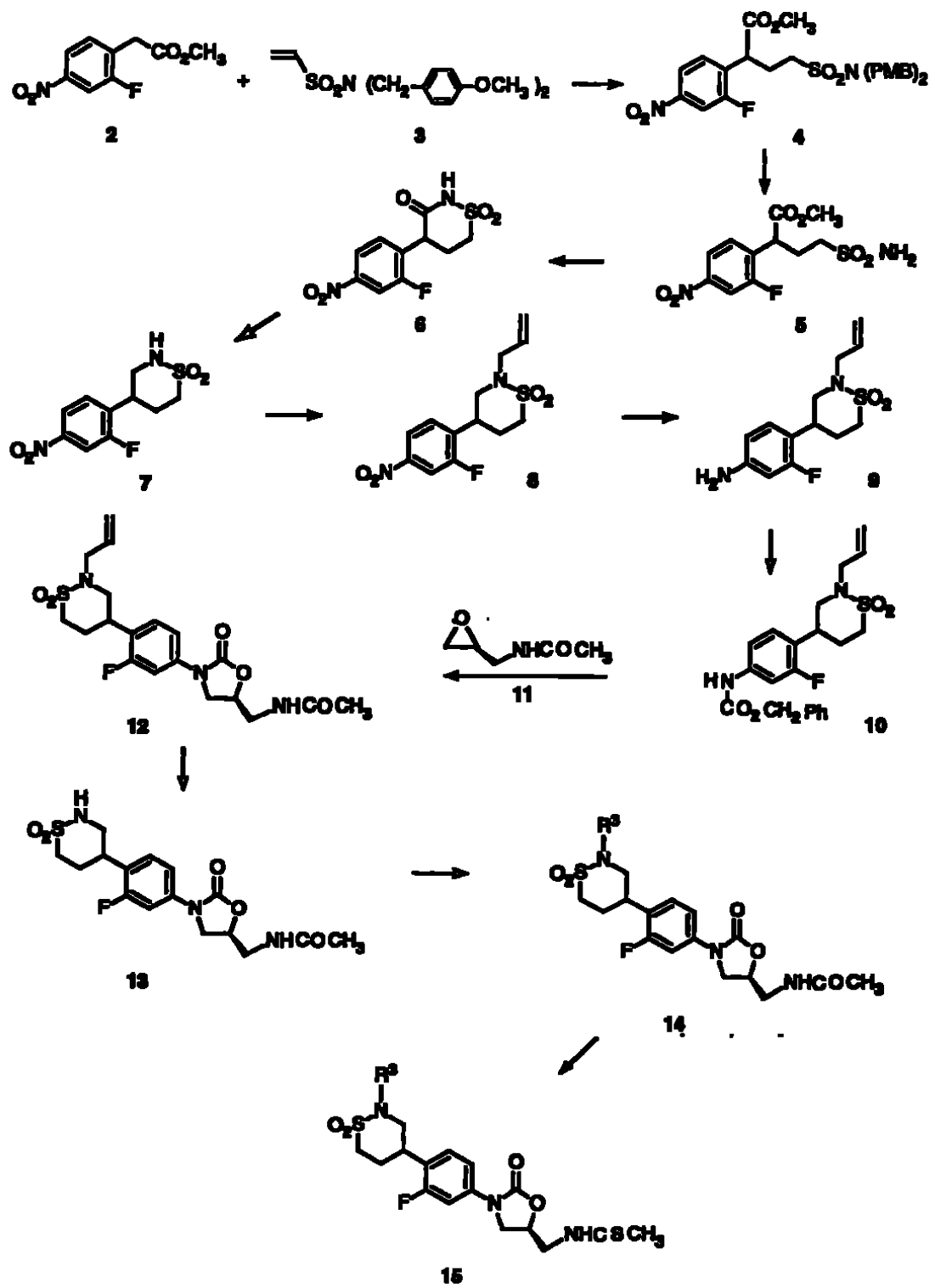
The 6-membered ring sultams ($n=1$, $X=NR^3$, R^3 is the same as defined above) may be prepared as outlined in Scheme 1. Also see Morris *et al.*, J. Org. Chem., 1991, 56, 3549. Addition of aryl acetic acid ester 2 to vinyl sulfonamide 3 in the presence of base gives adduct 4. Removal of the protecting groups from 4 with trifluoroacetic acid gives 5. Ring closure of 5 with sodium hydride affords 6 which in turn may be reduced with sodium borohydride-trifluoroacetic acid to give sultam 7. The nitrogen atom of the sultam ring may be protected with an allyl group to give 8 and the nitro group of 8 subsequently reduced with sodium borohydride-cuprous bromide: dimethyl sulfide complex to give amine 9.

