

Q.F.



Industria y Comercio
SUPERINTENDENCIA

SOLICITUD
PATENTE DE INVENCION

21 EXPEDIENTE N°

04 118236

54 TÍTULO "COMPUESTOS PARA EL TRATAMIENTO DEL ANTRAX E INHIBIDORES DEL FACTOR
LETAL"

51 CLASIFICACIÓN INTERNACIONAL A 61K 31/00 ; A61K31/18

71 SOLICITANTE MERCK & CO., INC.

DOMICILIO RAHWAY, ESTADO DE NEW JERSEY, ESTADOS UNIDOS DE AMERICA

74 REPRESENTANTE LEGAL ALICIA LLOREDA RICAURTE
T.P. 53.215

22 BOGOTÁ, D C 24 NOV 2004

Q.F.
(SS)

PETITORIO


Industria y Comercio
 SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
 Radicación: 84118236 00000000 Folios: 158
 Fecha (AGD): 2004-11-24 16:23:01
 Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTN
 Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

①

SOLICITUD DE:

☒ Patente de Invención ☐ Patente de Modelo de Utilidad

☐ Capítulo I. ☒ Capítulo II.

②

SOLICITANTE
(71)

Nombre: MERCK & CO., INC.

Dirección: 126 East Lincoln Avenue, Rahway,
Estado de New Jersey 07065-0907, Estados
Unidos de América.Nacionalidad o Domicilio: Rahway, Estado
de New Jersey, Estados Unidos de AméricaLugar de Constitución: Estado de New
Jersey, Estados Unidos de América.

Teléfono: 3264270 Fax: 6069701

E-mail: jlcco@lloredacamacho.com

IDENTIFICACION

C.C. ☐ NIT ☐
 C.E. ☐ Otro ☐

Cual _____

Número _____

③

REPRESENTANTE
O APODERADO

Nombre: ALICIA LLORED RICAURTE

Dirección: Calle 72 No. 5-83 Piso 5o.

Teléfono: 3264270 Fax: 6069701

E-mail: jlcco@lloredacamacho.com

C.C. ☒ NIT ☐
 C.E. ☐ Otro ☐

Cual _____

Número 39.690.713 TP53.215

④

INVENTOR(ES)
(72)Nombre: XIONG, Yusheng; CHAPMAN, Kevin; SINGH, Suresh; GUO, Jian y
PATCHETT, Arthur, A.

Dirección: 126 East Lincoln Avenue, Rahway, NJ 07065-0907.

Nacionalidad o Domicilio: Estados Unidos de América.

⑤

PCT (86)

Solicitud Internacional No. PCT/US2003/016336

Fecha: 23.05.2003

Publicación Internacional No. WO2003/101382 A3

Fecha: 11.12.2003

⑥

Título (54) "COMPUESTOS PARA EL TRATAMIENTO DEL ÁNTRAX E INHIBIDORES DEL
FACTOR LETAL"

⑦

Clasificación Internacional (51) A61 K 31/00 A61K31/18

⑧

Prioridad

(33) País de Origen

(32) Fecha

(31) Número de Solicitud

SI ☒ NO ☐

US

29.05.2002

60/383,998

⑨

Comprobante de Pago No. 04-90,695

Fecha: Noviembre 23 de 2004

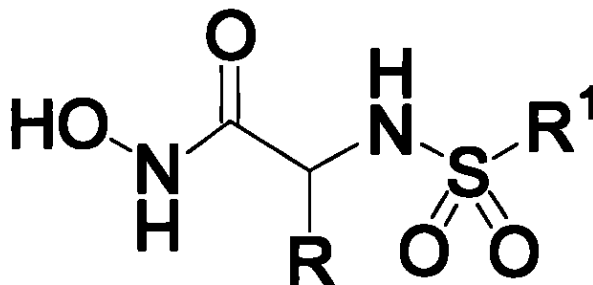
ANEXOS

10

- ☒ Comprobante de pago de la tasa de presentación de la solicitud.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Documento de Representación Legal.
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☐ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones)
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredita la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☒ Arte Final 12X12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros Reporte de Búsqueda Internacional con su traducción, Publicación con su traducción, Capítulo Reivindicatorio como fue presentado originalmente en Fase Internacional y Anexo Explicativo de Modificaciones a las Reivindicaciones.

11

FIGURA CARACTERISTICA:



FORMULA I

12

Solicito la concesión de la patente,

NOMBRE: ALICIA LLOREDA RICAURTEFIRMA: 

C.C. 39.690.713 Usaquén

T.P. 53.215

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04118236 00000000 Folios: 150
Fecha (RMB): 2004-11-24 16:23:01
Tramite : 011 PCT-PATENT 379 FASE INCI 411 PRESENTA
Dependencia: 2828 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 90,695
FECHA : NOVIEMBRE 23 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PBO	Vr. PAGO
LLOREDA Y CIA S. A	CONSIGNACION	BANCO POPULAR	050-00110-6	24585985	23/11/2004	6,969,000.00

***** CONCEPTO *****

CANT. HISTORICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
	TOTAL :	\$ 422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ANEXO

El documento que acredita la calidad de REPRESENTANTES LEGALES en Bogotá de los doctores ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ para TODOS LOS ASUNTOS RELACIONADOS CON LA PROPIEDAD INDUSTRIAL de la sociedad peticionaria, que faculta a cada uno de dichos abogados para actuar individualmente, se esta presentando con esta solicitud. En consecuencia, ruego a usted reconocer la personería de cada uno de dichos Representantes Legales para actuar dentro del presente expediente, a fin de que cualquiera de ellos pueda intervenir en cualquier tiempo respecto de la solicitud en él contenida.


ALICIA LLOREDA RICAURTE

T.P. No. 53.215

NOTARY PUBLIC

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

- 1. COUNTRY: UNITED STATES OF AMERICA
- 2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
BARBARA ANN COZZI
- 3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
- 4. BEARS THE SEAL/STAMP OF:
BARBARA ANN COZZI, NOTARY

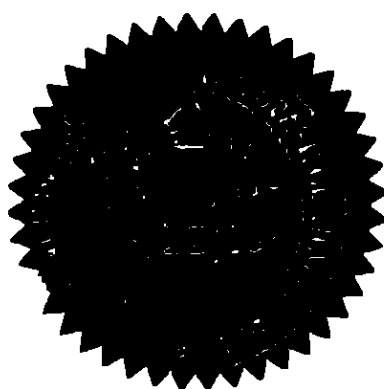
CERTIFIED

- 5. AT TRENTON, NEW JERSEY
- 6. THE 14TH DAY OF OCTOBER 2004
- 7. BY: John E McCormac, CPA, NEW JERSEY TREASURER
- 8. NO. A210632
- 9. SEAL/STAMP:

10. SIGNATURE

EL CIRCULO
DE NOTARIOS PUBLICOS
DE NEW JERSEY
COMPARE CON EL ORIGINAL
Y HA TENIDO A LA VISTA
27 OCT 2004
PABLO L'ENUEZ BARAJAS
NOTARIO (E)

John E McCormac



Los abajo firmados,
MERCK & CO., INC.
sociedad organizada y existente de conformidad con
las leyes del Estado de New Jersey, Estados Unidos
de América

con domicilio en
126 East Lincoln Avenue, Rahway, Estado de New
Jersey 07065-0907, Estados Unidos de América

nombramos por el presente a ALICIA LLOREDA y/o
GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA
y/o ENRIQUE ALVAREZ, domiciliados en Bogotá,
Colombia, con oficinas en dicha ciudad, Calle 72 No.
5-83, piso 6o., nuestros representantes legales y
verdaderos en Bogotá, con facultades para recibir
notificaciones y nombrar apoderados judiciales o
extrajudiciales, con el fin de dar cumplimiento al
párrafo 1o. del Artículo 543 del decreto 410 de
1971.

Los doctores ALICIA LLOREDA y/o GUSTAVO
TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE
ALVAREZ, o los apoderados que cualquiera de ellos
designare, quedan especialmente facultados para
representarnos ante las autoridades colombianas,
administrativas, judiciales o de policía, en todos los
trámites relativos a la propiedad industrial, a cuyo
efecto les facultamos para dar ante dichas
autoridades todos los pasos necesarios al objeto
indicado; elevar solicitudes, declaraciones, reclamos,
recursos y presentar desistimientos; formular
descripciones, enmiendas, limitar el alcance de las
solicitudes, presentar oposiciones y apelaciones;
instaurar cancelaciones, renunciar total o
parcialmente a los registros, abonar todos los
impuestos y cuotas y efectuar todo otro pago
determinado por la ley; recibir todos los documentos
y valores, dando el descargo respectivo; llenar
cualesquiera otros requisitos y tomar, en fin, todas
las medidas que creyeran conducentes al resguardo
de nuestros intereses; y en caso de producirse
oposición, pasando los antecedentes a los
tribunales, quedan facultados para tomar
intervención como demandantes o demandados ante
los jueces que sean competentes, pudiendo transar,
someter a árbitros, desistir, percibir y apelar, con
todas las demás facultades que resulten necesarias,
y por el presente declaramos desde ahora válido y
bueno cuanto dichos representantes y/o los
apoderados que cualquiera de ellos nombre hicieren
en nuestro beneficio.

Asimismo, facultamos a los doctores ALICIA
LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO
SANTAMARIA y/o ENRIQUE ALVAREZ, para
solicitar en la Oficina de Propiedad Industrial la
protocolización de este documento y de cualquier
poder que cualquiera de ellos otorgue a nombre
nuestro.

Dado y firmado

The undersigned,
MERCK & CO., INC.
a corporation organized and existing under the laws
of The State of New Jersey, United States of America

domiciled at
126 East Lincoln Avenue, Rahway, State of New
Jersey 07065-0907, United States of America

hereby appoint, ALICIA LLOREDA and/or
GUSTAVO TAMAYO and/or IGNACIO
SANTAMARIA and/or ENRIQUE ALVAREZ, of
Bogota, Colombia, with offices in said town, Calle 72
No. 5-83, Sixth Floor, our true and legal
representatives in Bogotá, with power to receive
notifications and to appoint judicial or extrajudicial
agents, so as to comply with paragraph 1o. of Article
543 of decree 410 of 1971.

Doctors ALICIA LLOREDA and/or GUSTAVO
TAMAYO and/or IGNACIO SANTAMARIA and/or
ENRIQUE ALVAREZ, or the agents by any one of
them appointed, are especially empowered to
represent us before the administrative, judicial or
police authorities of Colombia, in all proceedings
pertaining to industrial property, for which purpose
we authorize them to take before the said authorities
all the necessary steps for the said end; to file
petitions, declarations, claims, recourses and
withdrawals, to draw up specifications; to file
amendments, to limit the scope of applications, file
oppositions; file cancellations total or partially waive
registrations, to pay all installments and effect all
other payments prescribed by law; to receive proper
receipts, to comply with all other requirements and, in
short, to take all those measures which they may
deem fit for the protection of our interests; and in
case of opposition, where the proceedings be passed
over to the courts, we authorize said agents to act on
our behalf, as complainants as well as defendants,
before the competent judges, with full powers to
make arrangements, to submit to arbitrators, to
desist, to collect, to appeal and, in short, with all such
further powers as may be required, and we hereby
declare from now on as valid and good all that said
representatives and/or the agents by any one of
them appointed may do for our benefit.

We also authorize doctors ALICIA LLOREDA
and/or GUSTAVO TAMAYO and/or IGNACIO
SANTAMARIA and/or ENRIQUE ALVAREZ, to apply
for protocolization of this document and of any power
of attorney by any one of them conferred in our
name, before the Office of Industrial Property.

Given and signed this 4th day of October, 2004

x *Donna L. Marglotta*
Donna L. Marglotta, Senior Manager, Patent
Administration
NOTA RY SHOULD EXECUTE OTHER SIDE

BARBARA ANN GOZZI
Notary Public of New Jersey
My Commission Expires Nov. 30, 2005

NOTARIAL CERTIFICATE (CORPORATION)

CERTIFICADO NOTARIAL (SOCIEDAD)

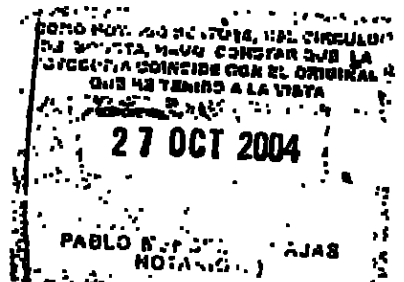
Estados Unidos de América
Estado de New Jersey (ss)
Condado de Union
Hoy 4 de Octubre de 2004, compareció
Donna L. Margiotto, a quien conozco y
de quien me consta que firmó el anterior documento,
y quien debidamente juramentado declaró y dijo que
él es
de Merck & Co., Inc.
la compañía nombrada en
el documento que antecede, una sociedad
debidamente organizada y existente conforme a las
leyes del Estado de Nueva Jersey, Estados
Unidos de América, domiciliada en la ciudad de
Rahway, Condado de Union,
Estado de Nueva Jersey Estados Unidos de
América, legalmente constituida para un período de
duración que aún no ha terminado, que ejerce su
objeto social; conforme a las leyes del Estado de
Estados Unidos de América;
que el declarante está autorizado por dicha
Compañía para conferir este poder; que el sello
estampado por él al ple de tal poder, en nombre y en
representación de la expresada Compañía, es el
sello oficial de ella; y que el objeto para el cual se
confiere este instrumento está comprendido dentro
del de la sociedad.
El suscrito Notario ha visto los Estatutos de
Incorporación firmados en
Estado de New Jersey, con fecha 28 Abril 1959,
y certifica que de conformidad con la legislación de
dicho Estado la anterior declaración juramentada es
prueba suficiente de que los hechos sobre que ella
versa son ciertos o verdaderos, de lo cual da fe.

Notary Public (Notario Público).

Barbara Ann Cozzi

BARBARA ANN COZZI
Notary Public of New Jersey
My Commission Expires Nov. 30, 2008

United States of America
State of New Jersey (ss)
County of Union
On this 4th day of October, 2004,
personally
Came Donna L. Margiotto,
to me known, and known to me to be the person who
signed the foregoing Instrument, who being by me
duly sworn did depose and say that she is the Senior
Manager, Patent Administration of Merck & Co., Inc.,
the company named within, a Corporation organized
and existing under the laws of the State of New
Jersey, United States of America, domiciled at the
City of Rahway,
County of Union, State of New Jersey,
United States of America, legally constituted for a
period of tenure not yet expired, which exercises its
corporate purposes according to the laws of the
State of New Jersey, United States of America; that
the deponent is authorized by said Company to
confer this power of attorney; that the seal affixed
hereunto by the deponent in the name and on behalf
of said Corporation is the corporate seal thereof; and
that the purpose for which this Instrument is granted
is included within the corporate purposes of the
Company.
The undersigned Notary Public has seen the
Certificate of Incorporation of said Corporation filed
and recorded at State of New Jersey, under date of
April 28, 1959, and hereby certifies that under the
laws of said State the foregoing acknowledgment is
sufficient proof that the facts therein contained are
true, which he attests.



TRADUCCION OFICIAL No. 2004-10-25-505 de un documento escrito en Inglés/ Español, la cual para efectos del presente lleva el sello personal de **Martha Lucia Arciniegas M.**, Traductora e Intérprete Oficial en virtud de la Res 1523 /88 del Ministerio de Justicia.

Legalización de un Poder de Representación Legal conferido a **ALICIA LLOREDA**,
y/o **GUSTAVO TAMAYO**, y/o **IGNACIO SANTAMARIA** y/ **ENRIQUE ALVAREZ**
otorgado por **MERCK & CO., INC.**

Dado y firmado el 4 de octubre del 2004

Por

Donna L. Margiotto, Gerente Senior, Administración de Patente

SE DEBE LEGALIZAR AL OTRO LADO

Barbara Ann Cozzi

Notaria Pública de New Jersey

Mi Comisión vence el 30 de Noviembre del 2008

CERTIFICADO NOTARIAL (CORPORACIÓN)

Legalización de la firma precedente

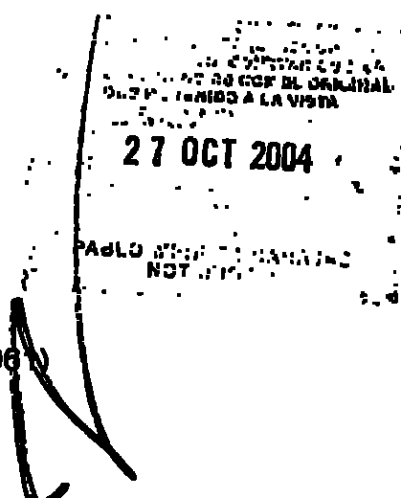
Barbara Ann Cozzi

Notaria Pública de New Jersey

APOSTILLA

(Convención de La Haya del 5 de octubre de 1961)

1. País: Estados Unidos de América



Este documento público

- 2. ha sido firmado por BARBARA ANN COZZI
- 3. actuando en su calidad como Notaria Pública de New Jersey
- 4. lleva el sello/estampilla de BARBARA ANN COZZI, Notaria

CERTIFICADO

- 5. en Trenton, New Jersey
- 6. el día 14 de octubre, 2004
- 7. por John E. McCormac, CPA, Tesorero New Jersey
- 8. Número A210632
- 9. Sello/Estampilla
- 10. Firma (ilegible)

Según mi leal saber y entender esta es una traducción fiel y completa de su original en Inglés, de la cual se deja copia para futuras referencias .

NO SE ASUME
 RESPONSABILIDAD POR EL TEXTO
 1004 OCT 26 P 10 58
 Jefe de LEGALIZACIONES
 SANTIAGO DE BOGOTA D.C.

MINISTERIO DE RELACIONES
 EXTERIORES
 U 5 6 6 5 5
 Martha Arciniegas
 CUYA FIRMA APARECE EN EL
 DOCUMENTO DESEMPLEA
 LAS FUNCIONES DE SECRETARIA

Martha Arciniegas
 MARTHA LUCIA ARCINIEGAS AL
 TRADUCTORA E INTERPRETE OFICIAL
 RESOLUCION 1523/88 MINJUSTICIA

EL NOTARIO PUBLICO DEL CIRCULO
 NOTARIAL, MARCO ANTONIO GARCIA, HA
 FOTOCOPIADO Y COMPROBADO CON EL ORIGINAL
 QUE ESTE DOCUMENTO ES VERDADERO
 27 OCT 2004

8

Expediente No		No de unidades	No de Follo
Item			✓
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: No contiene arte final			

10

TRATADO DE COOPERACION DE PATENTES
PCT
REPORTE DE BUSQUEDA INTERNACIONAL

(PCT Artículo 18 y Reglas 43 y 44)

Registro de referencia del solicitante o agente PCT 21111 Y	PARA FUTURAS ACCIONES ver Notificación o Transmisión del Reporte de Búsqueda Internacional (Forma PCT/ISA/220) así como, donde aplique, el ítem 5 a continuación.	
Solicitud internacional No. PCT/US2003/16336	Fecha de registro internacional (día/mes/año) 23 de mayo de 2003 (23.05.2003)	Fecha de Prioridad (Primera) (día/mes/año) 29 de mayo de 2003 (29.05.2002)
Solicitante MERCK & CO., INC.		
Este Reporte de Búsqueda Internacional ha sido preparado por esta Autoridad de Búsqueda Internacional y es transmitido al solicitante Según el Artículo 18. Una copia será transmitida a la Oficina Internacional. Este Reporte de Búsqueda Internacional consta de un total de <u> 3 </u> hojas. ☒ También está acompañado de una copia de cada documento técnico anterior citado en este reporte.		
1. Bases del reporte a. Respecto al lenguaje, la búsqueda internacional se llevó a cabo según la solicitud internacional en el lenguaje en el cual se presentó, a menos que se indique de otro modo en este ítem. ☐ la búsqueda internacional se llevó a cabo según la traducción de la solicitud internacional proporcionada a esta Autoridad (Regla 23.1(b)). b. Respecto a una secuencia de ácido nucleótico y/o amino revelado en la solicitud internacional, la búsqueda internacional se llevó a cabo según la lista de la secuencia: ☐ contenido en la solicitud internacional en forma escrita. ☐ presentada junto con la solicitud internacional en forma legible por computador. ☐ proporcionada subsiguientemente a esta Autoridad en forma escrita. ☐ proporcionada subsiguientemente a esta Autoridad en forma legible por computador. ☐ se ha proporcionado la afirmación de que el listado de secuencias escrito proporcionado subsiguientemente no va más allá de la revelación en la solicitud internacional según se presentó. ☐ se ha proporcionado la afirmación de que la información registrada en forma legible por computador es idéntica al listado de la secuencia escrita. 2. ☐ Ciertas reivindicaciones no pudieron localizarse (Ver Recuadro I). 3. ☐ Falta unidad de invención (ver Recuadro II). 4. Respecto al título, ☒ El texto es aprobado según lo presenta el solicitante. ☐ Esta Autoridad ha establecido que el texto se lee así: 5. Respecto al resumen, ☒ El texto es aprobado según lo presenta el solicitante. ☐ Esta Autoridad ha establecido el texto de acuerdo con la Norma 38.2(b), según aparece en el Recuadro III. El solicitante puede, un mes después de la fecha de haber enviado por correo este reporte de búsqueda internacional, presentar comentarios a esta Autoridad. 6. La figura de los dibujos que se publicará con el resumen es la Figura No. _____ ☐ como lo sugirió el solicitante. ☐ porque el solicitante no sugirió una figura. ☐ porque esta figura caracteriza mejor a la invención. ☒ Ninguna de las figuras.		

REPORTE DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No.
PCT/US2003/16336

A. CLASIFICACION DE MATERIA

IPC(7): A61K31/00, 35/00

US CL: 424/114,117; 514/183

Según la Clasificación de Patentes Internacional (CPI) o según la clasificación nacional y la CPI

B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido de símbolos de clasificación)

U.S.: 424/114, 117; 514/183

Documentación buscada fuera de documentación mínima hasta donde dichos documentos se incluyan en los campos buscados
IUBMB DATABASE

Base de datos electrónica consultada durante la búsqueda internacional (nombre de la base de datos y, donde sea práctico, buscar términos usados)
Favor ver siguiente hoja

C. DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría *	Citación de documento, con indicación, donde sea apropiado, de los textos relevantes	Relevante a la reivindicación No.
Y	BECKER, D.P. et al. Alpha-amino-beta-sulphone Hydroxamates as Potent MMP-13 Inhibitors that Spare MMP-1. Bioorganic & Medicinal Chemistry Letters. 2001, volumen 11, páginas 2719-2725, especialmente resumen, tablas 1 y 2.	1-13
Y	WO 98/18754 A1 (VERSICOR, INC) 7de mayo de 1998 (07.05.1998), página 67, línea 1 a página 84, línea 13.	1-11
Y	US 5,863,949 A (ROBINSON et al.) 26 de enero de 1999 (01.26.1999), columna 14, línea 60 a columna 15, línea 39.	1-9
Y,P	CLEMENTS, J.M. et al. Antimicrobial Activities and Characterization of Novel Inhibitors of LpxC. Antimicrobial Agents and Chemotherapy. Junio 2002, volumen 46, No.6, páginas 1793-1799, especialmente el resumen, Página 1794, Parágrafo 3, Líneas 1-6; Páginas 1795, columna 1, primer paragrafo bajo resultados, figura 1, tabla 2 y 3; páginas 1796, columna 1, segundo y tercero paragrafos completos bajo la figura 3.	1-9 y 13-15

☐ En el recuadro C se enumeran más documentos.

☐ En el anexo se enumeran miembros de la familia de patentes.