Amine 9 can be protected as a CBZ derivative 10 which in turn can be reacted with amido epoxide 11 in the presence of base to give oxazolidinone 12. Removal of the N-allyl group can be effected with palladium on carbon in the presence of boron trifluoride etherate in ethanol to give 13. Thioamide 14 may be prepared by treating amide 13 with Lawesson's Reagent. Finally, replacement of H with R^3 using methods known to those skilled in the art provides compound 15.

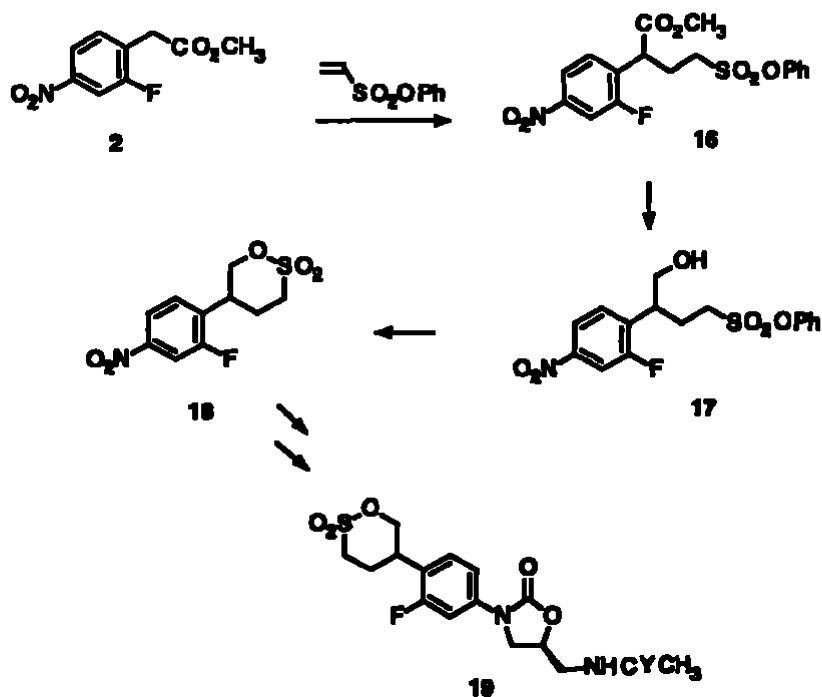
The 6-membered ring sultones ($n=1$, $X=O$) may be prepared analogously to the sultams and the syntheses are outlined in Scheme II. Addition of methyl arylacetate 2 to vinyl sulfonate in the presence of base affords adduct 16. Reduction of the ester of 16 with DIBAL gives alcohol 17 which may be cyclized to sultone 18 in the presence of sodium hydride. A similar sequence of steps to those outlined for the sultam in Scheme I, converts 18 to the sultone oxazolidinones 19.

The preparation of 5-membered ring sultam is outlined in Scheme III. Alkylation of methyl arylacetate 2 with bromomethylsulfonamide 20 gives the adduct 21, which in the presence of base may be cyclized to 22. A similar sequence of steps as outlined in Scheme 1 converts 22 to sultam oxazolidinones 23. See DuPriest *et al.*, J. Med. Chem. 1991, 34, 3229 and Morris *et al.*, J. Org. Chem., 1991, 56, 3549.