* Categorías especiales de documentos citados:

'A' documento que define el estado general de la técnica el cual no se considera de relevancia particular

'E' documento anterior pero publicado en o después de la fecha de presentación internacional

'L' documento que puede arrojar dudas sobre reivindicaciones de prioridad o que se cita para establecer la fecha de publicación de otra citación u otra razón especial (según se especifica)

'O' documento que se refiere a una revelación oral, uso, exhibición u otros medios

'T' documento publicado antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada

'T' documento posterior publicado después de la fecha de presentación internacional o fecha de prioridad y que no está en conflicto con la solicitud pero citado para entender el principio o teoría que sustentan la invención

'X' documento de relevancia particular; la invención reivindicada no puede considerarse nueva o no puede considerarse que comprende un paso inventivo cuando el documento se toma solo

'Y' documento de relevancia particular; la invención reivindicada no puede considerarse que comprende un paso inventivo cuando el documento se combina con uno o más documentos, siendo dicha combinación obvia para una persona experta en la técnica

'Z' documento miembro de la misma familia de patentes

Fecha de la terminación real de la búsqueda internacional

11 de mayo de 2004 (11.05.2004)

Fecha de envío por correo del reporte de búsqueda internacional

10 de junio de 2004

Nombre y dirección del correo de ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Fax: (703) 305-3230

Funcionario autorizado

Dr. Kailash C. Srivastava
Teléfono No.(571)-272-0700

Forma PCT/ISA/210 (segunda hoja) (Julio 1998)

REPORTE DE BUSQUEDA INTERNACIONAL**Solicitud Internacional No.
PCT/US2003/16336****Continuación de B. Campos Buscados Item 3:****USPT, PGPB, EPAB, JPAB, DWPI, REGISTRO, HCAPLUS, USPATFULL EN STN****METALOPROTEINASAS DE MATRIZ, AMINO-SULFONIL-HIDROXAMATOS, HIDROXAMATOS de
SULFONAMIDA, PENICILINA, TETRACICLINA, ANTIBIOTICOS, LNF, ANTRAX, PENICILINA,
IMIPENEM, PRIMAXINA, VANCOMICINA, CIPROFLAXINA, PROBECIDA, ACIDO
CLAVULANICO, CEFOXITINA, CILASTATINA, MEROPENEM**

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PCT 21111Y	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US03/16336	International filing date (day/month/year) 23 May 2003 (23.05.2003)	(Earliest) Priority Date (day/month/year) 29 May 2002 (29.05.2002)
Applicant MERCK & CO., INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (See Box II).

4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. _____



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/16336

A. CLASSIFICATION OF SUBJECT MATTER		
IPC(7) : A61K 31/00, 35/00 US CL : 424/114, 117; 514/183 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) U.S. : 424/114, 117; 514/183		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched IUBMB DATABASE		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Continuation Sheet		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BECKER, D.P. et al. Alpha-amino-beta-sulphone Hydroxamates as Potent MMP-13 Inhibitors that Spare MMP-1. <i>Bioorganic & Medicinal Chemistry Letters</i> . 2001, Volume 11, Pages 2719-2725, especially abstract, Tables 1 and 2.	1-13
Y	WO 98/18754 A1 (VERICOR, INC.) 07 May 1998 (07.05.1998), page 67, Line 1 to Page 84, Line 13.	1-11
Y	US 5,863,949 A (ROBINSON et al.) 26 January 1999(01.26.1999), Column 14, Line 60 to Column 15, Line 39.	1-9
Y,P	CLEMENTS, J.M. et al. Antimicrobial Activities and Characterization of Novel Inhibitors of LpxC. <i>Antimicrobial Agents and Chemotherapy</i> . June 2002, Volume 46, No. 6, Pages 1793-1799, especially abstract, Page 1794, Paragraph 3, Lines 1-6; Page 1795, Column 1, first paragraph under results, Figure 1, Tables 2 and 3; Page 1796, Column 1, 2nd and 3rd full paragraphs under Figure 3.	1-9 and 13-15
☐ Further documents are listed in the continuation of Board of Patent and Trademark Office (BPTO) annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family		
Date of the actual completion of the international search 11 May 2004 (11.05.2004)		Date of mailing of the international search report 10 JUN 2004
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230		Authorized officer Dr. Kailash C. Srivastava Telephone No. (571)-272-0700

INTERNATIONAL SEARCH REPORT

PCT/US03/16336

15

Continuation of B. FIELDS SEARCHED Item 3:

USPT, PGPE, EPAB, JPAB, DWPI, REGISTRY, HCAPLUS, USPATFULL ON STN

MATRIX METALLOPROTEINASES, AMINO-SULFONYL-HYDROXAMATES, SULFONAMIDE HYDROXAMATES,
PENICILLIN, TETRACYCLINE, ANTIBIOTICS, LNF, ANTHRAX, PENICILLIN, IMIPENEM, PRIMAXIN, VANCOMYCIN,
CIPROFLAXICIN, PROBENECID, CLAVULANIC ACID, CEFOXITIN, CILASTATIN, MEROPENEM, NORFLOXACIN

13

(12) SOLICITUD INTERNACIONAL PUBLICADA SEGÚN EL TRATADO DE COOPERACION DE PATENTES (PCT)

(19) Organización Mundial de Propiedad Intelectual
Oficina Internacional

(43) Fecha de Publicación Internacional

11 de diciembre de 2003 (11.12.2003)

PCT

(10) Número de Publicación Internacional

WO 2003/101382 A3

(51) Clasificación Internacional de Patentes⁷: A61K 31/00
35/00(74) Representante Común: MERCK G& CO., INC.; 126 East
Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(21) Número de Solicitud Internacional: PCT/US2003/016336

(22) Fecha de Registro Internacional: 23 de mayo de 2003
(23.05.2003)

(25) Idioma de registro: Inglés

(26) Idioma de Publicación: Inglés

(30) Información de Prioridad:
60/383,996 29 de mayo de 2002 (29.05.2002) US(71) Solicitante (para todos los Estados designados excepto Estados
Unidos): MERCK & CO., INC. [US/US]; 126 East
Lincoln Avenue, Rahway, NJ 07065-0907 (US).(81) Estados Designados (nacional): AE, AG, AL, AM, AT, AU, AZ,
BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE,
DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.(84) Estados Designados (regional): Patente ARIPO (GH, GM, KE, LS,
MW, MZ, SD, SI, SZ, TZ, UG, ZM, ZW), patente Eurasiática
(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM) Patente Europea
(AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR,
HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), Patente
OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

Publicando:

- con reports de búsqueda internacional
- antes de la expiración del límite de tiempo para modificar
las reivindicaciones y ser publicada de nuevo en el caso de
recibo de modificaciones

(72) Inventores; e

(75) Inventores/Solicitantes (para Estados Unidos solamente):
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0907 (US). PATCHETT, Arthur, A. [US/US]; 126 East
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29 de julio de 2004

Para los códigos de dos letras y otras abreviaturas, véase a "Las Notas
Guías sobre Códigos y Abreviaturas" que aparecen al comienzo de cada
edición regular de la Gaceta PCT.

(54) Título: COMPUESTOS PARA EL TRATAMIENTO DEL ÁNTRAX E INHIBIDORES DEL FACTOR LETAL

(57) Resumen: La invención se refiere a compuestos de fórmula I, y un método para el tratamiento del ántrax o inhibición del factor letal mediante la administración de una composición que contiene un compuesto de fórmula I y un transportador farmacéuticamente aceptable. Esta invención además se refiere al uso de los compuestos de fórmula I para tratar otras enfermedades relacionadas con la infección del ántrax.

Si 17

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
11 December 2003 (11.12.2003)

PCT

(10) International Publication Number
WO 2003/101382 A3

(51) International Patent Classification⁷: A61K 31/00, 35/00

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(21) International Application Number:
PCT/US2003/016336

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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(71) Applicant (*for all designated States except US*): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): XIONG, Yusheng [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). CHAPMAN, Kevin [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). SINGH, Suresh [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). GUO, Jian [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). PATCHETT, Arthur, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(88) Date of publication of the international search report:
29 July 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOUNDS USEFUL IN THE TREATMENT OF ANTHRAX AND INHIBITING LETHAL FACTOR

(57) Abstract: This invention relates to compounds of formula (I), and a method for treating anthrax or inhibiting lethal factor by administering a composition containing a compound of formula (I) and a pharmaceutically acceptable carrier. This invention further relates to the use of the compounds of formula (I) to treat other conditions related to an anthrax infection.

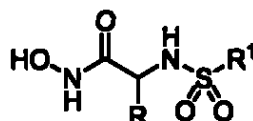
WO 2003/101382 A3

70

**CAPITULO REIVINDICATORIO COMO FUE
ORIGINALMENTE PRESENTADO EN FASE
INTERNACIONAL JUNTO CON SU
TRADUCCION**

REIVINDICACIONES:

1. Un compuesto de fórmula I:



5

FORMULA I

O una sal farmacéuticamente aceptable, enantiómero, diastereómero o éster hidrolizable in vivo o mezcla de ellos, donde,

- 10 R^1 representa C₆-10 aril, C₅-10 heteroaril o C₅-10 heterocíclico, dicho aril, heteroaril y heterocíclico opcionalmente substituido con de 1 a 3 grupos de R^a

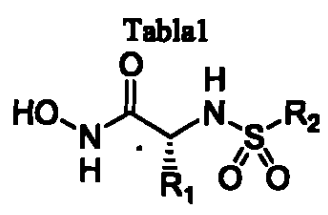
R^a representa C₁-6 alquil, halógeno, OH, aril(C₁-6)alquil, (C₁-6)alcoxi, (C₁-6)alcoxi(C₁-6)alquil, halo(C₁-6)alquil, nitro, amino, mono- o di-N-(C₁-

- 15 6)alquilamino, acilamino, aciloxi, carboxi, carboxi sales, carboxi ésteres, carbamoil, mono- y di-N-(C₁-6)alquilcarbamoil, (C₁-6)alcoxycarbonil, ariloxycarbonil, ureido, guanidino, sulfonilamino, aminosulfonil, (C₁-6)alquiltio, (C₁-6)alquilsulfinil, (C₁-6)alquilsulfonil, heterocíclico, heterocíclico(C₁-6)alquil; y

- 20 R representa C₁-8 alquil, C₃-10 cicloalquil, C₃-10 heterocicloalquil, C₅-10 heteroaril, o C₅-11 heterocíclico, dicho heteroaril y heterocíclico opcionalmente substituido con de 1 a 3 grupos de R^a y dicho alquil, opcionalmente substituido con de 1 a 3 grupos seleccionados del grupo consistente en aril, heterocíclico, (C₁-6)alquiltio, ciano, heteroaril, guanidino, ((1-aminoetil)carbonil)amino, ((aminometil)carbonil)amino, 25 ((2-amino)prop-2-il) carbonil)amino, acetamido, 4-(aminometil)fenil, tio, t-butil sulfonil, (C₂-6)alqueniltio, (C₂-6)alquinitio, amino, mono- o di-(C₁-6)alquilamino, ariltio, heterocíclicoltio, (C₁-6)alcoxi, aril(C₁-6)alcoxi, aril(C₁-6)alquiltio, cicloalquil, cicloalquenil, carboxi y ésteres de ellos, hidroxil y halógenos.

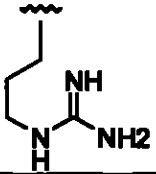
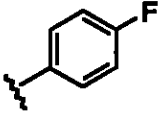
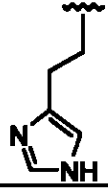
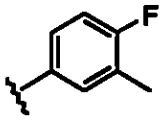
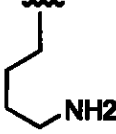
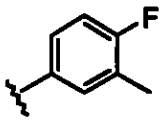
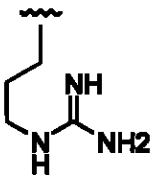
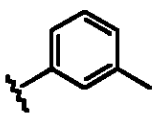
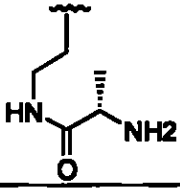
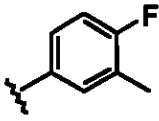
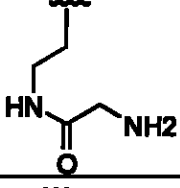
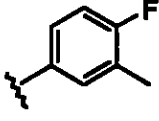
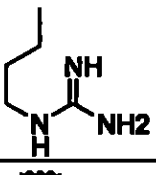
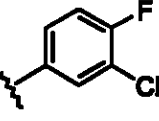
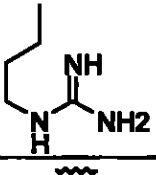
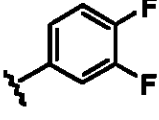
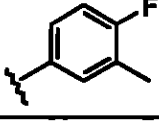
- 30 2. Un compuesto según la reivindicación 1 donde R es un heterocicloalquilo y todas las demás variables como se definieron originalmente.

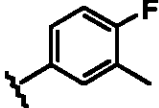
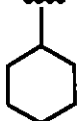
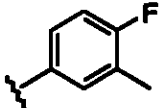
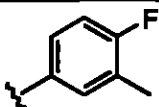
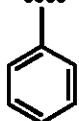
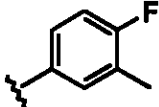
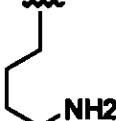
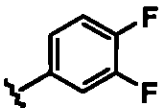
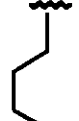
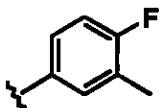
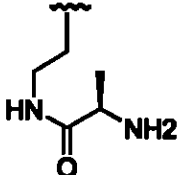
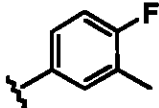
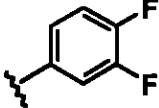
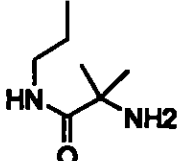
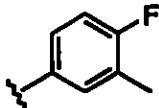
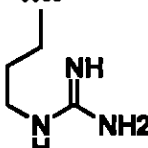
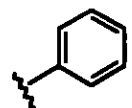
3. Un compuesto según la reivindicación 1 donde R es un heteroaril y todas las demás variables como se definieron originalmente.
4. Un compuesto según la reivindicación 1 donde R¹ es un grupo fenil opcionalmente sustituido con de 1 a 3 grupos de R^a y R es un grupo heterocicloalquil, o heteroaril.
5. Un compuesto según la reivindicación 1 donde R¹ es un grupo fenil opcionalmente sustituido con de 1 a 3 grupos entre metoxi, halógeno, metil, etil, propil, butil, naftil, 5-(2-piridil)tiofen-2-il o una mezcla de ellos, y R un heterocicloalquilo o heteroarilo.
6. Un compuesto según la reivindicación 1 el cual es seleccionado del grupo consistente en:
- 15 N-t-butoxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida;
N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida;
N-t-butoxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-2-(4'-tetrahidropiranyl)-acetamida;
N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-2-(4'-tetrahidropiranyl)-acetamida;
20 N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-(S)-ciclopropilbutiramida; y
de las tablas 1 y 2 siguientes

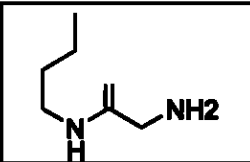
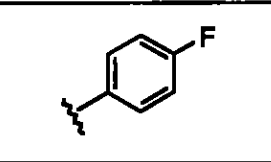
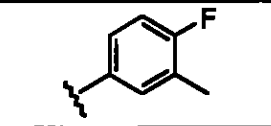
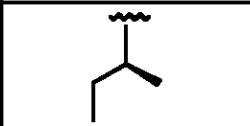
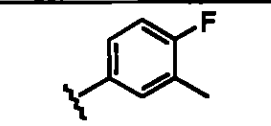
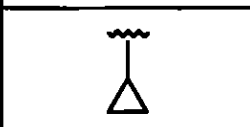
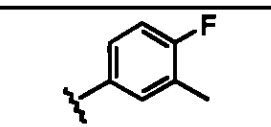
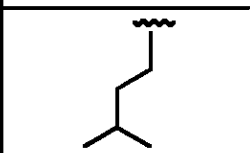
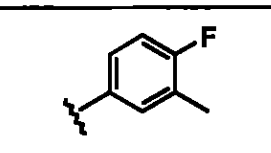
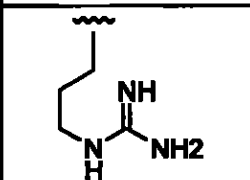
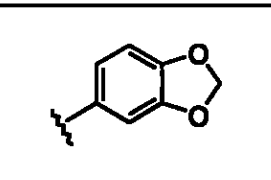
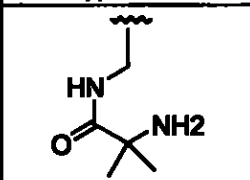
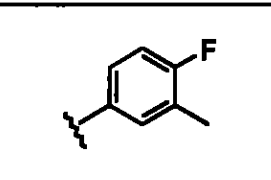
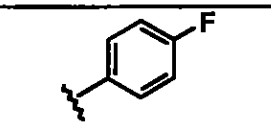
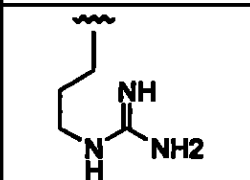
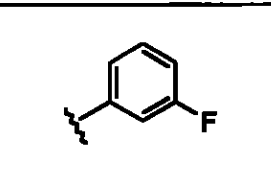
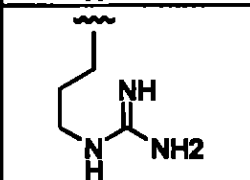
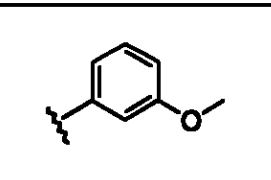
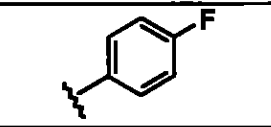


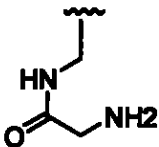
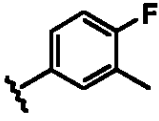
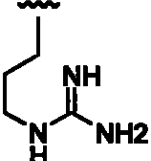
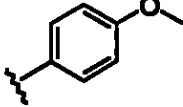
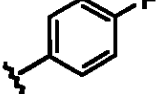
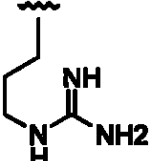
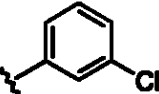
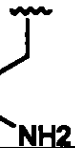
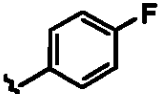
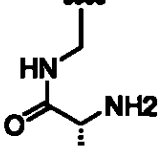
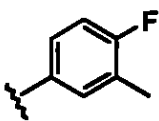
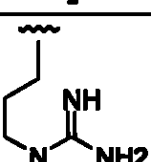
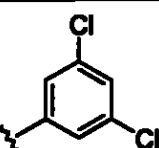
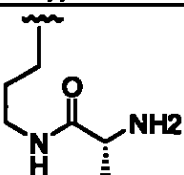
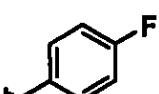
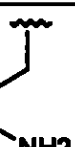
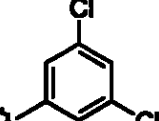
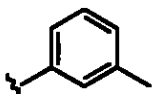
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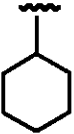
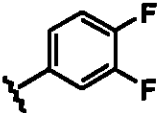
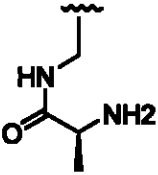
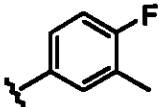
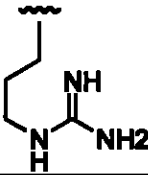
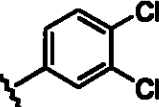
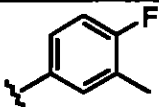
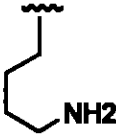
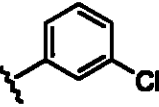
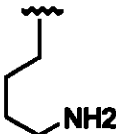
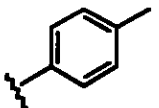
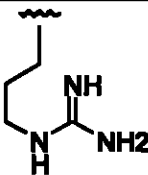
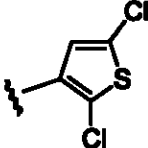
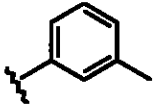
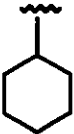
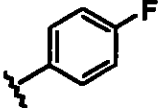
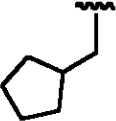
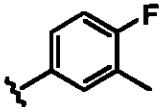
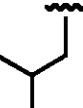
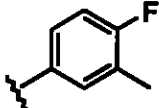
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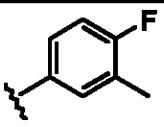
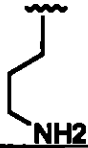
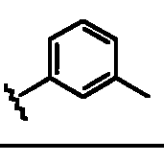
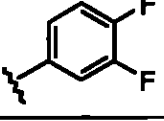
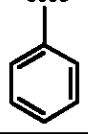
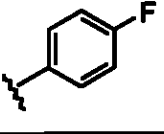
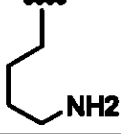
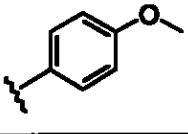
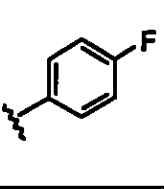
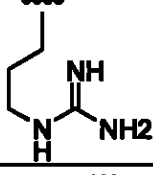
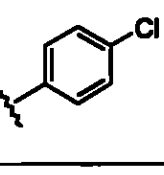
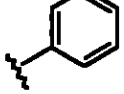
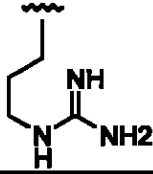
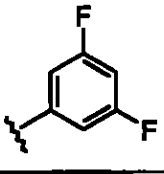
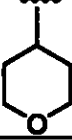
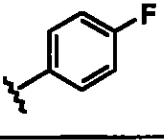
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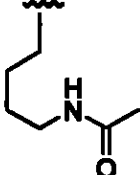
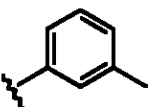
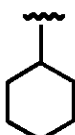
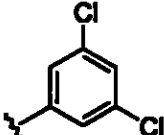
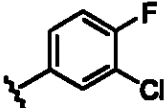
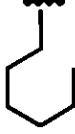
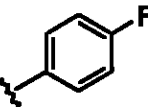
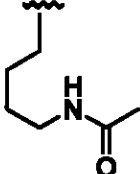
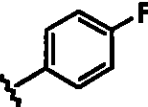
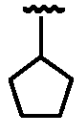
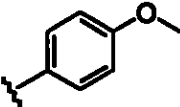
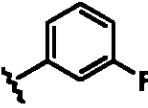
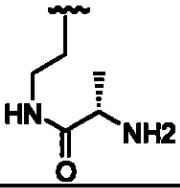
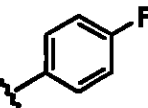
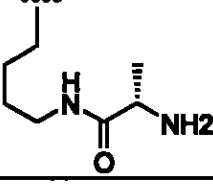
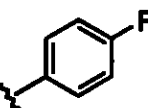
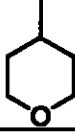
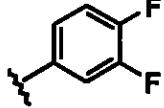
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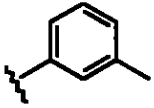
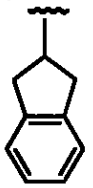
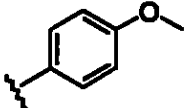
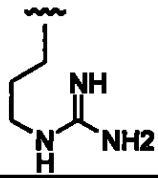
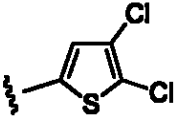
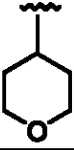
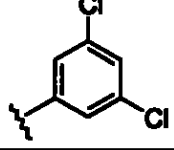
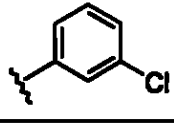
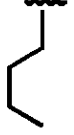
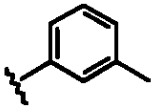
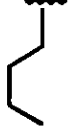
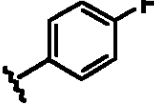
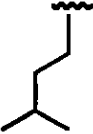
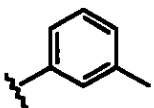
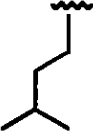
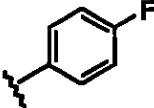
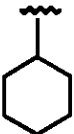
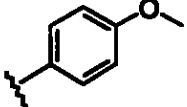
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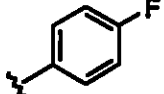
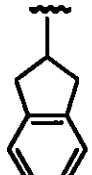
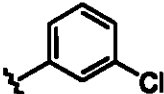
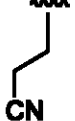
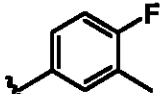
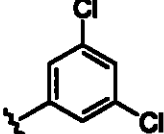
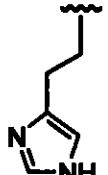
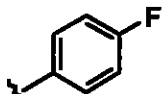
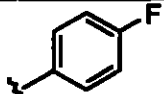
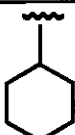
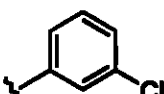
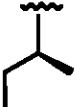
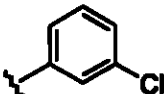
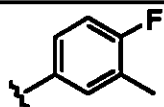
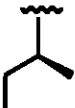
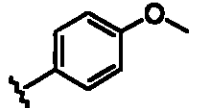
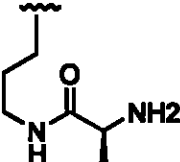
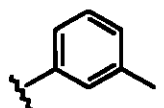
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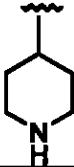
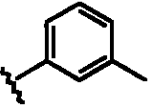
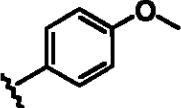
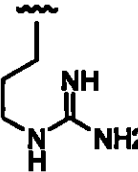
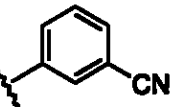
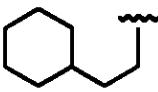
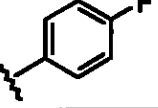
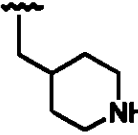
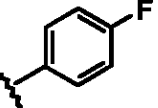
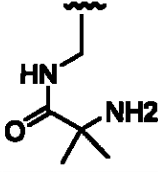
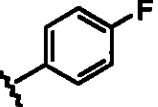
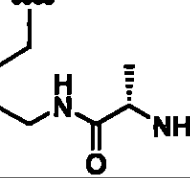
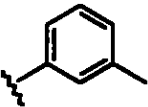
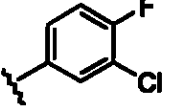
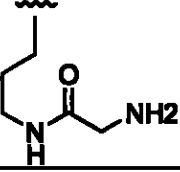
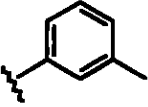
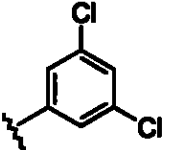
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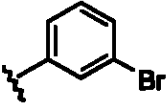
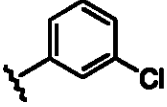
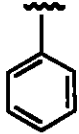
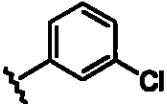
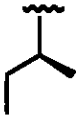
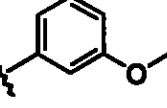
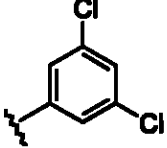
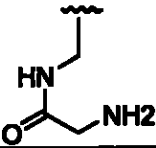
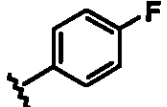
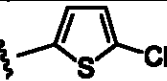
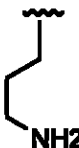
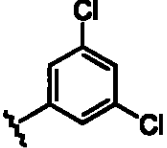
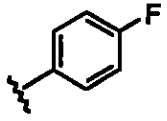
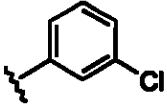
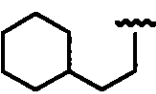
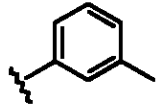
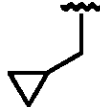
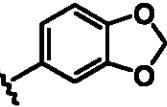
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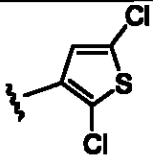
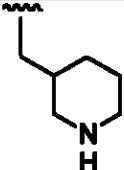
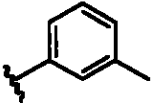
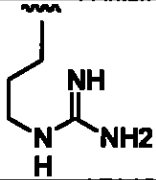
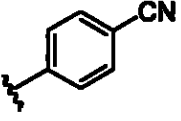
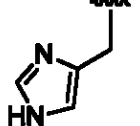
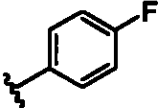
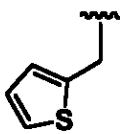
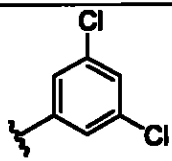
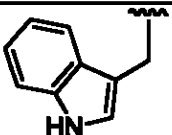
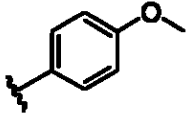
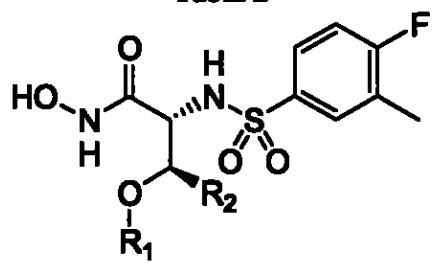
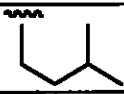
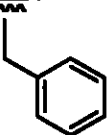
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Tabla 2