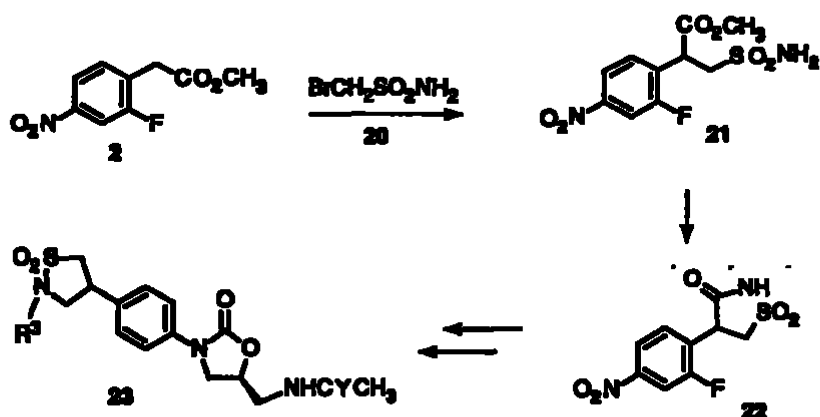
SCHEME I



SCHEME II



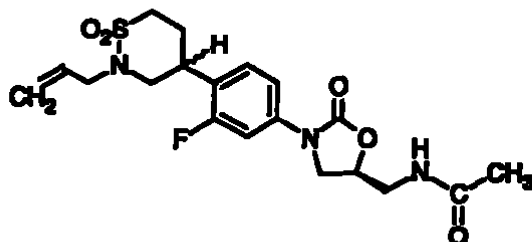
SCHEME III



The compounds and their preparations of the present invention will be better understood in connection with the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

EXAMPLES

Example 1 Preparation of N-[[[(5S)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide



5

Step 1 Preparation of methyl .alpha.-[2-[[bis[(4-methoxyphenyl)methyl]amino]sulfonyl]ethyl]-2-fluoro-4-nitrobenzeneacetate

Methyl 2-(2-fluoro-4-nitrophenyl)acetate (25.0 g, 117.4 mmol), vinyl sulfonamide (35.0 g, 100.9 mmol), anhydrous potassium carbonate (10.0 g, 72.5 mmol) and 18-crown-6 (2.64 g, 10.0 mmol) are heated under reflux in toluene (250 ml) for 3 hr. After cooling, ethyl acetate (500 ml) and water (300 ml) are added. The organic layer is washed with brine (200 ml), dried over MgSO_4 , filtered and evaporated. The resultant oil is chromatographed over silica gel (1 kg) eluting with 25-50% ethyl acetate-hexane. The title compound is obtained as white crystals (45.8 g, 81%) mp 79°.

15 Step 2 Preparation of methyl .alpha.-[2-(aminosulfonyl)ethyl]-2-fluoro-4-nitrobenzeneacetate

Methyl .alpha.-[2-[[bis[(4-methoxyphenyl)methyl]amino]sulfonyl]ethyl]-2-fluoro-4-nitrobenzeneacetate (41.6 g, 74.3 mmol) is dissolved in methylene chloride (200 ml) and trifluoroacetic acid (50 ml). The solution is stirred for 2 days then the solvents evaporated. 20 The residue is dissolved in ethyl acetate (750 ml) and washed with sodium bicarbonate solution (200 ml) and brine (100 ml). After drying (MgSO_4), filtration and evaporation the title compound is obtained as a solid (20.5 g, 86%) mp 99-101°.

Step 3 Preparation of 4-(2-Fluoro-4-nitrophenyl)dihydro-2H-1,2-thiazin-3(4H)-one 1,1-dioxide

25 A 60% sodium hydride oil dispersion (520 mg, 13.0 mmol) is washed with hexane (3x5 ml) then dry tetrahydrofuran (30 ml) added. To this stirred ice cooled mixture is added a solution of methyl .alpha.-[2-(aminosulfonyl)ethyl]-2-fluoro-4-nitrobenzeneacetate (3.20 g, 10.0 mmol) in dry tetrahydrofuran (30 ml). After stirring for 3 hr, additional sodium hydride (300 mg, 7.5 mmol) is added. Methanol (5 ml) is added after an additional

54
51

20 hr and the reaction evaporated to dryness. The residue is partitioned between 5% methanol-chloroform (150 ml) and 1N-HCl (50 ml), and the brown solid filtered. This solid is chromatographed over silica gel (150 g) eluting with 50% acetone-hexane. Recrystallization from acetone-hexane gives the title compound as solid. mp 218-219°.