Ejemplo #	R1	R2
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147		Me

148		Me
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150		Me
151		Me
152		Me
153		Me

y sales farmacéuticamente aceptables, enantiómeros, diastereómeros o ésteres hidrolizables in vivo o mezclas de ellos.

7.

Un compuesto de acuerdo con la reivindicación 6 el cual se
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selecciona del grupo consistente en:
- N-t-butoxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida;

N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida;

N-t-butoxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-2-(4'-tetrahidropiranyl)-acetamida;
- 10

N-hidroxi-2(R)-[(4-fluoro-3- metilfenilsulfonil)]amino-2-(4'-tetrahidropiranyl)-acetamida;
- N-hidroxi-2(R)-[(4-fluoro-3- metilfenilsulfonil)]amino-3-(S)-ciclopropilbutiramida; y

sales farmacéuticamente aceptables, enantiómeros, diastereómeros o ésteres hidrolizables in vivo o mezclas de ellos.

- 15

8.

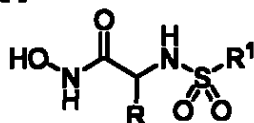
Un compuesto de acuerdo con la reivindicación 7 el cual es:
- N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida; o

N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-2-(4'-tetrahidropiranyl)-acetamida; o sales farmacéuticamente aceptables, enantiómeros, diastereómeros o
- 20

ésteres hidrolizables in vivo o mezclas de ellos.

9. Una composición de acuerdo con la reivindicación 1, que comprende un compuesto de fórmula I y un transportador farmacéuticamente aceptable.

- 5 10. Un método para inhibir la actividad del factor letal (FL) difundido desde bacterias en un mamífero que comprende la administración a un paciente con necesidad de ello de una cantidad terapéuticamente efectiva de un compuesto de fórmula estructural I



10

FORMULA I

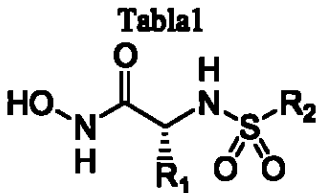
o una sal farmacéuticamente aceptable, enantiómero, diastereómero o éster hidrolizable o mezclas de ellos, donde,

- 15 R^1 representa C_6 -10 aril, C_5 -10 heteroaril o C_5 -10 heterocíclico, dicho arilo, heteroarilo y heterociclilo opcionalmente sustituido con de 1 a 3 grupos de R^a

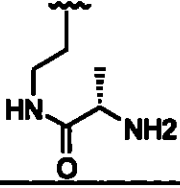
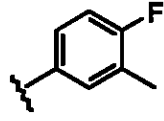
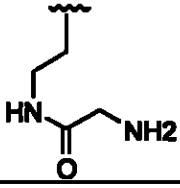
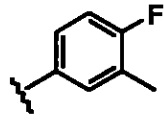
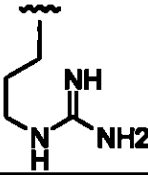
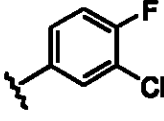
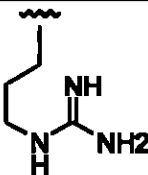
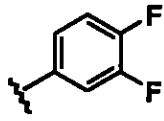
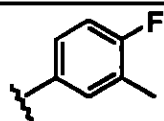
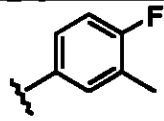
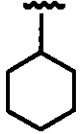
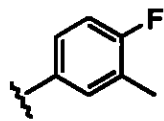
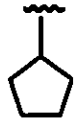
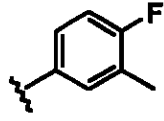
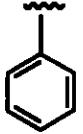
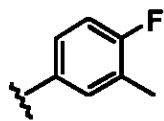
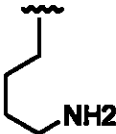
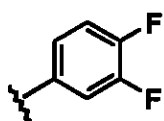
- 20 R^a representa C_1 -6 alquil, halógeno, OH, aril(C_1 -6)alquil, (C_1 -6)alcoxi, (C_1 -6)alcoxi(C_1 -6)alquil, halo(C_1 -6)alquil, nitro, amino, mono- o di-N-(C_1 -6)alquilamino, acilamino, aciloxi, carboxi, carboxi sales, carboxi ésteres, carbamoil, mono- y di-N-(C_1 -6)alquilcarbamoil, (C_1 -6)alcoxycarbonil, ariloxycarbonil, ureido, guanidino, sulfonilamino, aminosulfonil, (C_1 -6)alquiltio, (C_1 -6)alquilsulfinil, (C_1 -6)alquilsulfonil, heterociclil, heterociclil(C_1 -6)alquil; y

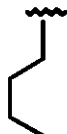
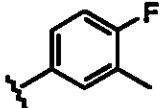
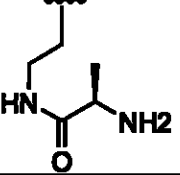
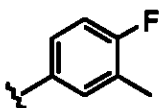
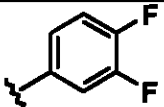
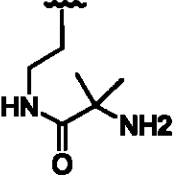
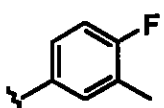
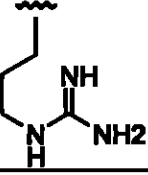
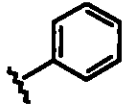
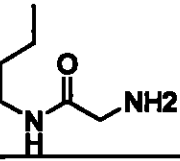
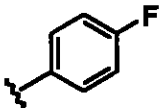
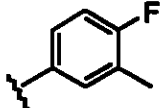
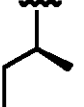
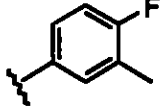
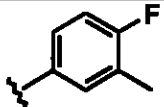
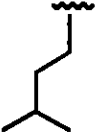
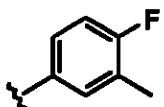
- 25 R representa C_1 -8 alquil, C_3 -10 cicloalquil, C_3 -10 heterocicloalquil, C_5 -10 heteroaril, o C_5 -11 heterociclil, dicho heteroaril y heterociclil opcionalmente sustituido con de 1 a 3 grupos de R^a y dicho alquil, opcionalmente sustituido con de 1 a 3 grupos seleccionados del grupo consistente en aril, heterociclil, (C_1 -6)alquiltio, ciano, heteroaril, guanidino, ((1-aminoetil)carbonil)amino, ((aminometil)carbonil)amino, ((2-amino)prop-2-il) carbonil)amino, acetamido, 4-(aminometil)fenil, tio, t-butil sulfonil, (C_2 -6)alqueniltio, (C_2 -6)alquiniltio, amino, mono- o di-(C_1 -6)alquilamino, ariltio, heterociciltio, (C_1 -6)alcoxi, aril(C_1 -6)alcoxi, aril(C_1 -6)alquiltio, cicloalquil, cicloalquenil, carboxi y ésteres de ellos, hidroxil y halógeno.

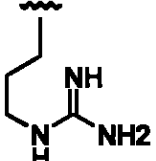
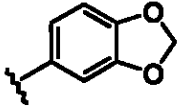
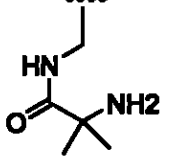
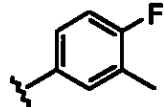
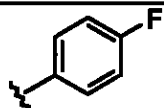
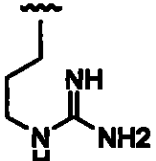
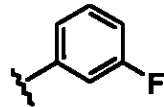
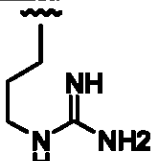
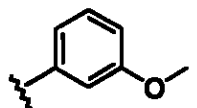
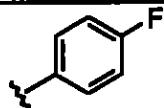
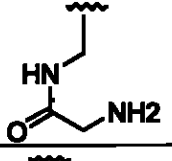
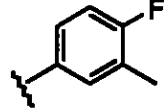
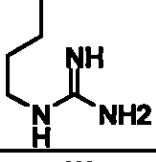
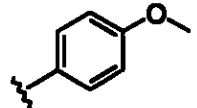
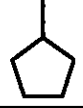
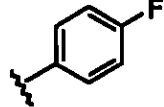
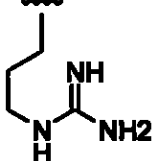
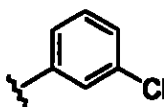
11. Un método de acuerdo con la reivindicación 11 donde el compuesto se selecciona del grupo consistente en:
- N-t-butoxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida;
N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida;
5 N-t-butoxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-2-(4'-tetrahidropiranyl)-acetamida;
N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-2-(4'-tetrahidropiranyl)-acetamida;
N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-(S)-ciclopropilbutiramida; y
10 de las tablas 1 y 2 de abajo



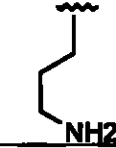
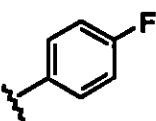
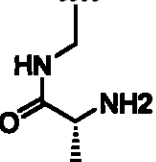
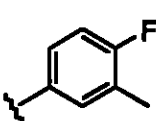
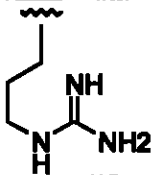
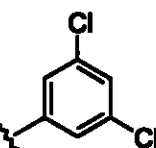
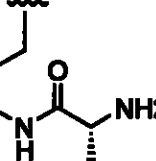
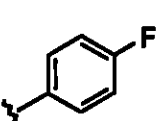
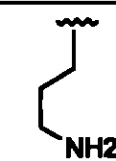
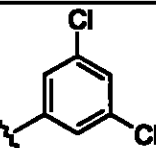
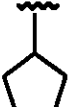
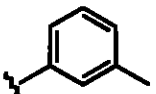
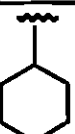
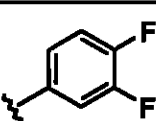
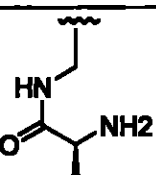
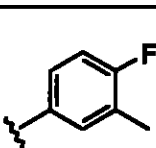
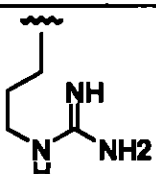
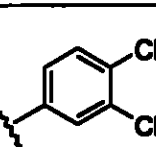
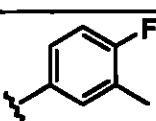
Ejemplo #	R1	R2
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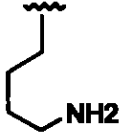
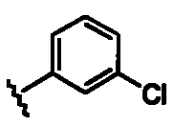
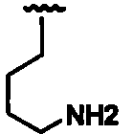
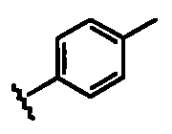
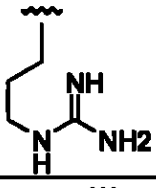
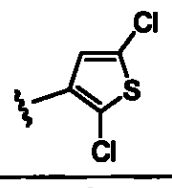
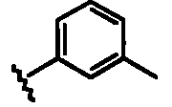
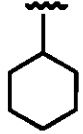
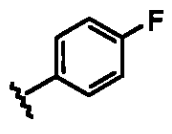
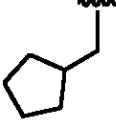
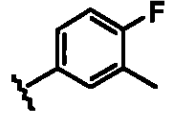
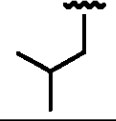
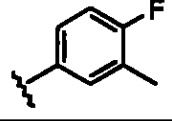
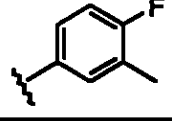
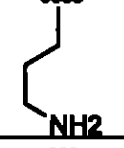
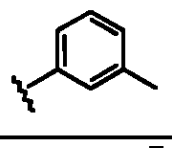
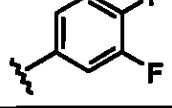
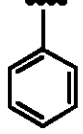
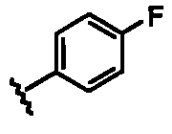
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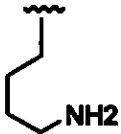
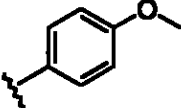
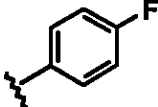
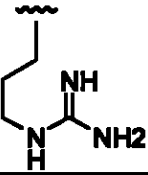
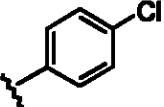
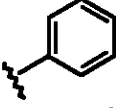
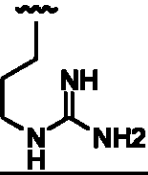
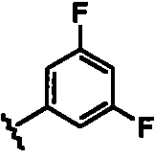
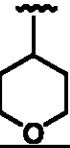
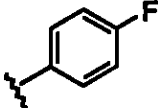
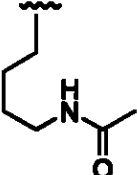
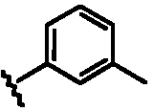
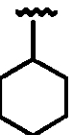
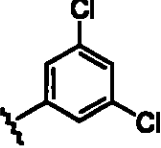
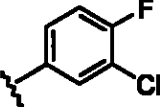
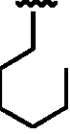
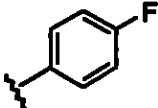
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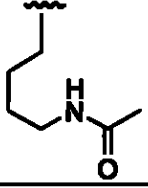
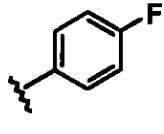
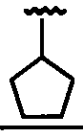
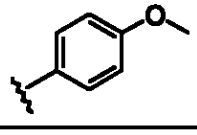
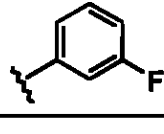
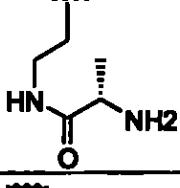
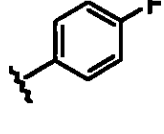
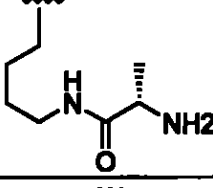
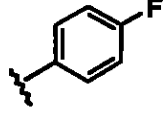
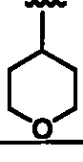
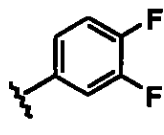
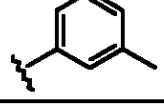
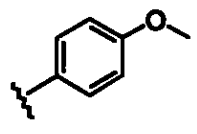
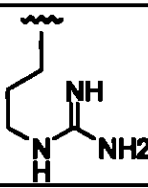
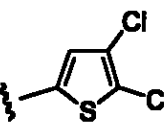
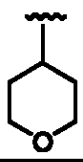
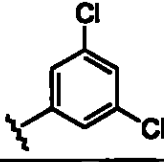
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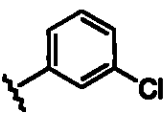
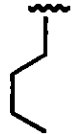
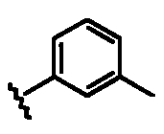
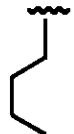
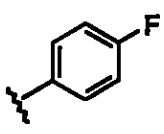
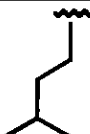
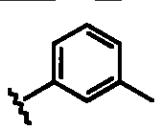
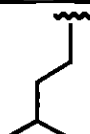
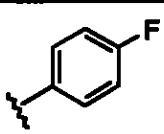
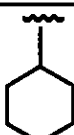
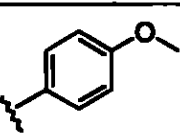
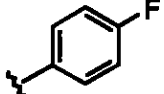
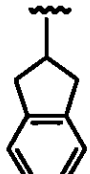
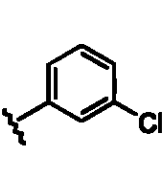
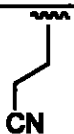
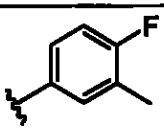
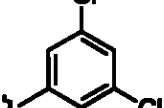
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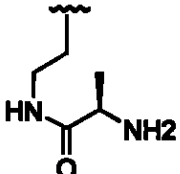
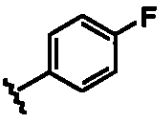
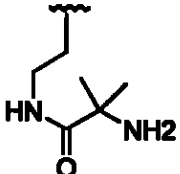
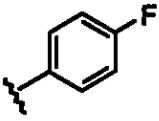
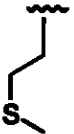
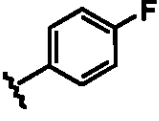
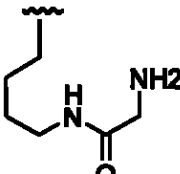
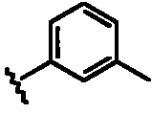
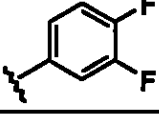
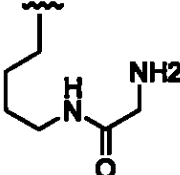
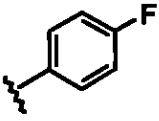
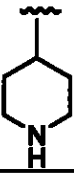
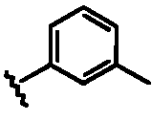
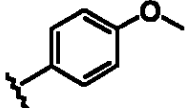
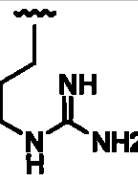
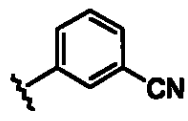
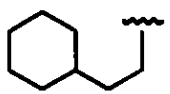
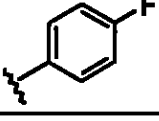
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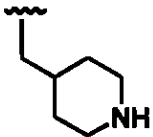
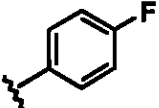
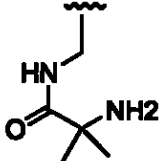
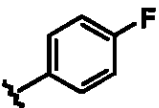
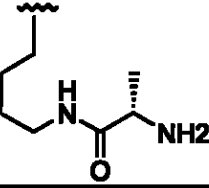
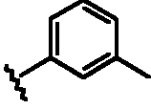
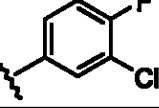
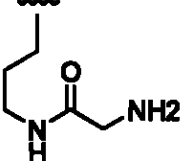
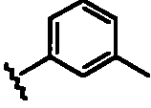
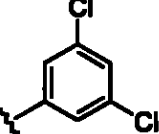
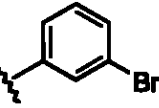
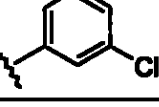
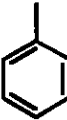
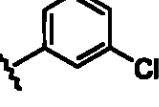
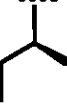
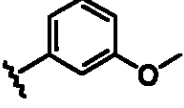
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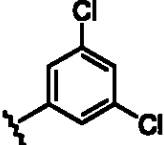
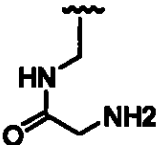
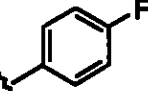
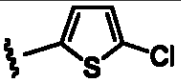
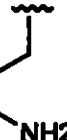
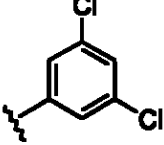
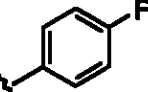
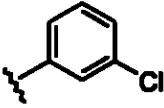
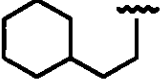
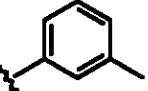
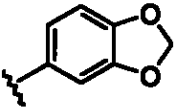
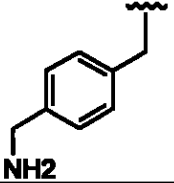
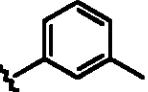
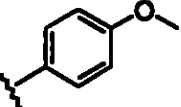
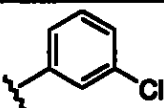
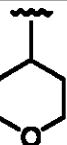
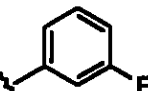
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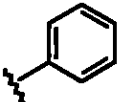
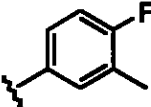
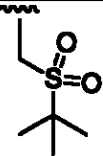
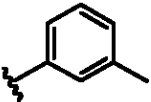
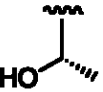
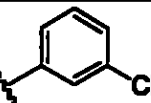
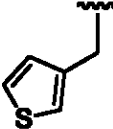
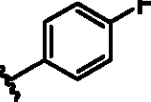
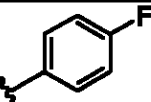
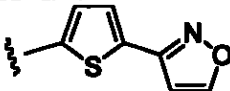
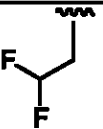
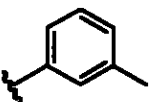
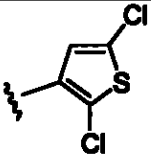
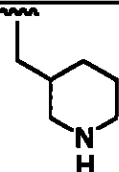
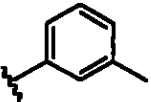
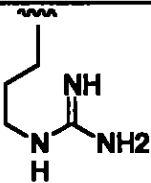
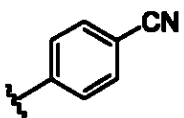
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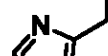
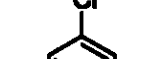
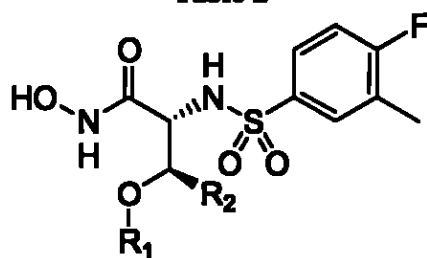
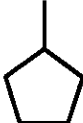
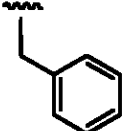
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Table 2



Example #	R1	R2
146		Me
147		Me
148		Me
149		H
150		Me
151		Me
152		Me

153		Me
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y sales farmacéuticamente aceptables, enantiómeros, diastereómeros o ésteres hidrolizables in vivo o mezclas de ellos.

12. Un método de acuerdo con la reivindicación 11 donde el compuesto es:

N-t-butoxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida;

N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida;

N-t-butoxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-2-(4'-tetrahidropiranyl)-acetamida;

10 N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-2-(4'-tetrahidropiranyl)-acetamida;

N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-(S)-ciclopropilbutiramida; y

sales farmacéuticamente aceptables, enantiómeros, diastereómeros o ésteres hidrolizables in vivo o mezclas de ellos.

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13. Un método de acuerdo con la reivindicación 12 donde el componente es:

N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida; o

N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-2-(4'-tetrahidropiranyl)-

20 acetamida; o sales farmacéuticamente aceptable, enantiómeros, diastereómeros o ésteres hidrolizables in vivo o mezclas de ellos.

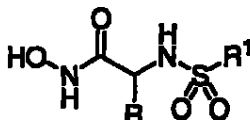
14. Un método según la reivindicación 10 donde el compuesto de fórmula I se combina con uno o más medicamentos conocidos seleccionados entre
25 beta-lactamas, aminoglicosidos, inhibidores de la beta-lactamasa, agentes bloqueantes renales tubulares e inhibidores de enzimas metabólicas, aminoácidos N-acilados.

15. Un método de acuerdo con la reivindicación 14 donde los medicamentos conocidos se seleccionan del grupo que consiste en imipenem,
30 meropenem, vancomicina, cilastatina, cefoxitina, penicilina, ácido clavulánico, probenecida, tetraciclina, ciprofloxacina, y norfloxacina o mezclas de ellos, donde

cuando el imipenem se utiliza como un medicamento se utiliza en combinación con una cilastatina como PRIMAXIN®.

WHAT IS CLAIMED IS:

1. A compound of formula I:



FORMULA I

or a pharmaceutically acceptable salt, enantiomer, diastereomer or in vivo hydrolysable ester or mixture thereof, wherein,

- 10 R^1 represents C₆-10 aryl, C₅-10 heteroaryl or C₅-10 heterocyclic, said aryl, heteroaryl and heterocyclyl optionally substituted with 1 to 3 groups of R^a

- 15 R^a represents C₁-6 alkyl, halogen, OH; aryl(C₁-6)alkyl, (C₁-6)alkoxy, (C₁-6)alkoxy(C₁-6)alkyl, halo(C₁-6)alkyl, nitro, amino, mono- or di-N-(C₁-6)alkylamino, acylamino, acyloxy, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- and di-N-(C₁-6)alkylcarbamoyl, (C₁-6)alkoxycarbonyl, aryloxy carbonyl, ureido, guanidino, sulphonylamino, aminosulphonyl, (C₁-6)alkylthio, (C₁-6)alkylsulphanyl, (C₁-6)alkylsulphonyl, heterocyclyl, heterocyclyl(C₁-6)alkyl; and

- 20 R represents C₁-8 alkyl, C₃-10 cycloalkyl, C₃-10 heterocycloalkyl, C₅-10 heteroaryl, or C₅-11 heterocyclyl, said heteroaryl and heterocyclyl optionally substituted with 1 to 3 groups of R^a and said alkyl, optionally substituted with 1-3 groups selected from the group consisting of aryl, heterocyclyl, (C₁-6)alkylthio, cyano, heteroaryl, guanidino, ((1-aminoethyl)carbonyl)amino, ((aminomethyl)carbonyl)amino, ((2-amino)prop-2-yl)carbonyl)amino, acetamido, 4-(aminomethyl)phenyl, thio, t-butyl sulfonyl, (C₂-6)alkenylthio, (C₂-6)alkynylthio, amino, mono- or di-(C₁-6)alkylamino, arylthio, heterocyclylthio, (C₁-6)alkoxy, aryl(C₁-6)alkoxy, aryl(C₁-6)alkylthio, cycloalkyl, cycloalkenyl, carboxy and esters thereof, hydroxy and halogen.

- 30 2. A compound according to claim 1 wherein R is a heterocycloalkyl and all other variables are as originally described.

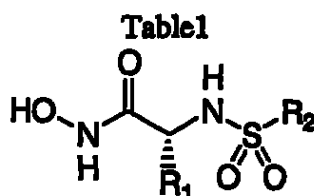
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3. A compound according to claim 1 wherein R is a heteroaryl and all other variables are as originally described.

4. A compound according to claim 1 wherein R¹ is a phenyl group optionally substituted with 1-3 groups of R^a and R is a heterocycloalkyl, or heteroaryl group.

5. A compound according to claim 1 wherein R¹ is a phenyl group substituted with 1 to 3 groups of methoxy, halogen, methyl, ethyl, propyl, butyl, naphthyl, 5-(2-pyridyl)thiophen-2-yl or a mixture thereof, and R a heterocycloalkyl or heteroaryl.

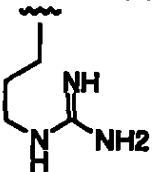
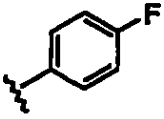
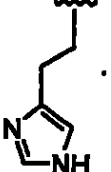
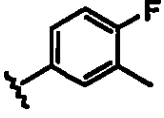
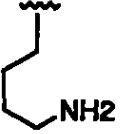
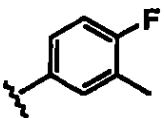
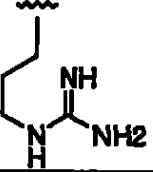
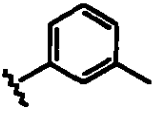
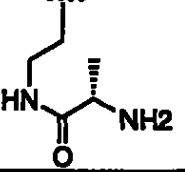
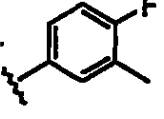
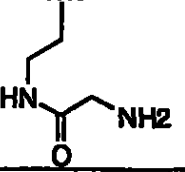
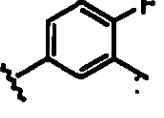
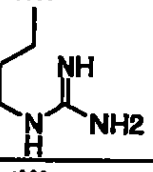
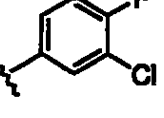
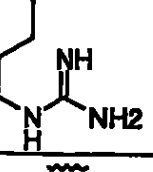
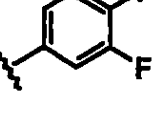
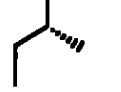
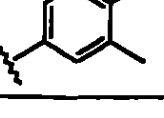
6. A compound according to claim 1 which is selected from the group consisting of:
 N-t-butoxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-3-methylbutyramide;
 N-hydroxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-3-methylbutyramide;
 N-t-butoxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-2-(4'-tetrahydropyranyl)-acetamide;
 N-hydroxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-2-(4'-tetrahydropyranyl)-acetamide;
 N-hydroxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-3-(S)-cyclopropylbutyramide; and from tables 1 and 2 below

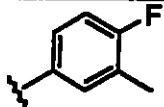
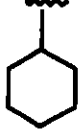
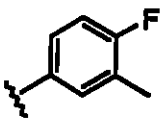
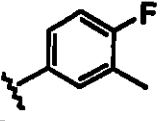
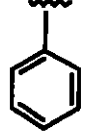
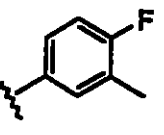
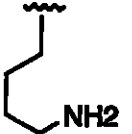
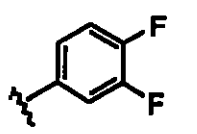
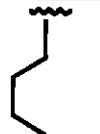
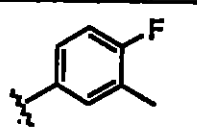
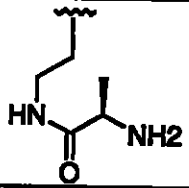
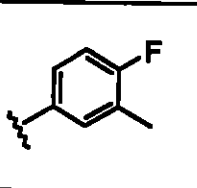
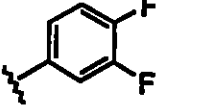
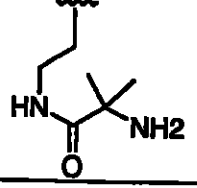
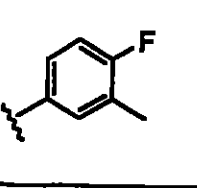
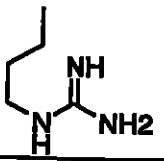
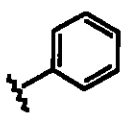


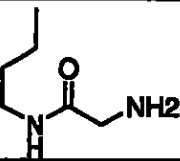
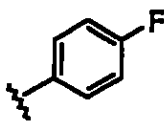
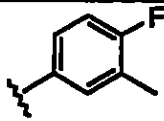
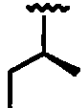
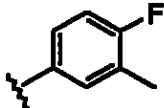
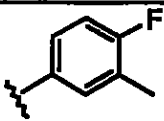
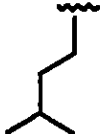
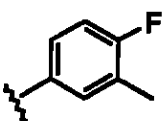
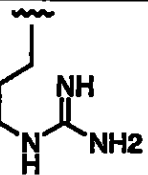
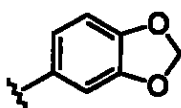
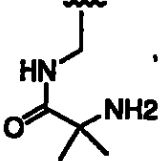
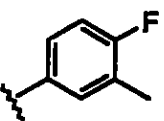
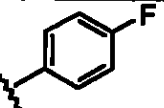
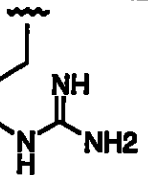
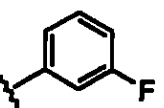
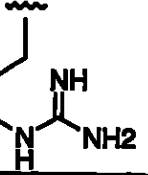
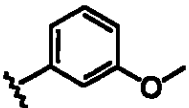
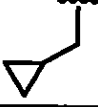
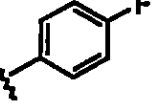
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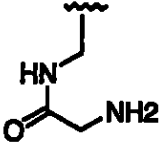
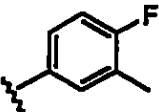
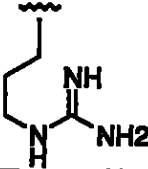
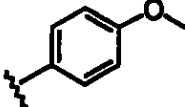
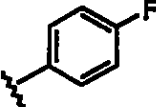
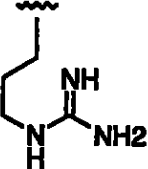
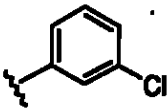
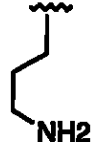
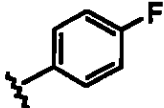
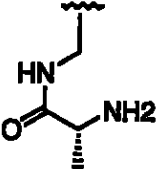
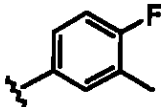
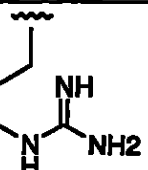
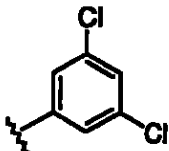
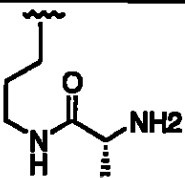
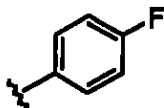
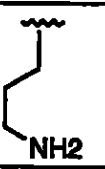
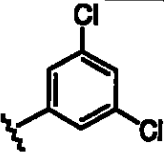
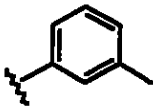
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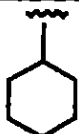
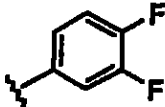
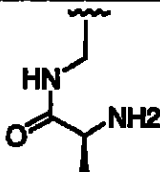
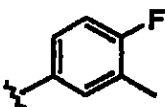
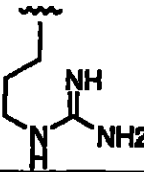
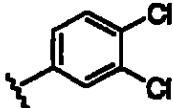
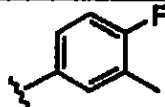
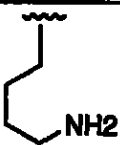
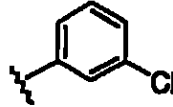
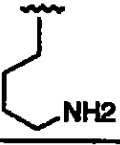
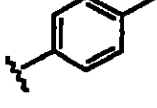
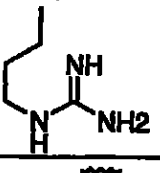
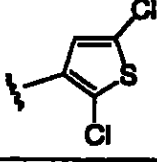
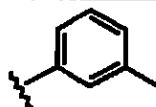
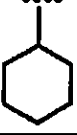
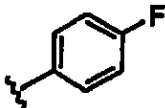
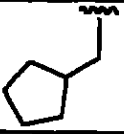
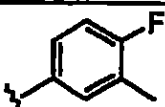
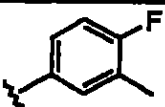
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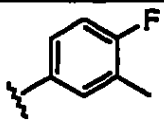
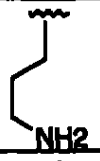
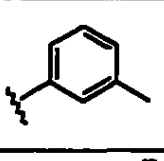
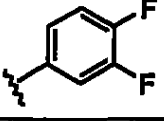
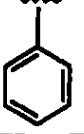
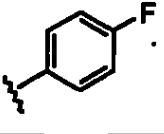
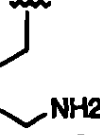
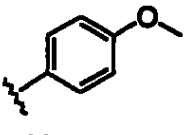
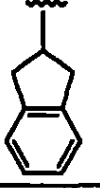
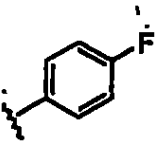
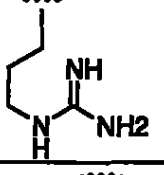
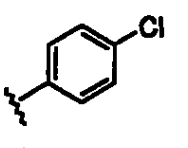
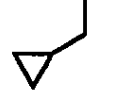
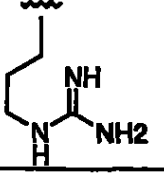
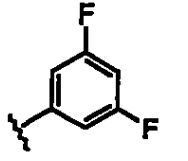
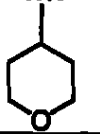
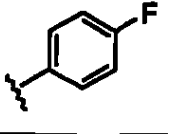
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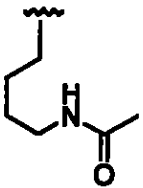
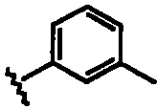
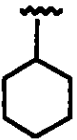
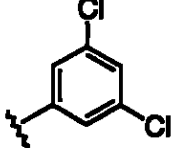
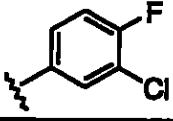
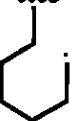
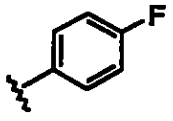
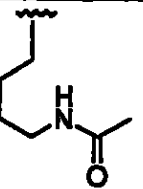
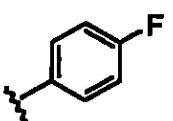
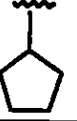
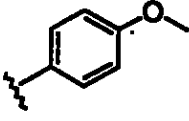
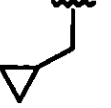
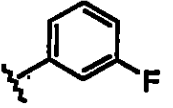
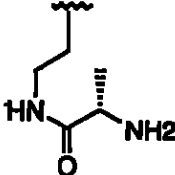
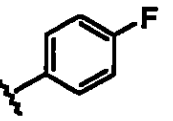
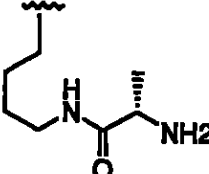
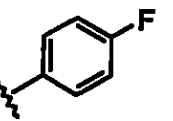
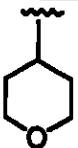
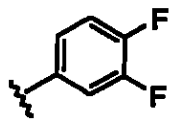
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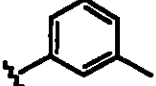
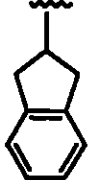
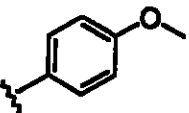
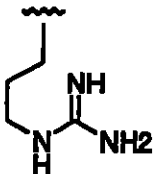
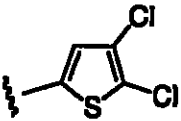
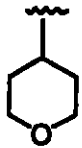
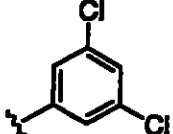
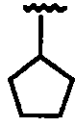
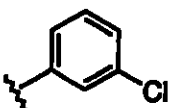
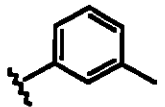
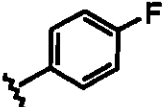
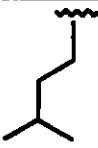
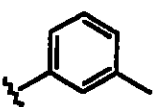
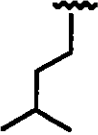
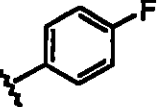
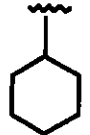
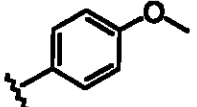
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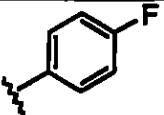
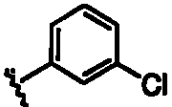
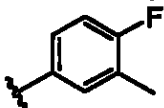
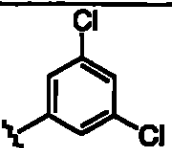
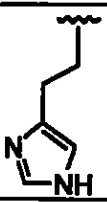
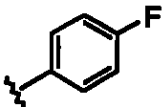
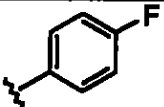
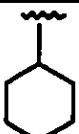
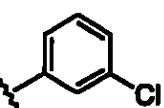
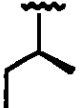
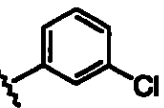
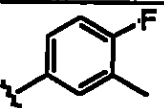
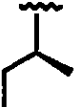
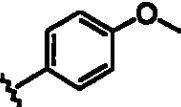
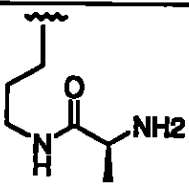
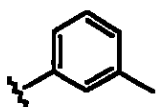
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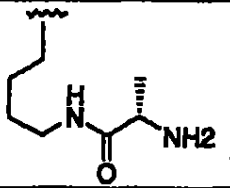
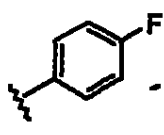
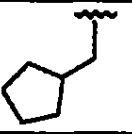
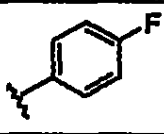
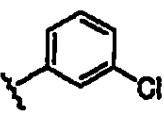
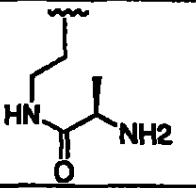
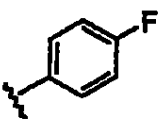
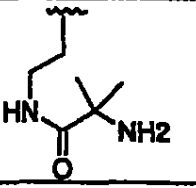
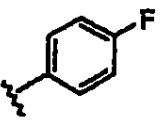
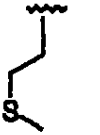
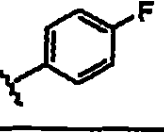
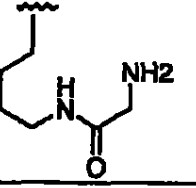
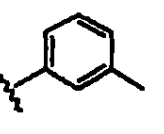
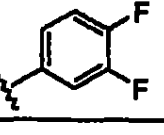
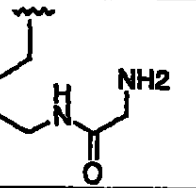
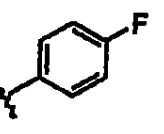
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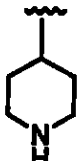
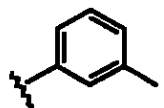
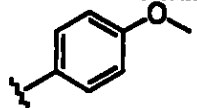
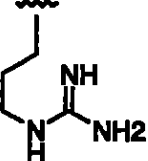
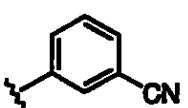
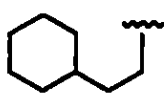
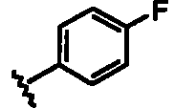
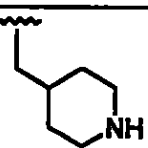
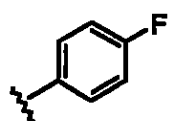
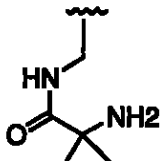
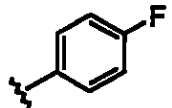
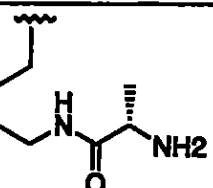
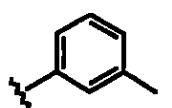
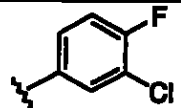
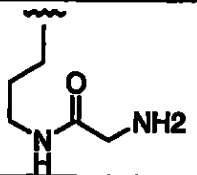
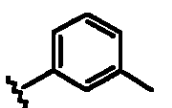
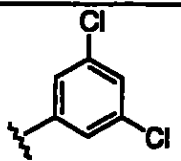
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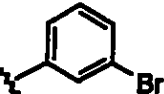
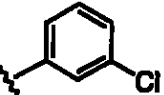
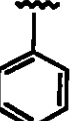
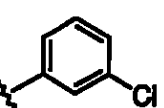
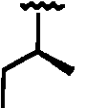
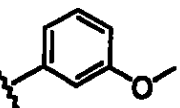
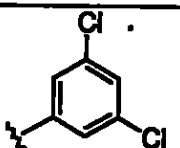
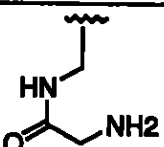
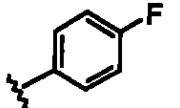
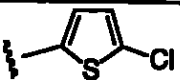
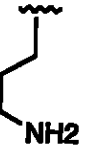
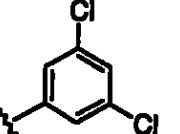
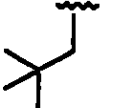
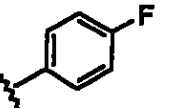
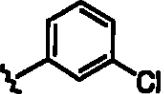
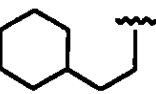
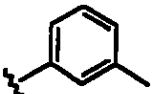
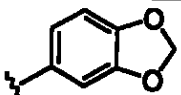
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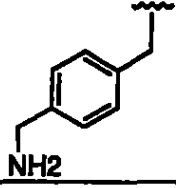
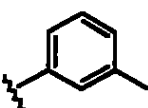
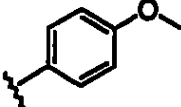
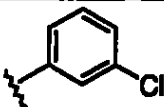
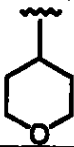
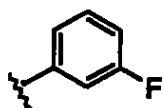
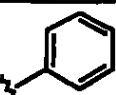
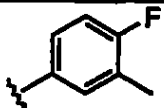
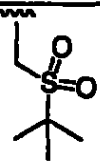
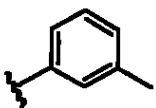
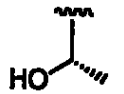
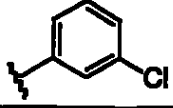
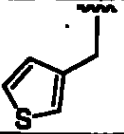
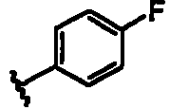
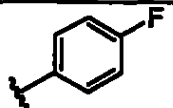
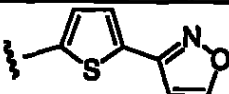
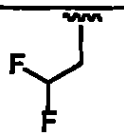
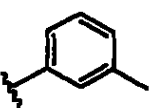
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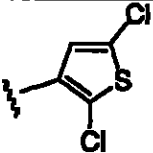
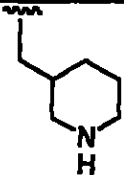
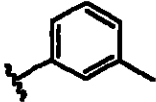
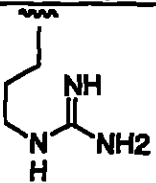
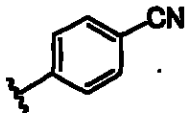
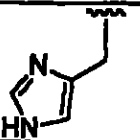
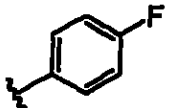
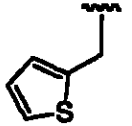
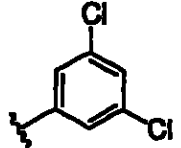
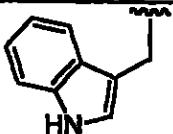
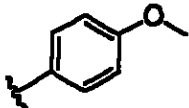
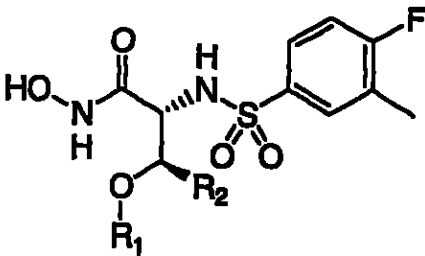
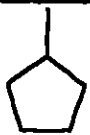
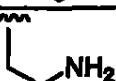
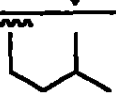
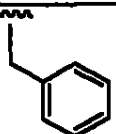
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Table 2



Example #	R1	R2
146		Me
147		Me

148		Me
149		H
150		Me
151		Me
152		Me
153		Me

and pharmaceutically acceptable salts, enantiomers, diastereomers or in vivo hydrolysable esters or mixtures thereof.