5 Step 4 Preparation of 4-(2-Fluoro-4-nitrophenyl)tetrahydro-2H-1,2-thiazine 1,1-dioxide

4-(2-Fluoro-4-nitrophenyl)dihydro-2H-1,2-thiazin-3(4H)-one 1,1-dioxide (2.43 g, 8.44 mmol) and sodium borohydride (3.83 g, 101.3 mmol) are placed under nitrogen and dry THF (70 ml) added. To the ice cooled suspension is added trifluoroacetic acid (7.8 ml, 101.3 mmol) over 5 min. After stirring for 16 hr additional trifluoroacetic acid (20.0 ml, 260 mmol) is added followed by methanol (20 ml). The solution is evaporated and the residue dissolved in ethyl acetate (150 ml) and washed with sodium bicarbonate solution (3x100 ml) and brine (50 ml). Evaporation gives a yellow gum which is chromatographed over silica gel (90 g) eluting with 1-3% methanol-chloroform. The title compound is obtained as a gum (1.99 g, 86%): Calcd for $C_{10}H_{11}FN_2O_4S$: C, 43.79; H, 4.04; N, 10.21. Found: C, 43.72; H, 4.07; N, 10.11.

15 Step 5 Preparation of 4-(2-fluoro-4-nitrophenyl)tetrahydro-2-(2-propenyl)-2H-1,2-thiazine 1,1-dioxide

Anhydrous potassium carbonate (3.6 g, 26.1 mmol) is added to a solution of 4-(2-fluoro-4-nitrophenyl)tetrahydro-2H-1,2-thiazine 1,1-dioxide (1.795 g, 6.54 mmol) and allyl bromide (2.0 ml, 23.1 mmol) in dry acetonitrile (25 ml). The mixture is heated to reflux for 5 min then cooled. After filtration and evaporation the residue is chromatographed over silica gel (150 g) eluting with 0-1% methanol-chloroform. The title compound is obtained as flakes (1.70 g, 83%) mp 121°.

25 Step 6 Preparation of 3-fluoro-4-[tetrahydro-1,1-dioxido-2-(2-propenyl)-2H-1,2-thiazin-4-yl]benzenamine

4-(2-Fluoro-4-nitrophenyl)tetrahydro-2-(2-propenyl)-2H-1,2-thiazine 1,1-dioxide (1.303 g, 4.15 mmol) and cuprous bromide: dimethyl sulfide complex (0.855 g, 4.15 mmol) are stirred at ice temperature in dry THF (30 ml). Sodium borohydride (1.25 g, 33.07 mmol) is added and the mixture stirred for 20min. Methanol (10 ml) is carefully added over 30 min followed by ammonium chloride solution (50 ml). The mixture is extracted with methylene chloride (2x100 ml), washed with water (50 ml) and brine (50 ml), dried ($MgSO_4$) and evaporated to yield the product as a cream solid (1.178 g, 100%) mp 96°.

664011-2555109

52

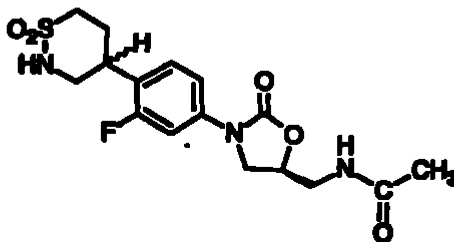
Step 7 Preparation of phenylmethyl [3-fluoro-4-[tetrahydro-1,1-dioxido-2-(2-propenyl)-2H-1,2-thiazin-4-yl]phenyl]carbamate

- 3-fluoro-4-[tetrahydro-1,1-dioxido-2-(2-propenyl)-2H-1,2-thiazin-4-yl]benzenamine (1.154 g, 4.06 mmol) is dissolved in THF (15 ml) to which is added benzyl chloroformate (765 mg, 4.48 mmol) followed by a solution of sodium bicarbonate (700 mg, 8.33 mmol) in water (10 ml). After stirring for 2 hr most of the THF is evaporated and the residue is extracted with ethyl acetate (100 ml). After washing with water (25 ml) and brine, the solution is dried (MgSO_4) and evaporated to afford the title compound as white crystals (1.70 g, 100%) mp 138-140°.