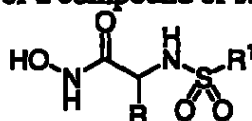
7. A compound according to claim 6 which is selected from the group consisting of:
- 5 N-t-butoxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-3-methylbutyramide;
 N-hydroxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-3-methylbutyramide;
 N-t-butoxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-2-(4'-tetrahydropyranyl)-acetamide;
- 10 N-hydroxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-2-(4'-tetrahydropyranyl)-acetamide;
 N-hydroxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-3-(S)-cyclopropylbutyramide; and pharmaceutically acceptable salts, enantiomers, diastereomers or in vivo hydrolysable esters or mixtures thereof.

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8. A compound according to claim 7 which is:
- N-hydroxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-3-methylbutyramide; or
 N-hydroxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-2-(4'-tetrahydropyranyl)-acetamide; or pharmaceutically acceptable salts, enantiomers, diastereomers or in vivo
- 20 hydrolysable esters or mixtures thereof.

9. A composition according to claim 1, comprising a compound of formula I and a pharmaceutically acceptable carrier.

10. A method of inhibiting the activity of lethal factor (LF) released from bacteria in a mammal comprising administration to a patient in need thereof a therapeutically effective amount of a compound of structural formula I



FORMULA I

or a pharmaceutically acceptable salt, enantiomer, diastereomer or in vivo hydrolysable ester or mixture thereof, wherein,

R^1 represents C₆-10 aryl, C₅-10 heteroaryl or C₅-10 heterocyclic, said aryl, heteroaryl and heterocyclyl optionally substituted with 1 to 3 groups of R^a

R^a represents C₁-6 alkyl, halogen, OH, aryl(C₁-6)alkyl, (C₁-6)alkoxy, (C₁-6)alkoxy(C₁-6)alkyl, halo(C₁-6)alkyl, nitro, amino, mono- or di-N-(C₁-6)alkylamino, acylamino, acyloxy, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- and di-N-(C₁-6)alkylcarbamoyl, (C₁-6)alkoxycarbonyl, aryloxycarbonyl, ureido, guanidino, sulphonylamino, aminosulphonyl, (C₁-6)alkylthio, (C₁-6)alkylsulphinyl, (C₁-6)alkylsulphonyl, heterocyclyl, heterocyclyl(C₁-6)alkyl; and

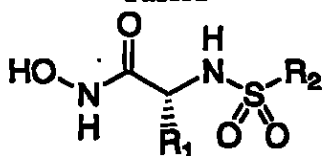
R represents C₁-8 alkyl, C₃-10 cycloalkyl, C₃-10 heterocycloalkyl, C₅-10 heteroaryl, or C₅-11 heterocyclyl, said heteroaryl and heterocyclyl optionally substituted with 1 to 3 groups of R^a and said alkyl, optionally substituted with 1-3 groups selected from the group consisting of aryl, heterocyclyl, (C₁-6)alkylthio, cyano, heteroaryl, guanidino, ((1-aminoethyl)carbonyl)amino, ((aminomethyl)carbonyl)amino, ((2-amino)prop-2-yl)carbonyl)amino, acetamido, 4-(aminomethyl)phenyl, thio, t-butyl sulfonyl, (C₂-6)alkenylthio, (C₂-6)alkynylthio, amino, mono- or di-(C₁-6)alkylamino, arylthio, heterocyclylthio, (C₁-6)alkoxy, aryl(C₁-6)alkoxy, aryl(C₁-6)alkylthio, cycloalkyl, cycloalkenyl, carboxy and esters thereof, hydroxy and halogen.

11. A method according to claim 11 wherein the compound is selected from the group consisting of:

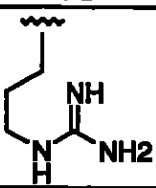
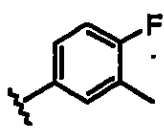
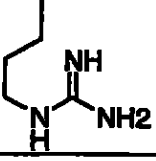
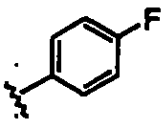
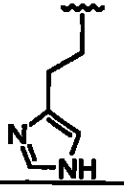
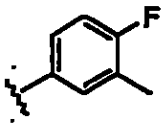
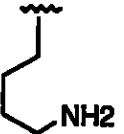
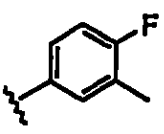
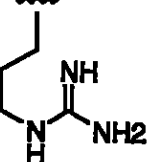
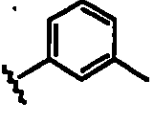
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N-t-butoxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-3-methylbutyramide;
 N-hydroxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-3-methylbutyramide;
 N-t-butoxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-2-(4'-tetrahydropyranyl)-
 acetamide;
 5 N-hydroxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-2-(4'-tetrahydropyranyl)-
 acetamide;
 N-hydroxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-3-(S)-
 cyclopropylbutyramide; and from tables 1 and 2 below

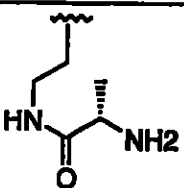
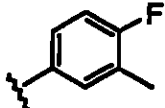
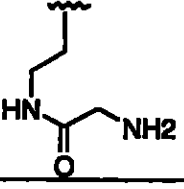
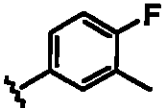
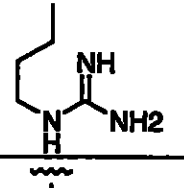
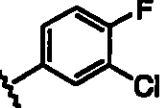
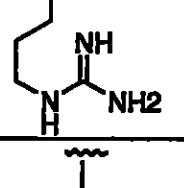
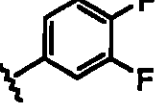
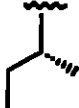
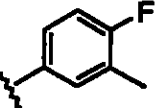
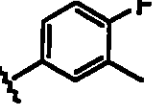
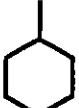
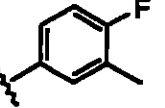
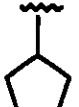
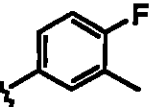
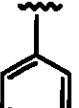
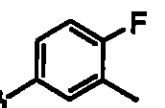
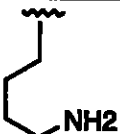
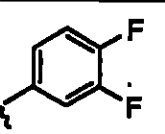
Table1

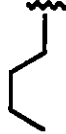
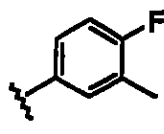
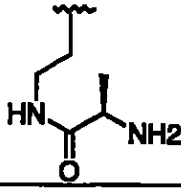
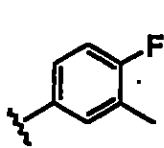
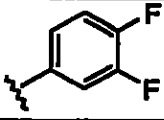
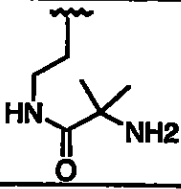
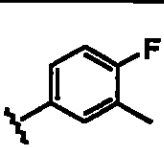
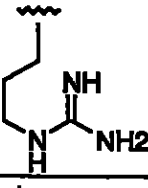
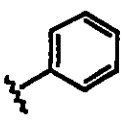
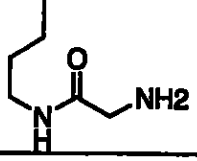
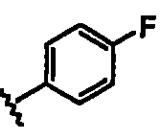
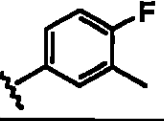
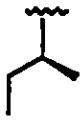
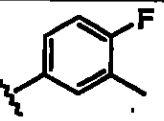
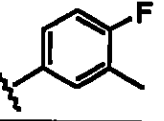
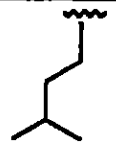
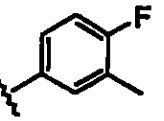


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Example #	R1	R2
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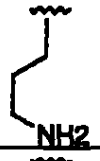
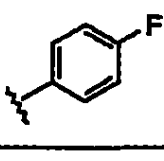
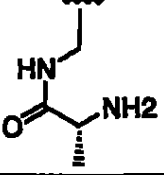
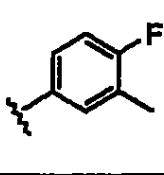
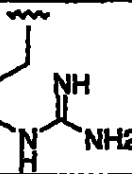
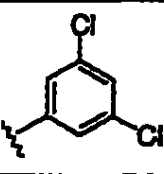
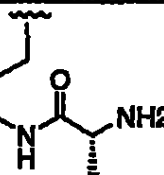
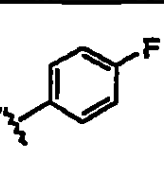
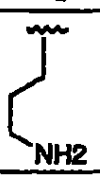
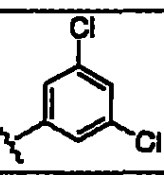
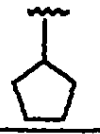
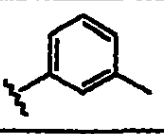
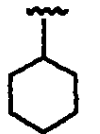
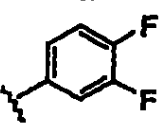
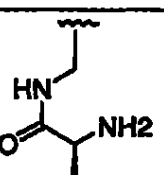
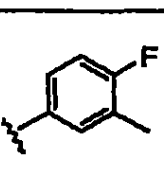
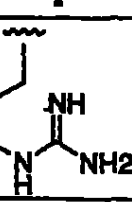
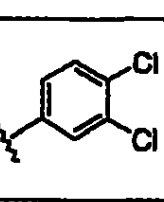
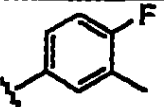
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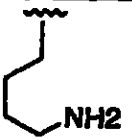
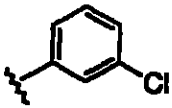
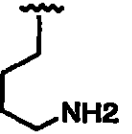
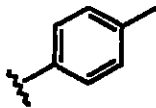
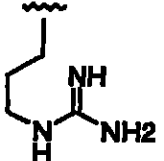
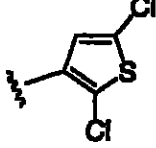
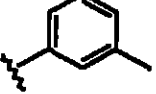
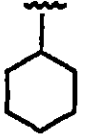
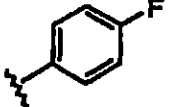
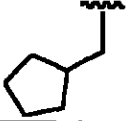
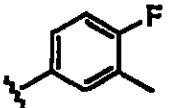
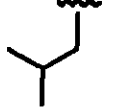
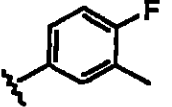
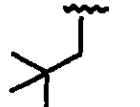
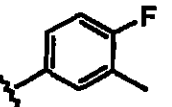
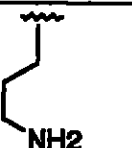
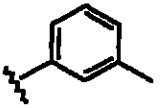
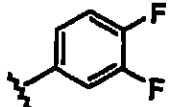
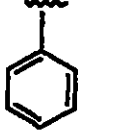
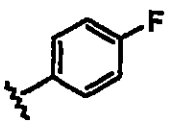
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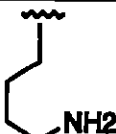
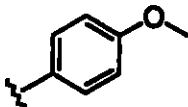
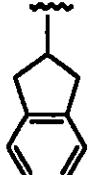
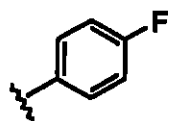
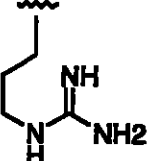
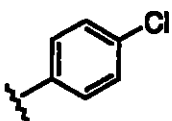
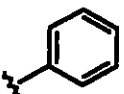
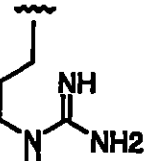
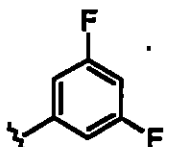
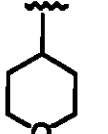
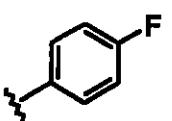
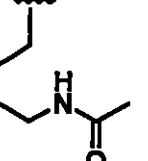
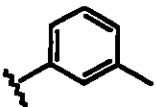
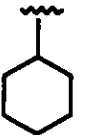
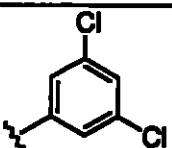
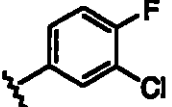
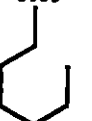
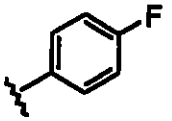
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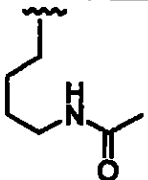
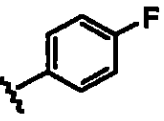
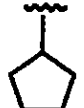
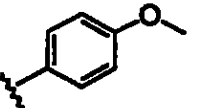
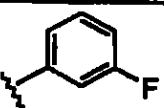
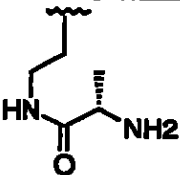
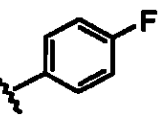
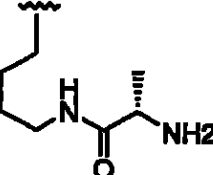
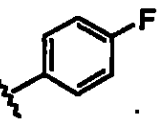
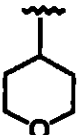
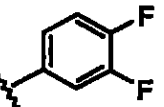
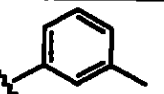
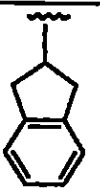
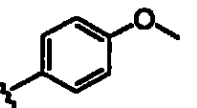
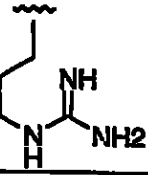
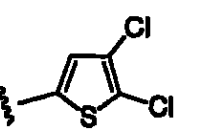
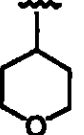
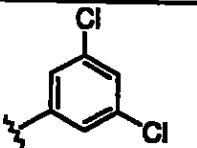
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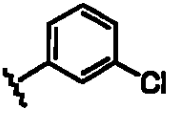
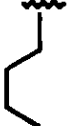
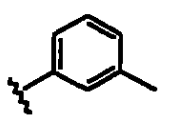
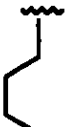
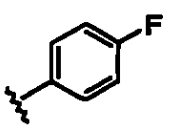
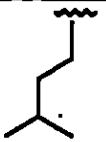
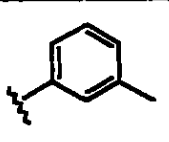
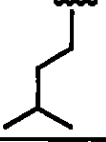
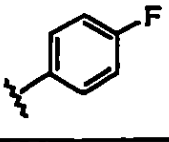
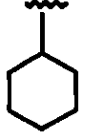
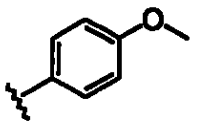
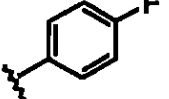
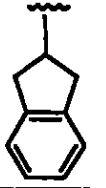
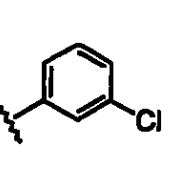
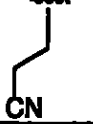
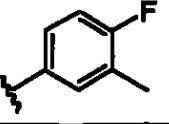
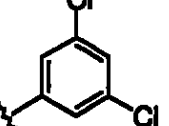
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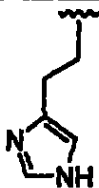
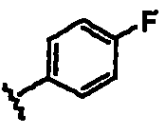
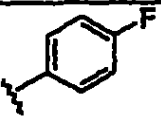
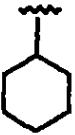
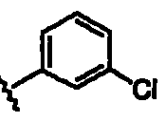
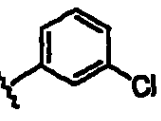
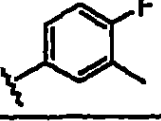
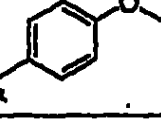
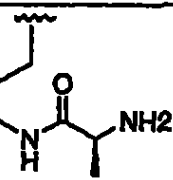
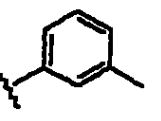
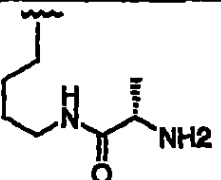
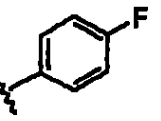
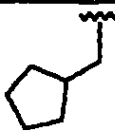
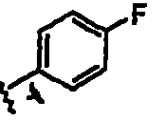
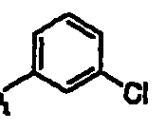
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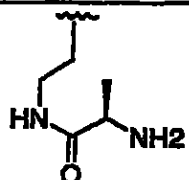
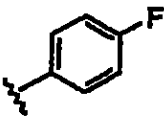
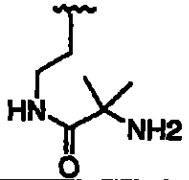
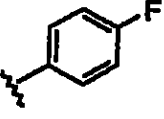
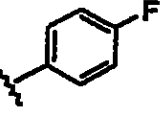
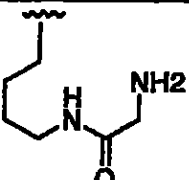
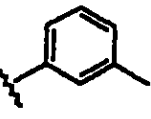
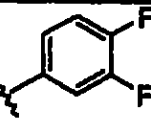
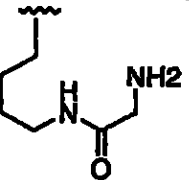
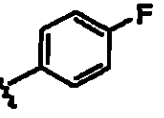
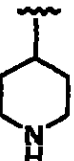
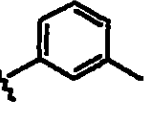
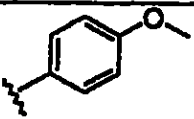
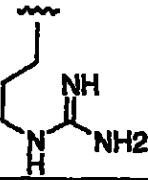
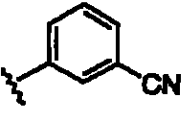
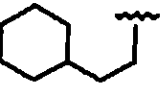
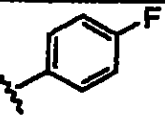
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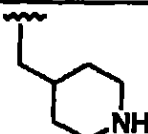
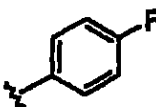
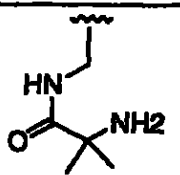
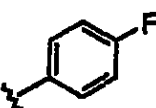
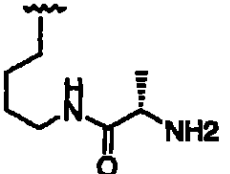
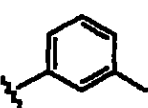
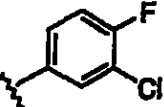
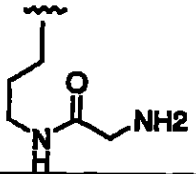
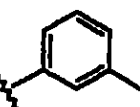
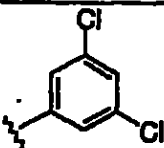
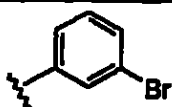
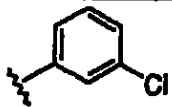
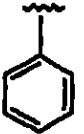
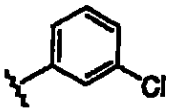
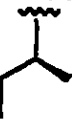
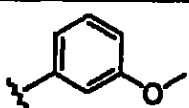
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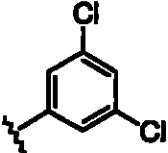
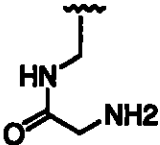
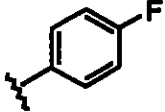
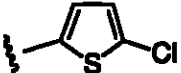
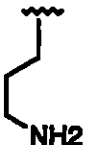
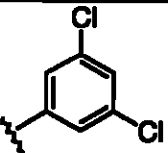
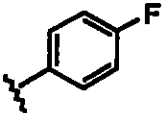
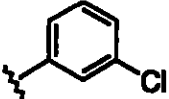
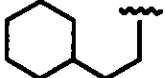
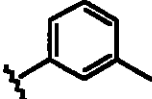
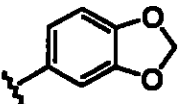
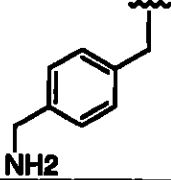
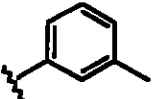
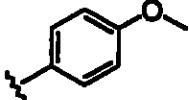
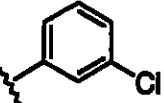
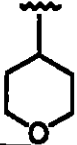
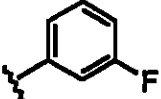
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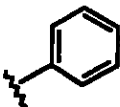
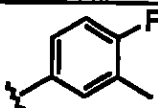
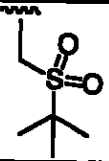
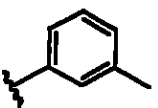
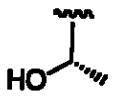
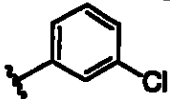
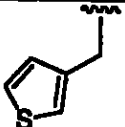
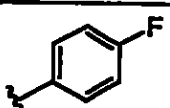
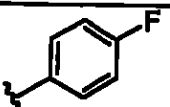
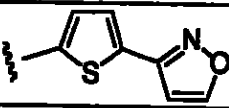
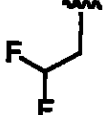
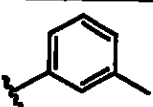
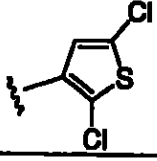
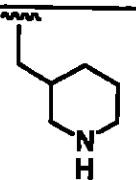
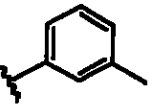
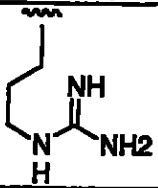
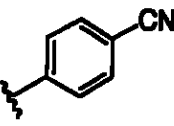
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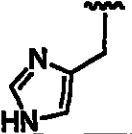
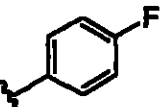
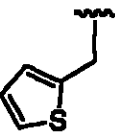
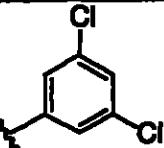
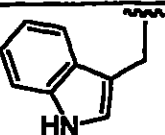
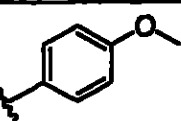
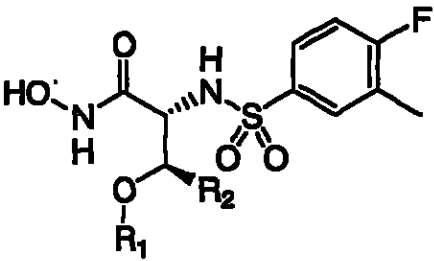
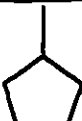
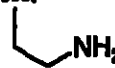
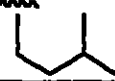
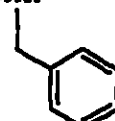
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Table 2



Example #	R1	R2
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147		Me
148		Me
149		H
150		Me
151		Me
152		Me

153		Me
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and pharmaceutically acceptable salts, enantiomers, diastereomers or in vivo hydrolysable esters or mixtures thereof.

12. A method according to claim 11 wherein the compound is:

- 5 N-t-butoxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-3-methylbutyramide;
 N-hydroxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-3-methylbutyramide;
 N-t-butoxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-2-(4'-tetrahydropyranyl)-
 acetamide;
 N-hydroxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-2-(4'-tetrahydropyranyl)-
 10 acetamide;
 N-hydroxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-3-(S)-
 cyclopropylbutyramide; and pharmaceutically acceptable salts, enantiomers,
 diastereomers or in vivo hydrolysable esters or mixtures thereof.

13. A method according to claim 12 wherein the compound is:

N-hydroxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-3-methylbutyramide; or
 N-hydroxy-2(R)-[(4-fluoro-3-methylphenylsulfonyl)]amino-2-(4'-tetrahydropyranyl)-
 acetamide; or pharmaceutically acceptable salts, enantiomers, diastereomers or in vivo
 hydrolysable esters or mixtures thereof.

14. A method according to claim 10 wherein the compound of
 formula I is combined with one or more known drugs selected from beta-lactams,
 aminoglycosides, inhibitors of beta-lactamase, renal tubular blocking agents and
 inhibitors of metabolising enzymes, N-acylated amino acids.

15. A method according to claim 14 wherein the known drugs are
 selected from the group consisting of imipenem, meropenem, vancomycin, cilastatin,
 cefoxitin, penicillin, clavulanic acid, probenecid, tetracycline, ciprofloxacin, and
 norfloxacin or a mixture thereof, wherein when imipenem is used as a drug it is used
 in combination with cilastatin as PRIMAXIN®.

ANEXO EXPLICATIVO DE MODIFICACIONES A LAS REIVINDICACIONES

En ejercicio del derecho conferido por el Artículo 28 numeral 1 del Tratado de Cooperación en materia de Patentes PCT, atentamente me permito informar a ese Despacho que el capítulo reivindicatorio tal como fue presentado originalmente en Fase Internacional ha sido modificado.

Las modificaciones realizadas se encuentran plenamente sustentadas en la descripción de la presente invención y en este sentido, no configuran una ampliación del invento o de la divulgación contenida en la solicitud presentada.

COMPUESTOS PARA EL TRATAMIENTO DEL ÁNTRAX E INHIBIDORES DEL FACTOR LETAL

5

RESUMEN, OBJETO Y FINALIDAD DE LA INVENCION

La invención se refiere a compuestos de fórmula I, y un método para el tratamiento del ántrax o inhibición del factor letal mediante la administración de una composición que contiene un compuesto de fórmula I y un transportador farmacéuticamente aceptable. Esta invención además se refiere al uso de los compuestos de fórmula I para tratar otras enfermedades relacionadas con la infección del ántrax.

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COMPUESTOS PARA EL TRATAMIENTO DEL ÁNTRAX E INHIBIDORES DEL FACTOR LETAL

ANTECEDENTES DE LA INVENCION

5 Las referencias citadas en la presente solicitud no son reconocidas como estado de la técnica respecto a la invención reivindicada.

El ántrax es una infección bacterial producida por *Bacillus anthracis*. Las endosporas del *Bacillus anthracis* pueden entrar en el cuerpo a través de abrasiones en la piel, inhalación o ingestión. El *Bacillus anthracis* produce una toxina de ántrax que suele ser letal. (Dixon *et al.*, (1999) *N. Engl. J. Med.* 341, 815-26.)

10 La toxina ántrax consiste en tres proteínas, un componente receptor de unión designado antígeno protector, y dos componentes enzimáticos llamados el factor edema y el factor letal ("FL"). (Mock *et al.*, (2001) *Annu. Rev. Microbiol.* 55, 647-71.) El factor letal es una metaloproteasa dependiente de zinc que parece ejercer efectos tóxicos mediante la hendidura de la proteinquinasa quinasa activada por mitógeno (en inglés *mitogen-activated protein kinase kinases* MKKs). (Vitale *et al.*, (1998) *Biochem. Biophys. Res. Commun.* 248, 706-11, Vitale *et al.*, (2000) *Biochem. J.* 352 Pt 3, 739-45, Duesbery *et al.*, (1998) *Science* 280, 734-7, Duesbery *et al.*, Publicación Internacional No. WO 99/50439, Fecha de Publicación Internacional 7 de Octubre de 1999.)

20 Vitale y colaboradores han utilizado microsecuencias para identificar los sitios en diferentes MKKs que son hendidos por el factor letal. (Ver Tabla 1, Vitale *et al.*, (2000) *Biochem. J.* 352 Pt 3, 739-45.) La escisión por el factor letal de diferentes MKKs ocurre en la región N terminal precedida del dominio quinasa. La alineación de las secuencias que flanquean el sitio de escisión reveló motivos consenso: un residuo hidrofóbico en la posición P2 y P1', y al menos un residuo básico entre P4 y P7. (Vitale *et al.*, (2000) *Biochem. J.* 352 Pt 3, 739-45.)

25 El factor letal ha sido indicado para escindir péptidos sintéticos *in vitro*. (Hammond *et al.*, (1998) *Infect. Immun.* 66, 2374-8.) La escisión *in vitro* se inhibió mediante 1,10 fenantrolina o EDTA 10 mM, ambos de los cuales quelatan zinc.

El *Bacillus anthracis* es una espora formada en un bacilo gram positivo, el cual es el agente etiológico del ántrax. El ántrax es una enfermedad que puede ser encontrada globalmente en zonas templadas (ej. América Central y del Sur,

Europa del Este y Sur, Asia, África, Medio este, y Caribe) y es transmisible a humanos a través del contacto o toma de productos animales contaminados (ej. comer carne poco hecha de animales infectados). Los animales salvajes tales como el ciervo, ñu, elefantes y ganado doméstico, tal como cabras, ovejas, vacas, caballos, y cerdos

5 tienen un alto riesgo de contraer la enfermedad. El contagio generalmente ocurre al pacer en tierras contaminadas, comer pienso contaminado o beber de fuentes contaminadas de agua. Las esporas de *Bacillus anthracis* pueden permanecer viables en el suelo durante muchos años. Ver Helgason et al., *Applied and Environmental Microbiology* 2000 66(6) pgs. 2627-2630; Wber et al., *Antimicrob Agents and*

10 *Chemotherapy* 1988 32(5): 642-645; y Doganay et al., *Scand. J. Inf. Dis.* 1991 23:333-335 para más datos del *Bacillus anthracis*.

En los hombres pueden ocurrir tres formas de infecciones de ántrax, cutánea, gastrointestinal e inhalacional. Con la forma cutánea, las infecciones ocurren cuando la bacteria o espora entran a través de la piel por un corte o una abrasión, Ver

15 Synder, J.W., Shapiro, D.S., Gilchrist, M.J.R., et al., "*Basic Diagnostic Testing Protocols for Level A Laboratories (For The Presumptive Identification of Bacillus anthracis)*" en www.ban.asm.la.cp.102401f, Oct. 24, 2001, pgs. 1-20 y Dixon, et al., *NEJM* 341:815-826 Sept 9, 1999 Número 11. Los síntomas de la infección de la piel son generalmente aumento de picazón o granos que parecen picotazos de insectos. En

20 uno o dos días, los picotazos o picotazo se desarrollan para formar una vesicular llena de fluido, la cual se rompe para formar una ulcera dolorosa con una característica área negra necrótica (muerta) en el centro. Si no se trata, la muerte puede ocurrir, sin embargo, las muertes son raras si los antibióticos apropiados son administrados.

El ántrax gastrointestinal generalmente ocurre por la consumición de

25 carne contaminada con la bacteria, la cual resulta en una inflamación aguda del tracto intestinal. Los signos son náuseas, pérdida de apetito, vómitos, fiebre, y junto con el dolor abdominal, los vómitos de sangre y las diarreas severas son indicativas del ántrax gastrointestinal. La ratio de mortalidad para esta forma de ántrax humano se estima en un 25%-60%.

La inhalación de ántrax ocurre mayoritariamente como el resultado del

30 desarrollo intencional de un aerosol de *Bacillus anthracis*, por ejemplo en un acto de bioterrorismo. Esta forma de infección humana de ántrax tiene normalmente un periodo de incubación de uno a seis días, con fiebre, indisposición, fatiga, una tos seca y/o molestias en el pecho a veces siendo los primeros signos. Estos síntomas iniciales

35 suelen estar seguidos por un corto periodo de mejora, seguido por un abrupto

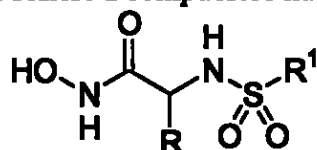
desarrollo de dificultades severas respiratorias con respiración cansada, perspiración, y color de piel azulado. La muerte normalmente ocurre entre 24-36 horas después del comienzo de las dificultades respiratorias a pesar del tratamiento agresivo.

La mayoría de las cepas de *Bacillus anthracis* son sensibles a un amplio rango de antibióticos. Las terapias prescritas comúnmente hoy en día son ciprofloxacina, penicilina, o doxiciclina. Sin embargo, la eficacia y los efectos secundarios de estos agentes no son los ideales.

Mientras los antibióticos pueden matar la bacteria que causa el ántrax, la toxina tripartita del ántrax continua dañando el cuerpo incluso cuando las propias bacterias están muertas. Por ello, todavía existe la necesidad de unas terapias efectivas con eficacia mejorada, con pocos o sin efectos secundarios los cuales inhiben la capacidad del factor letal para escindir moléculas hospedadoras importantes.

DESCRIPCIÓN DE LA INVENCION

La invención se refiere a compuestos nuevos de fórmula I



FORMULA I

o una sal farmacéuticamente aceptable, enantiómero, diastereómero o éster hidrolizable in vivo o mezcla de ellos, donde,

R¹ representa C₆-10 aril, C₅-10 heteroaril o C₅-10 heterocíclico, dicho arilo, heteroarilo y heterociclil están opcionalmente substituido con de 1 a 3 grupos de R^a

R^a representa C₁-6 alquil, halógeno, OH, aril(C₁-6)alquil, (C₁-6)alcoxi, (C₁-6)alcoxi(C₁-6)alquil, halo(C₁-6)alquil, nitro, amino, mono- o di-N-(C₁-6)alquilamino, acilamino, aciloxi, carboxi, carboxi sales, carboxi ésteres, carbamoil, mono- y di-N-(C₁-6)alquilcarbamoil, (C₁-6)alcoxicarbonil, ariloxycarbonil, ureido, guanidino, sulfonilamino, aminosulfonil, (C₁-6)alquiltio, (C₁-6)alquilsulfinil, (C₁-6)alquilsulfonil, heterociclil, heterociclil(C₁-6)alquil; y

R representa C₁₋₈ alquil, C₃₋₁₀ cicloalquil, C₃₋₁₀ heterocicloalquil, C₅₋₁₀ heteroaril, o C₅₋₁₁ heterociclil, dicho heteroaril y heterociclil están opcionalmente substituidos con de 1 a 3 grupos de R^a y dicho alquil, opcionalmente substituido con de 1 a 3 grupos seleccionados del grupo consistente en aril, heterociclil, (C₁₋₆)alquiltio, ciano, heteroaril, guanidino, ((1-aminoetil)carbonil)amino, ((aminometil)carbonil)amino, ((2-amino)prop-2-il) carbonil)amino, acetamido, 4-(aminometil)fenil, tio, t-butil sulfonil, (C₂₋₆)alqueniltio, (C₂₋₆)alquiniltio, amino, mono- o di-(C₁₋₆)alquilamino, ariltio, heterociciltio, (C₁₋₆)alcoxi, aril(C₁₋₆)alcoxi, aril(C₁₋₆)alquiltio, cicloalquil, cicloalquenil, carboxi y ésteres de ellos, hidroxí y halógeno.

Esta invención además se refiere al uso de los compuestos de fórmula I en el tratamiento del ántrax y otras enfermedades relacionadas con la infección del ántrax.

Este y otros aspectos de la invención se realizarán bajo la inspección de la invención como un todo.

DESCRIPCIÓN DETALLADA DE LA INVENCION

La presente invención se dirige a los compuestos de fórmula I, y un método para el tratamiento del ántrax o inhibición del factor letal mediante administración, preferentemente intravenosa o intramuscular, de una composición que contiene un compuesto de fórmula I y un transportador farmacéuticamente aceptable.

La invención se describe aquí en detalle utilizando términos definidos abajo a menos que otra cosa sea especificada.

Cuando alguna variable (ej. aril, heterociclo, R¹, R etc.) aparece más de una vez en algún constituyente, se define cada vez que aparezca independientemente de otras veces que se presente. También, combinaciones de substituyentes/ o variables son permitidas solo si de tales combinaciones resultan combinaciones estables.

El término "alquil" se refiere a un alcano monovalente (hidrocarbano) derivado de un radical desde 1 a 10 átomos de carbonos al menos que otra cosa se defina. Puede ser lineal, ramificado o cíclico. Preferentemente los grupos alquilo incluyen metil, etil, propil, isopropil, butil, t-butil, ciclopentil y ciclohexil. Cuando el grupo alquil se dice que está substituido con un grupo alquilo, esto es como decir "grupo alquilo ramificado".

Preferentemente, alquenal es C₂-C₆ alquenal.

Preferentemente, alquenal es C₂-C₆ alquenal.

El cicloalquil es una especie de alquilo que contiene de 3 a 15 átomos de carbono, a menos que otra cosa sea especificada, sin dobles enlaces alternos o resonantes entre átomos de carbono. Puede contener desde 1 a 4 anillos que están fusionados. Los ejemplos de los grupos cicloalquilo son ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, y cicloheptilo. El heterocicloalquilo se entiende que significa grupos anulares cicloalquilo los cuales consisten en átomos de carbono y de uno a cuatro heteroátomos seleccionados del grupo consistente en N, O, y S, e incluyendo algún bicíclico. Dicho heterocicloalquilo puede opcionalmente estar substituido con de 1 a 3 grupos de R^a descritos aquí. Ejemplos de heterocicloalquilos son oxano, metiloxano, dioxano, pirano, tiolano, piperidina, pirrolidina, aziridina, azetidina, etc.

Alcoxi se refiere a C₁-C₆ alquil-O-, con el grupo alquilo opcionalmente substituido como se describe aquí. Ejemplos de los grupos alcoxi son metoxi, etoxi, propoxi, butoxi y grupos isoméricos de ellos.

Halo es la forma abreviada para halógeno y se refiere a cloro, fluor, bromo y yodo.

Como se usa aquí "aril" se entiende que significa algún anillo de carbono estable monocíclico o bicíclico de hasta siete miembros en cada anillo, donde al menos un anillo es aromático. Los ejemplos de tales elementos arilo incluyen fenilo, naftilo, tetrahidronaftilo, indanilo, bifenilo, fenantrilo, antrilo, o acenafilo.

El término heterociclicil o heterocíclico, como se usa aquí, representa un monociclo estable de 5 a 7 miembros o un anillo heterocíclico biciclo estable de 8 a 11 miembros el cual puede ser saturado o insaturado, y el cual consiste en átomos de carbono y desde uno a cuatro heteroátomos seleccionado del grupo consistente en N, O, y S, y que incluyen cualquier grupo biciclo en el cual cualquiera de los anillos heterocíclicos definidos arriba está fusionado a un anillo de benceno. El anillo heterocíclico puede estar unido a cualquier heteroátomo o átomo de carbono lo cual resulta en la formación de una estructura estable. Un sistema anular heterocíclico fusionado puede incluir anillos carbocíclicos y necesita incluir sólo un anillo heterocíclico. El término heterociclo o heterocíclico incluye moléculas de heteroarilo. Los ejemplos de tales elementos heterocíclicos incluyen, pero no están limitados a, azepinil, benzimidazolil, benzisoxazolil, benzofurazanil, benzopirasil,

benzotiopiranil, benzofuril, benzotiazolil, benzotienil, benzoxazolil, cromanil, cinolinil, dihidrobenzofuril, dihidrobenzotienil, dihidrobenzotiopiranil, dihidrobenzotiopiranil sulfona, 1,3-dioxolanil, furil, imidazolidinil, imidazolil, imidazolil, indolinil, indolil, isocromanil, isoindolinil, isoquinolinil, isotiazolidinil, isotiazolil, isotiazolidinil, morfolinil, naftiridinil, oxadiazolil, 2-oxoazepinil, oxazolil, 2-oxopiperazinil, 2-oxopiperdinil, 2-oxopirrolidinil, piperidil, piperazinil, piridil, pirazinil, pirazolidinil, pirazolil, piridazinil, pirimidinil, pirrolidinil, pirrolil, quinazolinil, quinolinil, quinoxalinil, tetrahidrofuril, tetrahidroisoquinolinil, tetrahidroquinolinil, tiamorfolinil, tiamorfolinil sulfoxido, tiazolil, tiazolinil, tienofuril, tienotienil, y tienil. Una materialización de los ejemplos de tales elementos heterocíclico incluyen, pero no está limitado a, azepinil, benzimidazolil, benzisoxazolil, benzofurazanil, benzopiranil, benzotiopiranil, benzofuril, benzotiazolil, benzotienil, benzoxazolil, cromanil, cinnolinil, dihidrobenzofuril, dihidrobenzotienil, dihidrobenzotiopiranil, dihidrobenzotiopiranil sulfona, furil, imidazolidinil, imidazolil, imidazolil, indolinil, indolil, isocromanil, isoindolinil, isoquinolinil, isotiazolidinil, isotiazolil, isotiazolidinil, morfolinil, naftiridinil, oxadiazolil, 2-oxoazepinil, oxazolil, 2-oxopiperazinil, 2-oxopiperdinil, 2-oxopirrolidinil, piperidil, piperazinil, piridil, 2-piridinonil, pirazinil, pirazolidinil, pirazolil, piridazinil, pirimidinil, pirrolidinil, pirrolil, quinazolinil, quinolinil, quinoxalinil, tetrahidrofuril, tetrahidroisoquinolinil, tetrahidroquinolinil, tiamorfolinil, tiamorfolinil sulfóxido, tiazolil, tiazolinil, tienofuril, tienotienil, tienil y triazolil.

Preferentemente, el heterociclo se selecciona a partir de 2-azepinonil, benzimidazolil, 2-diazapinonil, imidazolil, 2-imidazolidinonil, indolil, isoquinolinil, morfolinil, piperidil, piperazinil, piridil, pirrolidinil, 2-piperidinonil, 2-pirimidinonil, 2-pirrolidinonil, quinolinil, tetrahidrofuril, tetrahidroisoquinolinil, y tienil.

Como se utiliza aquí, "heteroaril" se entiende como un anillo de carbono monocíclico o bicíclico de hasta siete miembros en cada anillo, donde al menos un anillo es aromático, y donde de uno a cuatro átomos de carbono se reemplazan por un heteroátomo seleccionado del grupo consistente en N, O, y S.

Ejemplos de tales elementos heterocíclicos incluyen, pero no están limitados a, benzimidazolil, benzisoxazolil, benzofurazanil, benzopiranil, benzotiopiranil, benzofuril, benzotiazolil, benzotienil, benzoxazolil, cromanil, cinnolinil, dihidrobenzofuril, dihidrobenzofuranil, dihidrobenzotienil, dihidrobenzotiopiranil, dihidrobenzotiopiranil sulfona, furil, imidazolil, indolinil, indolil, isocromanil, isoindolinil, isoquinolinil, isotiazolil, naftiridinil, oxadiazolil, piridil, pirazinil,

pirazolil, piridazinil, pirimidinil, pirrolil, quinazolinil, quinolinil, quinoxalinil, tetrahydroisoquinolinil, tetrahydroquinolinil, tiazolil, tienofuril, tienotienil, tienil y triazolil.

5 En una materialización de esta invención relativa a los compuestos de fórmula I R es un heterocicloalquilo y todas las demás variables son como originalmente se describieron.

En otra materialización de esta invención relativo a los compuestos de fórmula I R es un heteroarilo y todas las demás variables son como se describieron originalmente.

10 En aún otra materialización de esta invención referente a los compuestos de fórmula I R¹ es un grupo fenilo opcionalmente substituido con de 1 a 3 grupos de R^a y R es un heterocicloalquilo, o grupo heteroarilo.

15 En aún otra materialización de la invención en relación con los compuestos de formula I R¹ es un grupo fenil substituido con de 1 a 3 grupos de metoxi, halógeno, metil, etil, propil, butil, naftil, 5-(2-piridil)tiofen-2-il o una mezcla de ellos, y R un heterocicloalquil o heteroaril.

En todavía otra materialización de esta invención en referencia a los compuestos de fórmula Ia R es un heterocicloalquilo y todas las demás variables son como originalmente se describieron.

20 En otra materialización de esta invención en relación con los compuestos de fórmula Ia R es un heteroarilo y todas las demás variables son como originalmente se describieron.

25 En otra materialización de esta invención en relación con los compuestos de fórmula Ia R es un C₁₋₄ alquil y todas las demás variables son como originalmente se describieron.

En aún otra materialización de esta invención referida a los compuestos de formula Ia R¹ es un grupo fenil opcionalmente substituido con de 1 a 3 grupos de R^a y R es un alquilo, heterocicloalquilo, o grupo heteroarilo.

30 En todavía otra materialización de la invención en relación con los compuestos de fórmula Ia R¹ es un grupo fenil substituido con de 1 a 3 grupos metoxi, halógeno, metilo, etilo, propilo, butilo, naftilo, 5-(2-piridil)tiofen-2-il o una mezcla de ellos, y R es un alquilo, heterocicloalquilo o heteroarilo.

35 Otra materialización de esta invención se refiere a una composición farmacéutica que comprende un compuesto de fórmula I y un transportador farmacéuticamente aceptable.

Otra materialización de esta invención incluye el uso de un compuesto de fórmula I para la producción de un medicamento para el tratamiento o profilaxis del ántrax y enfermedades relacionadas. Todavía en otra materialización de la invención el uso de un compuesto de fórmula I para la producción de un medicamento que inhiba el factor letal.

Los compuestos de fórmula I pueden estar combinados con uno o más medicamentos seleccionados de agentes antibacterianos útiles clínicamente (como por ejemplo otras betalactamas o aminoglicósidos), inhibidores de beta-lactamasa, agentes bloqueantes de túbulos renales (ej. probenecid) e inhibidores del metabolismo de enzimas (por ejemplo inhibidores de las dehidropeptidasas, por ejemplo propanoatos Z-2-acilamino-3-substituido tal como cilastatin) y aminoácidos N-acilados (por ejemplo ver la EP-A-178911) la cual reduce los efectos adversos en el riñón. Ejemplos de medicamentos que pueden combinarse con los compuestos de fórmula I son imipenem, meropenem, vancomicina, cilastatina, cefoxitina, penicilina, ácido clavulánico, probenecida, tetraciclina, ciprofloxacina, norfloxacina o una mezcla de ellos. Es mejor que cuando el imipenem se utilice como un medicamento se utilice en combinación con cilastatina (dicha combinación se vende como PRIMAXIN®).

Salas farmacéuticamente aceptables indicadas de estos compuestos que se usan en la invención incluyen sales de adición ácida tales como clorhidrato, bromohidrato, citrato, maleato y sales formadas con ácido fosfórico y sulfúrico. En otro aspecto las sales indicadas son sales básicas tales como las sales de metales alcalinos por ejemplo sodio o potasio, una sal de metal alcalinotérreo como por ejemplo calcio o magnesio, una sal de una amina orgánica como por ejemplo trietilamina, morfina, N-metilpiperidina, N-etilpiperidina, procaina, dibenzilamina, N,N-dibenziletilamina o aminoácidos como por ejemplo lisina. Las sales farmacéuticas aceptables preferentes son sales de sodio y potasio.