Step 8 Preparation of N-[(5S)-3-[3-fluoro-4-[tetrahydro-1,1-dioxido-2-(2-propenyl)-2H-1,2-thiazin-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

- Phenylmethyl [3-fluoro-4-[tetrahydro-1,1-dioxido-2-(2-propenyl)-2H-1,2-thiazin-4-yl]phenyl]carbamate (1.70 g, 4.07 mmol) is dissolved in dry THF (18 ml) under nitrogen and cooled to -78°. A 1.6 M solution of n-butyl lithium (2.7 ml, 4.32 mmol) in hexane is added and stirred for 1 hr. A solution of N-[(2S)oxiranylmethyl]acetamide 11 (960 mg, 8.35 mmol) in dry THF (6.5 ml) is added and the stirred mixture allowed to come to 25° overnight. Solvent is evaporated and the residue partitioned between chloroform (100 ml) and ammonium chloride solution (50 ml). The organic layer is washed with brine (40 ml), dried (MgSO_4) and evaporated. The residue is chromatographed over silica gel (150 g) eluting with 2-4% methanol-chloroform to afford the oxazolidinone as a white foam (1.275 g, 73%). HRMS(FAB) calcd for $m+H = 426.1499$; Found: 426.1506.

Example 2 Preparation of N-[(5S)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



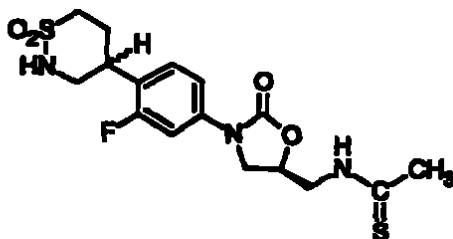
N-[(5S)-3-[3-Fluoro-4-[tetrahydro-1,1-dioxido-2-(2-propenyl)-2H-1,2-thiazin-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (350 mg, 0.82 mmol), 10% palladium

60163537-110499

56
53

on carbon (500 mg), boron trifluoride etherate (179 mg, 1.26 mmol) and absolute ethanol (8 ml) are heated under reflux for 5 hr. Upon cooling the suspension is filtered and evaporated. Chromatography over silica gel (55 g) eluting with 2-6% methanol-chloroform affords the title compound as a foam (186 mg, 59%). HRMS(FAB): calcd for m+H = 386.1186; Found: 386.1194.

Example 3 Preparation of N-[[[(5S)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]ethanethioamide



10

N-[[[(5S)-3-[3-Fluoro-4-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (180 mg, 0.47 mmol), Lawesson's Reagent (310 mg, 0.77 mmol) and dioxane (10 ml) is heated under reflux for 1 hr. After cooling, the solvent is evaporated and the residue chromatographed over silica gel (40 g) eluting with 2-4% methanol-chloroform gives the title compound as a foam (173 mg, 92%). HRMS(FAB): calcd for m+H = 402.0957; Found: 402.0954.

15

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

20

25

60163537.1104 9

12
54

systems, optionally containing suitable conventional coloring agents, flavoring agents, stabilizers and thickening agents.

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

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

In therapeutic use for treating, or combatting, bacterial infections in human and other 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 an amount, or blood-level of active component in the mammals 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 3.0 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 also 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,

60163537-110499

55

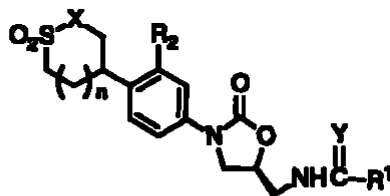
sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine to name but a few representative buffering agents. The compounds according to formula I generally will be dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 mg/ml to about 400 mg/ml of solution. The
5 resulting liquid pharmaceutical composition will be administered so as to obtain the above-mentioned antibacterially effective amount of dosage. The compounds of formulas I according to this invention are advantageously administered orally in solid and liquid dosage forms.