Ésteres hidrolizables in vivo son estos ésteres farmacéuticamente aceptables que hidroliza el cuerpo humano para producir un compuesto precursor. Tales ésteres pueden ser identificados mediante la administración, ej. intravenosamente a un animal test, del compuesto testado y el subsecuente examen de los fluidos del cuerpo del animal testado. Adecuados ésteres hidrolizables a carboxi in vivo adecuados incluyen ésteres C1-6alcóximetil por ejemplo metoximetil, C1-6 ésteres alcanoliloximetil por ejemplo pivaloiloximetil, ésteres ftalidil y ésteres

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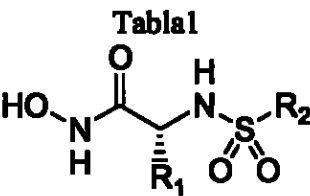
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adicionales descritos en la patente US con No. 5,478,820, la cual se incorpora aquí como referencia en su integridad.

Los compuestos utilizados en esta invención son:

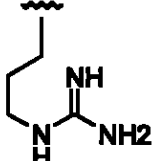
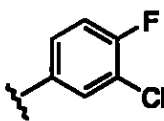
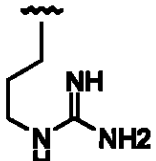
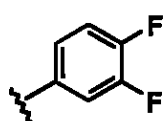
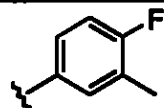
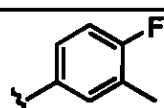
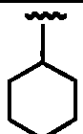
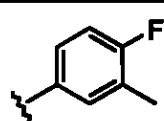
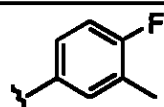
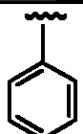
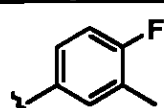
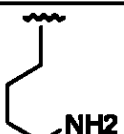
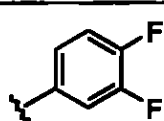
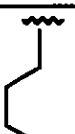
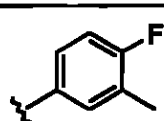
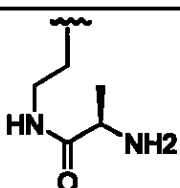
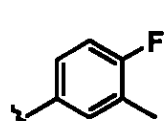
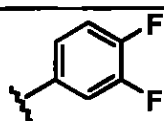
- N-t-butoxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida;
- 5 N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida;
- N-t-butoxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-2-(4'-tetrahidropiranyl)-acetamida;
- N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-2-(4'-tetrahidropiranyl)-acetamida;
- 10 N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-(S)-ciclopropilbutiramida; y sales farmacéuticamente aceptables, enantiómeros, diastereómeros o ésteres hidrolizables in vivo o mezclas de ellos.

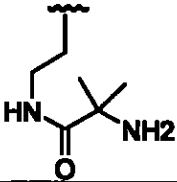
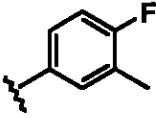
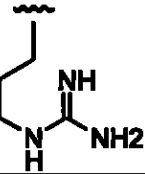
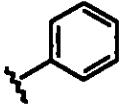
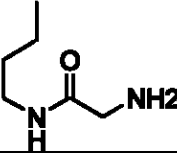
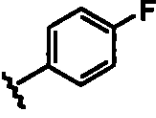
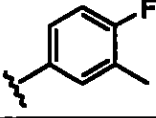
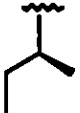
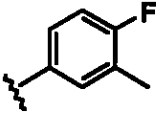
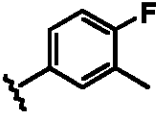
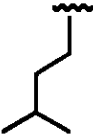
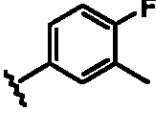
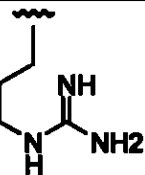
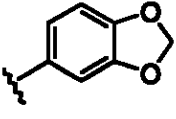
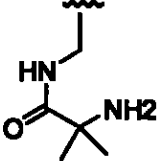
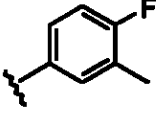
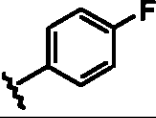
Los compuestos adicionales de esta invención se describen en la Tabla 1:



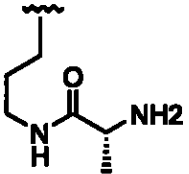
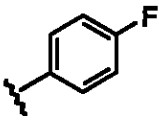
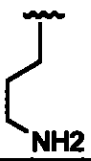
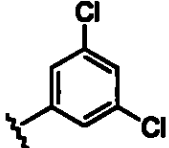
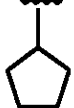
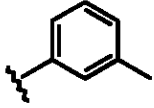
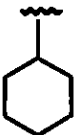
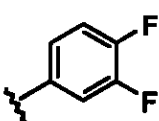
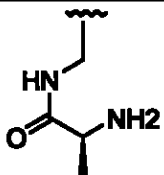
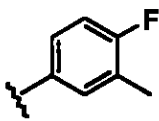
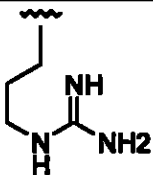
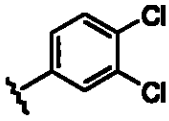
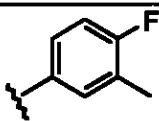
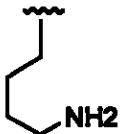
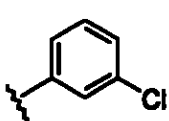
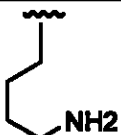
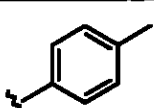
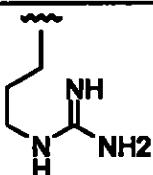
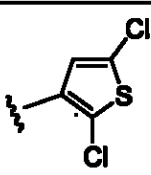
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Ejemplo #	R1	R2
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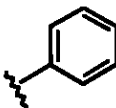
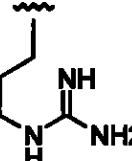
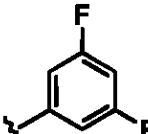
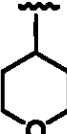
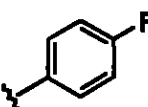
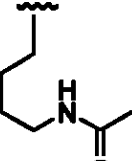
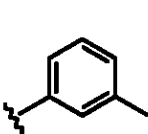
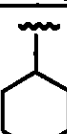
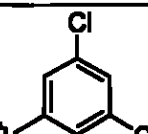
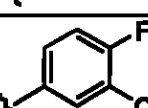
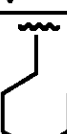
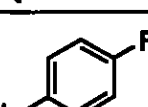
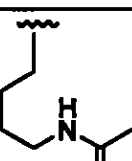
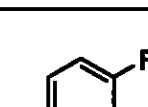
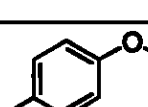
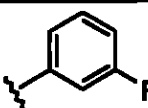
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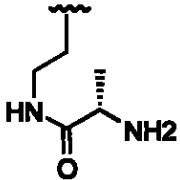
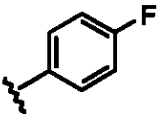
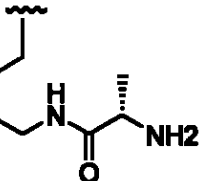
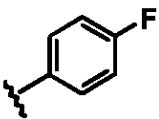
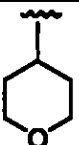
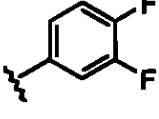
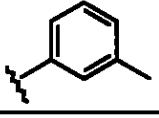
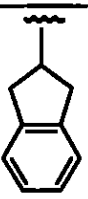
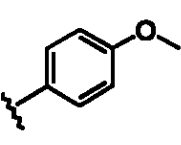
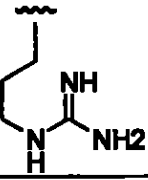
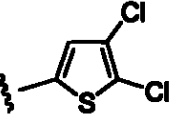
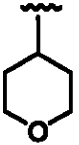
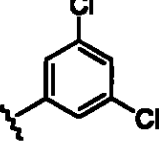
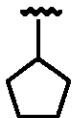
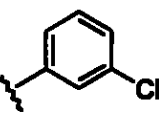
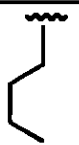
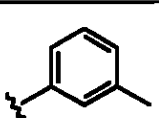
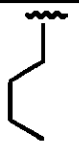
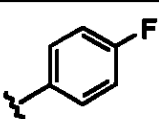
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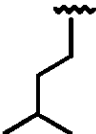
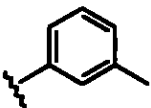
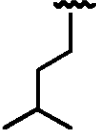
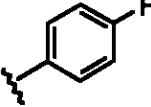
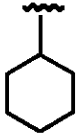
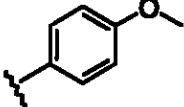
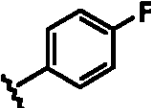
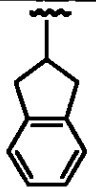
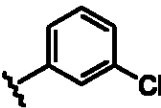
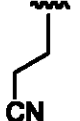
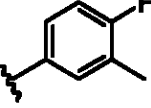
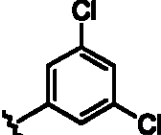
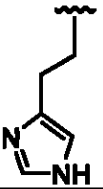
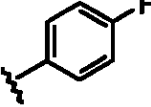
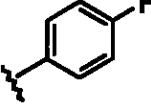
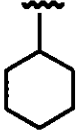
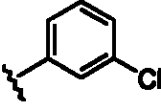
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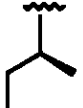
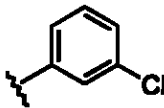
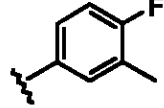
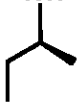
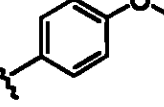
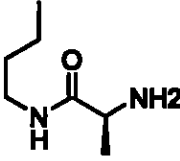
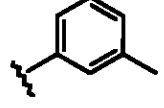
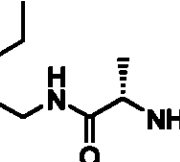
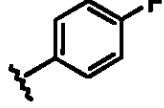
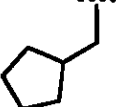
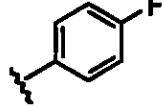
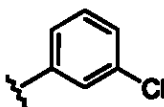
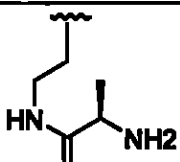
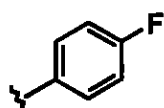
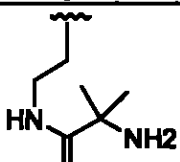
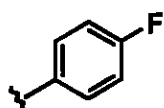
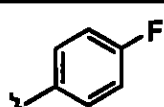
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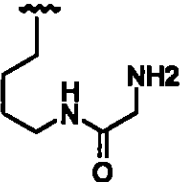
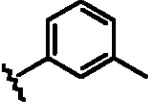
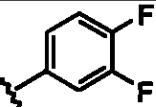
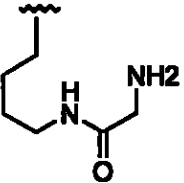
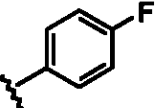
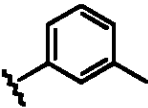
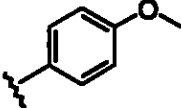
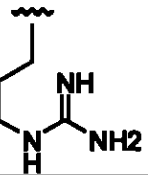
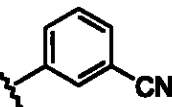
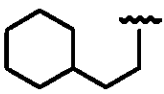
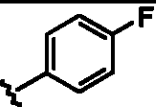
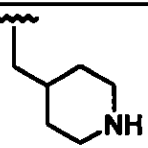
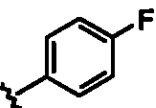
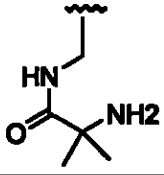
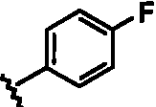
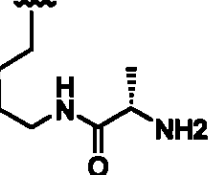
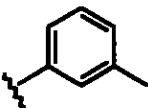
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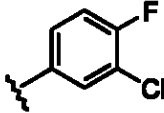
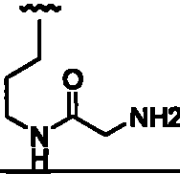
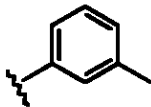
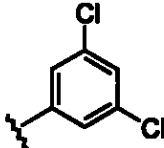
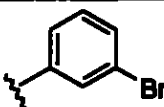
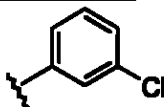
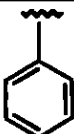
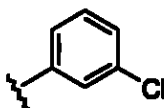
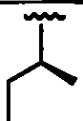
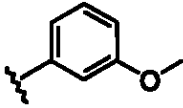
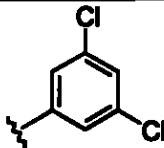
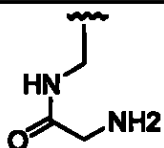
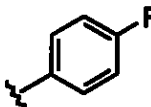
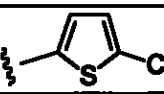
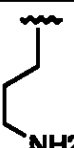
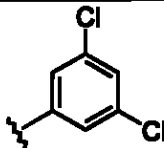
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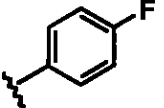
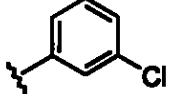
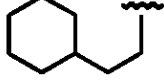
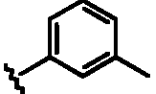
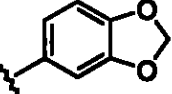
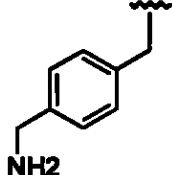
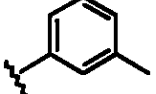
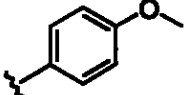
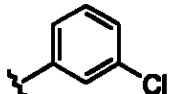
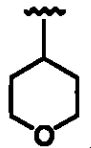
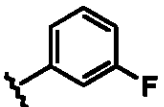
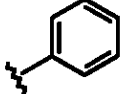
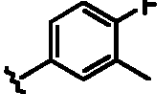
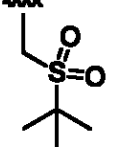
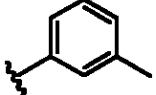
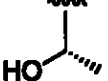
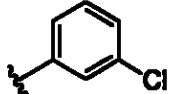
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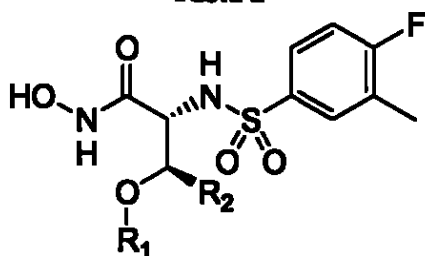
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y sales farmacéuticamente aceptables, enantiómeros, diastereómeros o ésteres hidrolizables in vivo o mezclas de ellos.

Aún otros compuestos de esta invención se describen en la Tabla 2:

Tabla 2



Ejemplo #	R1	R2
146		Me
147		Me
148		Me
149		H
150		Me
151		Me
152		Me
153		Me

5 y sales farmacéuticamente aceptables, enantiómeros, diastereómeros o ésteres hidrolizables in vivo o mezclas de ellos.

Los compuestos preferentes utilizados en esta invención son:

N-t-butoxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida;

N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida;

10 N-t-butoxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-2-(4'-tetrahidropiranyl)-acetamida;

N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-2-(4'-tetrahidropiranyl)-acetamida;

N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-(S)-ciclopropilbutiramida; y sales farmacéuticamente aceptables, enantiómeros, diastereómeros o ésteres

5 hidrolizables in vivo o mezclas de ellos.

En orden a utilizar un compuesto de formula I o una sal farmacéuticamente aceptable, enantiómero, diastereómero o éster hidrolizable in vivo o mezcla de ellos para el tratamiento terapéutico de mamíferos, incluyendo humanos, en particular el tratamiento del ántrax, o inhibiendo el factor letal, es normalmente
10 formulada de acuerdo con prácticas farmacéuticas estándar como una composición farmacéutica.

El compuesto utilizado en la presente invención puede ser administrado en una cantidad terapéuticamente efectiva, intravenosamente, subcutáneamente, intramuscularmente, o por cualquier otro método de los conocidos
15 en la técnica (ej., rectal, oral, parenteral). Una composición farmacéutica posible utilizada en esta invención es una, la cual se realiza en una inyección estéril que contiene entre 1 y 50% p/p de los compuestos utilizados en esta invención.

Sujetos posibles para la administración de la formulación de la presente invención incluyen primates, hombres y otros animales, particularmente
20 hombres y animales domésticos tales como gatos, conejos y perros.

Los ejemplos siguientes no limitantes, dados a modo de ilustración es demostrativo de la presente invención, que los compuestos utilizados en esta invención son útiles para el tratamiento del ántrax e inhiben el factor letal.

25 Definiciones de términos son:

HOBT – hidroxibenzotriazol

DMF – dimetilformamida

DIEA -diisopropiletilamina

TMSONH₂ – O-trimetilsililhidroxilamina

30 PyBOP – benzotrizolo-1-il-oxi-tris-pirrolidino-fosfonio hexafluorofosfato

TFA – ácido trifluoroacético

HPLC – cromatografía líquida de alta resolución

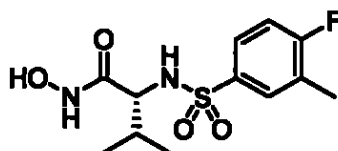
DCM – diclorometano

EDC – 1-(3-dimetilaminopropil)-3-etilcarbodiimida

35 THF – tetrahidrofurano

- DIC – N,N'-diisopropilcarbodiimida
 MDF – dimetilformamida
 DMAP – 4-dimetilaminopiridina
 NMP – 1-metil-2-pirrolidinona
 5 EDTA – ácido etilenediaminatetraacético

EJEMPLO 1



- N-t-butoxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-
 10 metilbutiramida (1.8 g, 4.99 mmol) se disolvió en 75 ml de dicloro-etano anhidro
 conteniendo etanol (0.30 ml, 5 mmol) a 0 °C. Se burbujeó ácido clorhídrico gas
 durante 30 min. El matraz se cerró con un diafragma y la mezcla de reacción se agitó
 durante dos días. Después se eliminó el solvente en un rotavapor, el residuo se
 disolvió en metanol (1 ~ 2 ml), y se diluyó con DCM (20 ml). Los cristales formados
 15 se recogieron y se lavaron con más DCM para dar, después de secar al vacío, N-
 hidroxí-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida. RMN (500
 MHz, CD₃OD) δ: 0.86 (d, 3H), 0.91 (d, 3H), 1.86 (m, 1H), 2.30 (d, 3H), 3.30 (d, 1H),
 7.16 (t, 1H), 7.67 (m, 1H), 7.72 (m, 1H).

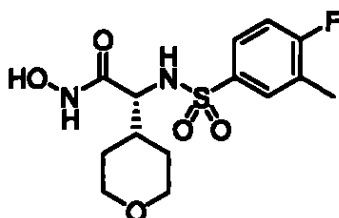
El material de partida para el ejemplo 1 se preparó como sigue:

- 20 Se disolvió D-Valina (1.39 g, 11.9 mmol) en 80 ml de dioxano/agua
 (1:1) que contiene K₂CO₃ (3.3 g, 24 mmol). Una solución de 4-fluoro-3-metilfenil-
 sulfonilcloruro (10 mmol) en dioxano (4 ml) se añadió gota a gota con buena
 agitación. La mezcla de reacción se agitó a temperatura ambiente durante 30 min. Se
 añadió etilacetato (80 ml), HCl (50 ml) 1N. La capa orgánica se lavó dos veces con
 25 HCl 1N, y se extrajo con K₂CO₃ 5% (3x 25ml). Los extractos base combinados se
 acidificaron y extrajeron con etilacetato (80 ml). La capa orgánica se lavó con
 salmuera (2x), se secó con Na₂SO₄. El solvente se eliminó en un rotavapor, y el
 residuo se tritó con hexano. El sólido resultante se secó para dar ácido 2(R)-[(4-
 fluoro-3-metilfenil-sulfonil)]amino-3-metilbutírico.

- 30 El ácido 2(R)-[(4-Fluoro-3-metilfenilsulfonil)]amino-3-metilbutírico
 (2.64 g, 9.12 mmol) se disolvió en DCM (30 ml), seguido de la adición de DIEA

(3.18 ml, 2 eq.) e hidrocloreuro de O-t-butilhidroxilamina (2.3 g, 2 eq.). EDC.HCl (2.1 g, 1.2 eq.) se añadió en porciones como sólido. Se añadió más EDC (0.6, 0.5 eq.) después de 40 min y la reacción se agitó durante otros 30 min. El solvente se eliminó en un rotavapor a temperatura ambiente, y el residuo se dividió con etilacetato (80 ml), HCl 1N (50 ml). La capa orgánica se lavó con HCl 1N, salmuera, y se secó sobre Na₂SO₄. El producto en bruto se purificó en una columna flash con un gradiente del 5% al 12% de etilacetato en DCM para dar el producto N-t-butoxi-2(R)-[(4-fluoro-3-metilfenilsulfonyl)]amino-3-metilbutiramida como una espuma blanca. TLC (1:10 etilacetato:DCM) R_f 0.16. RMN (500 MHz, CD₃OD) δ: 0.89 (d, 3H), 0.90 (d, 3H), 1.08 (s, 9H), 1.86 (m, 1H), 2.30 (d, 3H), 3.44 (d, 1H), 7.18 (t, 1H), 7.70 (m, 1H), 7.77 (m, 1H).

EJEMPLO 2

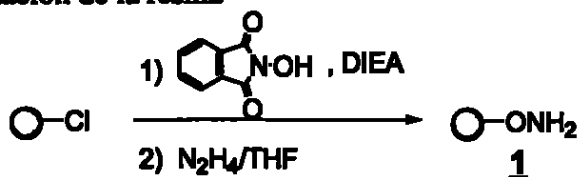


Ejemplo 2, N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonyl)]-amino-2-(4'-tetrahidropiranyl)-acetamida, se preparó de D-4'-tetrahidro-piranylglucina de la misma manera que en el ejemplo 1. RMN (500 MHz, CD₃OD) δ: 1.19 (m, 1H), 1.34 (m, 1H), 1.40 (m, 1H), 1.74(m, 1H), 1.80(m, 1H), 2.32 (d, 3H), 3.31 (m, 2H), 3.37 (d, 1H), 3.90 (m, 2H), 7.18 (t, 1H), 7.65 (m, 1H), 7.72 (m, 1H).

Ejemplo 3 a 144

Los ejemplos 3 a 144, se encuentran en la Tabla 1, se hicieron en fase sólida y se ilustran como sigue:

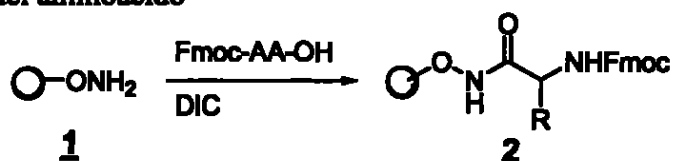
Paso 1. Funcionalización de la resina



Una solución de N-hidroxifthalimida (2.8 g, 17 mmol), DIEA (3.0 ml, 17 mmol) en diclorometano (30 ml) y DMF (15 ml) se añadió rápidamente a 4.39 g de

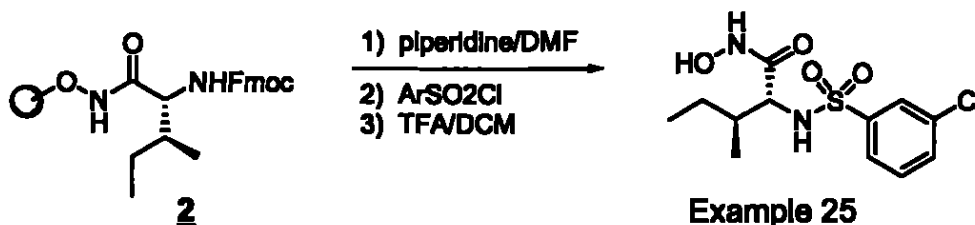
2-Clorotritil resina (1.1 mmol/g cargado) en un cartucho fijo frito. La suspensión de la resina fue sacudida intermitentemente y dejada sobre el banco durante la noche. La resina se lavó 5x con DMF, y luego se trató con una solución de 40 ml de una solución de hidrazina (0.5 M en THF) durante 2 hr. Una gran cantidad de sólido blanco se formó alrededor de la resina. Se lavó con DMF-H₂O(1:1) 2x, DMF 4x. El tratamiento con hidracina se repitió una vez más durante otras tres horas. La resina se lavó con DMF-H₂O (1:1) 2x, DMF 4x, DCM 5x, se secó al vacío durante la noche para dar 4.53 g de la resina 1. La carga es alrededor de 1.0 mmol/g por cambio de peso.