0163537-110499

CLAIMS

We claim:

1. A compound of formula I



I

or a pharmaceutically acceptable salt thereof wherein

R^1 is

- (a) H,
- (b) C_{1-8} alkyl, optionally substituted with one to three F, Cl, OH, $OC(=O)C_{1-4}$ alkyl, or OC_{1-4} alkyl,
- (c) C_{3-8} cycloalkyl,
- (d) amino,
- (e) C_{1-8} alkylamino,
- (f) C_{1-8} dialkylamino, or
- (g) OC_{1-8} alkyl;

R^2 is H or F;

X is O or NR^3 ;

R^3 is

- (a) H,
- (b) C_{1-8} alkyl, optionally substituted with one to three F, Cl, OH, CN, NH_2 , $OC(=O)C_{1-4}$ alkyl, or OC_{1-4} alkyl,
- (c) C_{3-8} alkene, or
- (d) $C(=O)NR^4R^5$;

R^4 and R^5 are independently

- (a) H, or
- (b) C_{1-8} alkyl, optionally substituted with one to three F, Cl, OH, CN, or NH_2 ;

Y is O or S; and

n is 0 or 1.

2. A compound of claim 1 wherein R^1 is methyl.

(6)
57

3. A compound of claim 1 wherein Y is oxygen atom
4. A compound of claim 1 wherein Y is sulfur atom.
- 5 5. A compound of claim 1 wherein R² is fluoro atom.
6. A compound of claim 1 wherein X is oxygen atom.
7. A compound of claim 1 wherein X is NH.
- 10 8. A compound of claim 1 wherein n is 1.
9. A compound which is
- 15 a) N-[(5S)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-4-yl)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide,
- b) N-[(5S)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-4-yl)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide,
- c) N-[(5S)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-4-yl)phenyl]-2-oxo-5-oxazolidinyl)methyl]ethanethioamide
- 20 d) N-[(5S)-3-[3-fluoro-4-(tetrahydro-2-methyl-1,1-dioxido-2H-1,2-thiazin-4-yl)phenyl]-2-oxo-5-oxazolidinyl)methyl]ethanethioamide,
- e) N-[(5S)-3-[4-(2,2-dioxido-1,2-oxathian-5-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl)methyl]ethanethioamide, or
- f) N-[(5S)-3-[4-(1,1-dioxido-4-isothiazolidinyl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl)methyl]ethanethioamide.
- 25
10. A method for treating microbial infections in a mammal which comprises administering to said mammal in need thereof an effective amount of a compound of formula I as shown in claim 1.
- 30
11. The method of claim 10 wherein said compound of formula I is administered orally, parenterally, transdermally, or topically in a pharmaceutical composition.

6 163537-110499

58

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

13. A method for treating microbial infections of claim 10 wherein the infection is skin
5 infection.

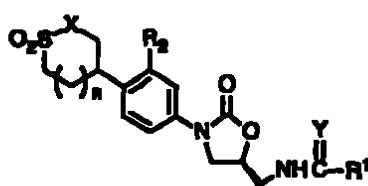
14. A method for treating microbial infections of claim 10 wherein the infection is eye infection.

10 15. A pharmaceutical composition comprising a compound of formula I as shown in claim 1 and a pharmaceutically acceptable excipient.

60163537.110499

ABSTRACT

The present invention provides a compound of formula I



I

5

These compounds are useful as antibiotic agents.

60163537.110499

2do. EXAMEN DE FORMA PATENTE DE INVENCION

Folio 64

Radicación no. 00-83532

Concepto Técnico no 1352 Clasificación Internacional de Patentes A61K 31 / 39//31/4385

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 ☐ NO ES APLICABLE ☒ 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)

1. Anexa la copia y traducción de la solicitud de patente estadounidense No. 60/163,158 del 04/11/1999 a partir del folio No. 38

EXAMINADOR TÉCNICO

202047

Bogotá D. C., Septiembre 12 de 2002

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 281 31 25 e-mail: info@alc.gov.co
Santa Fe de Bogotá D.C. - Colombia

Folio 65

2020
Bogotá DC

Doctor
JOSE ANTONIO LLOREDA
Apoderado

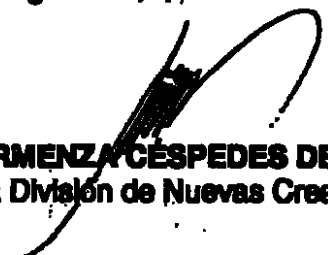
REFERENCIA: Radicación No. 00-83532
 Trámite 002
 Evento 001
 Actuación 416
 Oficio No. 1839
 Folios 001

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

27 de mayo de 2020


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

202047

526