10 Paso 2. Carga del aminoácido



La resina O-ancorada hidroxilamina 1, 500 mg (~1.0 mmol/g carga), fue aumentado con DCM en un cartucho fijo de cerámica frita y desecado. Se añadió una solución de Fmoc-D-alo-isoleucina (530 mg, 1.5 mmol, 3 eq.), DIC (0.120 ml, 0.75 mmol, 1.5 eq.) en 3 ml de DMF. El cartucho se agitó brevemente y se dejó sobre la balda durante una hora. Se añadió otra dosis de DIC (0.04 ml, 0.25 mmol, 0.5 eq.). Después de otra hora, la resina se lavó con DMF 4x, DCM 4x y se secó al vacío durante la noche para dar la resina 2. La carga aproximada es 0.70 mmol/g por peso ganado.

20 Paso 3



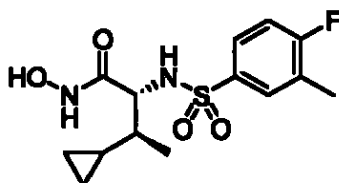
La resina 2, 150 mg, ~0.7mmol/g se cargó, se trató con 2 ml de piperidina/DMF (25%) durante 2 hr. La resina se lavó con DMF 3x, DCM 3x. Una solución de DIEA (73 ul, 0.42 mmol, 4 eq.) en THF-DCM (1:1, 0.5 ml) que contiene DMAP (~2 mg) se añadió a la resina, seguida de una solución de cloruro 3-clorofenilsulfonil (66 mg, 3 eq.) en THF-DCM (0.5 ml). Después de 3 hr, la resina se lavó con DMF 3x, DCM 3x, y se unió dos veces con 5% TFA/DCM (0.5 ml) durante 30 min. La solución de unión combinada se evaporó, y el residuo se disolvió en

CH₃CN:H₂O y se purificó en HPLC de fase reversa para dar el Ejemplo 25, N-hidroxi-2(R)-(3-clorofenilsulfonyl)amino-3(S)-metilvalerico amida. RMN (500 MHz, CD₃OD) δ: 0.82 (d, d, 6H), 1.04 (m, 1H), 1.35 (m, 1H), 1.64 (m, 1H), 3.52 (d, 1H), 7.50 (t, 1H), 7.60(d, 1H), 7.76(d, 1H), 7.84 (m, 1H).

5 La tabla 1 lista las estructuras de los ejemplos 3 a 144. Como se aprecia por un técnico en la material, los ejemplos 4 a 144 fueron realizados, con alguna modificación, de acuerdo con la descripción del ejemplo 3. Algunos compuestos requirieron un paso de desprotección (tratamiento con 50% TFA/DCM) después de separarla de la resina.

10

Ejemplo 145



15 El ácido 2-(R)-[(4-fluoro-3-metilfenil)sulfonyl]amino-3-(S)-ciclopropilbutírico (10 mg, 31 umol) se disolvió en DMF (0.3 ml) con HOBt (4.5 mg, 0.031 mmol), DIEA (11 ul, 0.062 mmol), O-trimetilsililhidroxilamina (20 ul, 0.16 mmol). Se añadió una solución de PyBOP (20 mg, 0.038 mmol) en DMF (0.3 ml). La reacción se paró después de 30 min con CH₃CN:H₂O (1:1, 5% TFA) y se hizo pasar a través de HPLC de fase reversa para dar, después de la liofilización, N-hidroxi-2-(R)-[(4-fluoro-3-metilfenil)sulfonyl]amino-3-(S)-ciclopropilbutiramida. RMN (500 MHz, CD₃OD) δ: -0.04 (m, 1H), 0.20 (m, 1H), 0.35 (m, 1H), 0.41 (m, 1H), 0.54 (m, 1H), 0.90 (d, 3H), 1.08 (m, 1H), 2.32 (d, 3H), 3.60 (d, 1H), 7.17 (t, 1H), 7.68 (m, 1H), 7.75 (m, 1H). MS: 331.1 (M + H⁺).

25

El material de partida para el ejemplo 145 se preparó como sigue:

30 Se puso a reflujo metil glicolato (10.4 g, 114 mmol), crotil alcohol (100ml, en exceso), en la presencia de K₂CO₃ (0.8 g) durante 1 hr, durante este tiempo alrededor de 10 ml del condensado se eliminó a través del separador Dean-Stock. Después de diluir con hexano (100 ml), el sólido se filtró a través de una columna corta de silica gel de corta (50 g), se lavó con 1:5 etilacetato:hexano (250

ml). El combinado filtrado y lavado se concentró a 100 ml, y se diluyó de nuevo con hexano (100 ml), se pasó a través de una columna de silica gel y se lavó. La solución se concentró a ~12.5 g de aceite, la cual se destiló al vacío para dar crotil glicolato: 9.3 g (97 °C/20 mmHg) como una mezcla de cis:trans (1:10). RMN (500 MHz, CDCl_3) δ : 1.3 (m, 3H), 4.15 (s, 2H), 4.62 (d, 2H), 5.6 (m, 1H), 5.84 (m, 1H). isómero cis: 1.71 (m, 3H), el resto de los picos se solapan con un isómero trans.

- El crotil glicolato de arriba (9.3 g, 71 mmol) en THF (10 ml) se añadió lentamente a una solución de $\text{LiN}(\text{TMS})_2$ (200 ml, 1.0 M) en THF (200 ml) a -78 °C. Después de 40 min a esta temperatura, se añadió trimetilsilil cloruro (25.5 ml, 200 mmol). El baño frío se eliminó y la reacción se agitó durante la noche. La mezcla de reacción se concentró a ~150 ml y se diluyó con etilacetato (500 ml). Esto se lavó dos veces con HCl 2N. Los lavados fueron de nuevo extraídos con más etilacetato. Las capas orgánicas combinadas se extrajeron con K_2CO_3 3X 5% . La solución base combinada se acidificó con HCl concentrado frío, y se extrajo con etilacetato. La solución de etilacetato se lavó con NaCl saturado, y se secó sobre Na_2SO_4 . La evaporación del solvente y el secado al vacío dio el ácido 2-hidroxi-3-metilpropen-4-enoico como una mezcla de diastereómeros. El RMN (500 MHz, CD_3OD) para el diastereómero 1 [(2R, 3S) y (2S, 3R)] δ : 1.02 (d, 3H), 2.60 (m, 1H), 4.05 (d, 1H), 5.02 (m, 1H), 5.09 (m, 1H), 5.87 (m, 1H); diastereómero 2 [(2R, 3R) y (2S, 3S)] δ : 1.11(d, 3H), 2.6 (m, 1H), 4.03 (d, 1H), 5.0 (m, 1H), 5.09 (m, 1H), 5.80 (m, 1H). El ratio diastereomérico mediante RMN es alrededor de 7 a 1 con el diastereómero 1 como el mayor.

- El ácido realizado arriba (8.5 g, 65 mmol) se disolvió en DMF seco (100ml) y DIEA (16 ml, 91 mmol). Se añadió metil ioruro (11.7 ml, 85 mmol). Esto se agitó durante 15 hr, y se diluyó con etilacetato (500 ml), se lavó con HCl 0.1N 3x, salmuera 2x, se secó sobre Na_2SO_4 . La evaporación del solvente deja éster metil 2-hidroxi-3-metilpenten-4-enoico. RMN (500 MHz, CD_3OD) para diastereómero 1 [(2R, 3S) y (2S, 3R)] δ : 1.02 (d, 3H), 2.55 (m, 1H), 3.70 (s, 3H), 4.04 (d, 1H), 5.02 (m, 1H), 5.06 (m, 1H), 5.81 (m, 1H); diastereómero 2 [(2R, 3R) y (2S, 3S)] δ : 1.08 (d, 3H), 2.58 (m, 1H), 3.70 (s, 3H), 4.07 (d, 1H), 5.00 (m 1H), 5.06 (m, 1H), 5.80 (m, 1H).

- El metil éster realizado arriba (2.9 g, 20 mmol) se disolvió en DCM seco (100 ml) con diiodometano (8.1 ml, 100 mmol), y se enfrió a 0°C. Se añadió una solución de dietilzinc (100ml, 1.0 M en hexano). El baño frío fue eliminado y la mezcla se agitó en nitrógeno durante 3 días. Una solución de NH_4Cl se añadió para

parar la reacción. La capa orgánica se lavó con HCl 2x, salmuera 2x, y se secó sobre Na_2SO_4 . La evaporación del solvente dejó un aceite que contiene un 70% del producto metil 2-hidroxi-3-ciclopropilbutirato y el 30% del material de partida. Se usa sin más purificación.

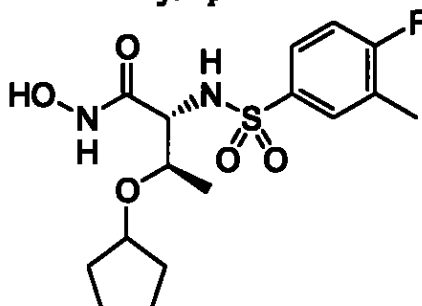
5 Una solución del éster hecho arriba (3 g, 20 mmol), piridina (2.0 ml, 24 mmol) en DCM seco (10 ml) se añadió lentamente a una solución agitada de TiF_2O (4.0 ml, 24 mmol) en DCM (100 ml) a 0 °C. Después de 1 hr a 0 °C, se añadió agua para parar la reacción. Esto luego se lavó con HCl (0.1 N) diluido, salmuera, y se secó sobre Na_2SO_4 . La evaporación del solvente dio 5.3 g de triflato como un aceite. Esto
10 se agitó con NaN_3 (2.4 g, 36 mmol) en DMF (80 ml) durante 15 hr. La mezcla de reacción se diluyó con etilacetato (400 ml), se lavó con HCl diluido 3x, salmuera 2x, y se secó sobre Na_2SO_4 . La evaporación del solvente dejó 2.96 g de aceite. El paso a través de una columna flash de cromatografía silica gel, eluyendo con 5% de éter en hexano dio metil 2-azido-3-ciclopropil-butirato como un aceite sin color. El
15 diastereómero deseado 1 [(2R, 3S) y (2S, 3R)] puede ser aislado a través de una HPLC preparativa de fase reversa eluyendo con solvente en gradiente $\text{CH}_3\text{CN}:\text{H}_2\text{O}$. RMN (500 MHz, CDCl_3) para el diastereómero 1 [(2R, 3S) y (2S, 3R)] δ : 0.04 (m, 1H), 0.18 (m, 1H), 0.48 (m, 2H), 0.74 (m, 1H), 1.09 (d, 3H), 1.35 (m, 1H), 3.80 (s, 3H), 3.92 (d, 1H).

20 El azida aislada arriba diastereómero [(2R, 3S) y (2S, 3R)] (400 mg, 2.2 mmol) se disolvió en MeOH (10 ml), se enfrió en un baño de agua a 20 °C. Se añadió cloruro de estaño (860 mg, 4.4 mmol). Esto se agitó durante 15 hr. A la mezcla de reacción se añadió dioxano (10 ml), K_2CO_3 (1.5g 10.1 mmol)/ H_2O (10 ml). El sólido se filtró, se lavó con dioxano (5 ml). Al combinado filtrado y lavado
25 se añadió una solución de 4-fluoro-3-metilfenilsulfonil cloruro (560 mg, 2.4 mmol) en dioxano (5 ml). Alrededor de 30 min. Después, la reacción se acidificó con HCl a pH 3, se diluyó con $\text{CH}_3\text{CN}:\text{H}_2\text{O}$. El producto se aisló a través de HPLC en fase reversa preparativa (repetidas inyecciones) a metil 2-(4-fluoro-3-metilfenilsulfonamido)-3-ciclopropilbutirato. Otras separaciones a través de la columna Chiralpak AD eluyendo
30 con 7% EtOH en heptano dio dos enantiómeros, con el deseado isómero 1 (2R, 3S) eluido primero. RMN (500 MHz, CD_3OD) δ : 0.01 (m, 2H), 0.39 (m, 2H), 0.62 (m, 1H), 1.01 (d, 3H), 1.19 (m, 1H), 2.312 (d, 3H), 3.23 (s, 3H), 3.90 (d, 1H), 7.18 (t, 1H), 7.68 (m, 1H), 7.73 (m, 1H).

 Ester metil 2(R)-[(4-fluoro-3-metilfenil)sulfonil]amino-3-(S)-
35 ciclopropil-butírico (20 mg, 0.061 mmol) se disolvió en MeOH (0.2 ml), seguido de la

- adición de LiOH (8 mg, en exceso)/H₂O (0.15 ml). Después de 2 hr la reacción se acidificó con 1.5 ml de CH₃CN:H₂O (1:1, 5% TFA) y se cromatografió con HPLC en fase reversa para dar ácido 2-(R)-(4-fluoro-3-metilfenil-sulfonamida)-3-(S)-ciclopropilbutírico. RMN (500 MHz, CD₃OD) δ : -0.01 (m, 1H), 0.15 (m, 1H), 0.40 (m, 2H), 0.65 (m, 1H), 1.02 (d, 3H), 1.22 (m, 1H), 2.31 (d, 3H), 4.83 (d, 1H), 7.16 (t, 1H), 7.69 (m, 1H), 7.75 (m, 1H).

Ejemplo 146



- Se disolvió ácido 2(R)-[(4-Fluoro-3-metilfenil)sulfonyl]amino-3(R)-ciclopentoxilbutírico (11 mg, 0.03 mmol) en DMF (200ul) con DIEA (12 ul, 0.12 mmol), HOBT (8 mg, 0.06 mmol), y TMSNH₂ (10 ul, 0.08 mmol). Se añadió una solución de PyBOP (31 mg, 0.06 mmol) en DMF (100 ul). La reacción se paró después de 20 min con 5% TFA/ H₂O, y el producto se aisló en HPLC en fase reversa para dar, después liofilización, N-hidroxi-2(R)-[(4-fluoro-3-metilfenil)sulfonyl]amino-3(R)-ciclopentoxilbutiramida. RMN (500 MHz, CD₃OD) δ : 0.97 (d, 3H), 1.44~1.68 (m, 8H), 2.32 (d, J_{H-F}, 3H), 3.61 (d, 1H), 3.72 (m, 1H), 3.67 (m, 1H), 7.18 (m, 1H), 7.70 (m, 1H), 7.76 (m, 1H).

El material de partida del ejemplo 146 se preparó como sigue:

- El éster N-tritil-D-treonina bencil (2.5 g, 5.5 mmol), TEA (2.8 ml, 20 mmol) se disolvieron en 100 ml de tolueno seco a -50 °C. Una solución de sulfúrico cloruro (800 ul, 8 mmol) en tolueno (20 ml) se añadió en 15 min. La reacción se templó a temperatura ambiente. Se añadió etilacetato (100 ml) y se lavó con NaCl sat, se secó sobre Na₂SO₄. El producto se cristalizó en MeOH (10 ml) para dar bencil N-tritil-3(S)-metilaziridina-2(R)-carboxilato. RMN (500 MHz, CDCl₃) δ : 1.37 (d, 3H), 1.64 (m, 1H), 1.95 (d, 1H), 5.15(d, J = 12 Hz, 1H), 5.28(d, J = 12 Hz, 1 H), 7.19~7.28 (m, 12 H), 7.33~7.36 (m, 1H), 7.36~7.39 (m, 3H), 7.51~7.54 (m, 4H).

Se disolvió bencil N-tritil-3(S)-metilaziridina-2(R)-carboxilato, (2.13 g, 4.92 mmol) en 20 ml de MeOH:DCM (1:1) a 0 °C, seguido por la adición de TFA

(20 ml). Después de agitar a temperatura ambiente durante 1 hr, el exceso de reactivo y el solvente se eliminaron en un rotavapor ($T < 25\text{ }^{\circ}\text{C}$). El residuo se separó con DCM (50 ml) y H_2O (100 ml). La fase acuosa se lavó una vez con DCM, y el pH se ajustó a básico con NaHCO_3 se extrajo con etilacetato, y se secó sobre Na_2SO_4 . La
 5 eliminación del solvente dejó 650 mg de bencil 3(S)-metilaziridina-2(R)-carboxilato. Esto se disolvió en DMF (15 ml) a $0\text{ }^{\circ}\text{C}$. Se añadió TEA (2.1 ml, 15 mmol), seguido de Boc_2O (1.64 g, 7.5 mmol). La reacción se agitó a temperatura ambiente durante la noche. Se añadieron etilacetato (100 ml), H_2O (100 ml), y la capa orgánica se lavó dos veces con un 10% de ácido cítrico, aguas madre, y se secó sobre Na_2SO_4 . El producto
 10 bruto se cromatografió en una columna flash, se eluyó con un solvente en gradiente del 5% ~ 10% EA/hexano conteniendo 0.1% TEA, para dar bencil N-Boc-3(S)-metilaziridina-2(R)-carboxilato. RMN (500 MHz, CD_3OD) δ : 1.21(d, 3H), 1.44(s, 9H), 2.82 (m, 1H), 3.21(d, 1H), 5.2 (q, 2H), 7.30~7.38(m, 5H).

Se disolvió bencil N-Boc-3(S)-metilaziridina-2(R)-carboxilato (50 mg,
 15 0.17 mmol), ciclopentil alcohol (0.5 ml, 5.5 mmol) en DCM (0.5 ml), seguido por unas pocas gotas de $\text{BF}_3\cdot\text{Et}_2\text{O}$. Esto se agitó a temperatura ambiente durante 10 hr. El solvente se eliminó, y el residuo se purificó a través de HPLC en fase reversa. El producto recogido y tratado con 50% TFA/DCM dio bencil 2(R)-amino-3(R)-ciclopentoxilbutirato trifluoroacetato. RMN (500 MHz, CD_3OD) δ : 1.28 (d, 3H),
 20 1.4~1.7 (m, 8 H), 3.92 (m, 1H), 4.06 (d, 1H), 4.14 (dq, 1H), 5.26 (d, $J = 12\text{ Hz}$, 1H), 5.31 (d, $J = 12\text{ Hz}$, 1 H), 7.38 (m, 3H), 7.43 (m, 2H).

Bencil 2(R)-amino-3(R)-ciclopentoxilbutirato trifluoroacetato (63 mg, 0.16 mmol), DIEA (174 μl , 1.0 mol), DMAP (1 mg) fueron disueltos en dioxano (2 ml), seguido por la adición lenta de una solución de 4-fluoro-3-metilfenilsulfonil
 25 cloruro (~0.33 mmol) en dioxano (1 ml). Después de 15 min, la reacción se paró con 5% TFA/ H_2O , y se purificó a través de HPLC en fase reversa para dar bencil 2(R)-[(4-Fluoro-3-metilfenil)sulfonil]amino-3(R)-ciclopentoxilbutirato. El grupo protector del bencil éster se eliminó mediante hidrogenación en $\text{MeOH}:\text{EA}$ (1 ml) con 10% Pd/C (2 mg) durante toda la noche para dar ácido 2(R)-[(4-Fluoro-3-metilfenil)-
 30 sulfonil]amino-3(R)-ciclopentoxilbutírico.

Con algunas modificaciones conocidas por los expertos en la materia, los ejemplos 147 a 153 de la Tabla 2 se hicieron de acuerdo con el ejemplo 146.

Ensayo para la determinación de la inhibición del factor letal

El siguiente ensayo se describe en Cummings et al., PNAS, May 14, 2002, vol. 99, no. 10, página 6603-6606 y solicitud PCT US03/05552, solicitada el 2/21/2003 (solicitud de patente EEUU No. 60/359,707, solicitada 2/25/2002), incorporada aquí como referencia en su integridad, Se usa para determinar la inhibición del factor letal después de reaccionar con un compuesto que se cree que es un inhibidor del factor letal.

Los compuestos inhibidores del factor letal pueden ser usados también para el estudio de la actividad del factor letal, y estos compuestos inhibidores tienen propiedades farmacológicas adecuadas que pueden ser utilizadas para ayudar al tratamiento y prevención del ántrax. Las propiedades farmacológicas apropiadas incluyen eficacia, metabolismo y ausencia de efectos secundarios indeseados.

Un screening a gran escala de inhibidores del factor letal puede ser usado para la criba de un gran número de compuestos que identifiquen aquello que afecta a la actividad del factor letal. Un screenig a gran escala se facilita mediante este ensayo que se automatiza y se utiliza en bajos niveles de enzima purificada.

Medida de la Actividad

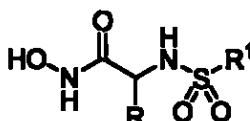
Los sustratos del factor letal pueden ser utilizados en métodos de medida de la actividad del factor letal del *Bacillus anthracis* y el efecto de un compuesto de tal actividad. Tales métodos implican la incubación de un sustrato del factor letal descrito aquí con el factor letal de *Bacillus anthracis* utilizando un medio de incubación donde el factor letal *Bacillus anthracis* es activo, y puede incluir la presencia de un compuesto que es testado. El anclaje del sustrato puede ser detectado como una medida de la actividad del factor letal de *Bacillus anthracis* o del efecto de un compuesto en la actividad del factor letal. La medida puede ser cuantitativa o cualitativa. El ensayo de unión de la enzima del factor letal IC50 resulta de los compuestos de la invención en un rango de 15 uM o menos. Específicamente el IC50 para

N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida y N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-2-(4'-tetrahidopiranyl)-acetamida son 0.13 uM y 0.06 uM respectivamente.

dsc

REIVINDICACIONES:

1. Un compuesto de fórmula I:



FORMULA I

O una sal farmacéuticamente aceptable, enantiómero, diastereómero o éster hidrolizable in vivo o mezcla de ellos, donde,

- 10 R^1 representa C₆-10 aril, C₅-10 heteroaril o C₅-10 heterocíclico, dicho aril, heteroaril y heterociclil opcionalmente substituido con de 1 a 3 grupos de R^a

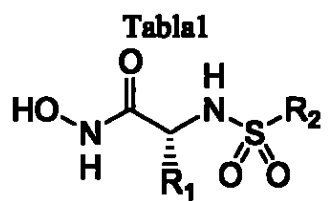
R^a representa C₁-6 alquil, halógeno, OH, aril(C₁-6)alquil, (C₁-6)alcoxi, (C₁-6)alcoxi(C₁-6)alquil, halo(C₁-6)alquil, nitro, amino, mono- o di-N-(C₁-

- 15 6)alquilamino, acilamino, aciloxi, carboxi, carboxi sales, carboxi ésteres, carbamoil, mono- y di-N-(C₁-6)alquilcarbamoil, (C₁-6)alcoxycarbonil, ariloxycarbonil, ureido, guanidino, sulfonilamino, aminosulfonil, (C₁-6)alquiltio, (C₁-6)alquilsulfinil, (C₁-6)alquilsulfonil, heterociclil, heterociclil(C₁-6)alquil; y

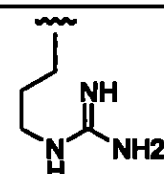
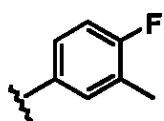
- 20 R representa C₁-8 alquil, C₃-10 cicloalquil, C₃-10 heterocicloalquil, C₅-10 heteroaril, o C₅-11 heterociclil, dicho heteroaril y heterociclil opcionalmente substituido con de 1 a 3 grupos de R^a y dicho alquil, opcionalmente substituido con de 1 a 3 grupos seleccionados del grupo consistente en aril, heterociclil, (C₁-6)alquiltio, ciano, heteroaril, guanidino, ((1-aminoetil)carbonil)amino, ((aminometil)carbonil)amino, 25 ((2-amino)prop-2-il) carbonil)amino, acetamido, 4-(aminometil)fenil, tio, t-butil sulfonil, (C₂-6)alqueniltio, (C₂-6)alquiniltio, amino, mono- o di-(C₁-6)alquilamino, ariltio, heterociciltio, (C₁-6)alcoxi, aril(C₁-6)alcoxi, aril(C₁-6)alquiltio, cicloalquil, cicloalquenil, carboxi y ésteres de ellos, hidroxil y halógenos.

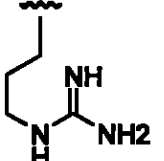
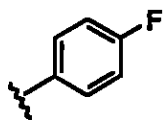
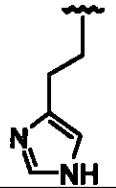
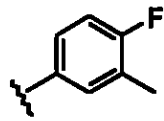
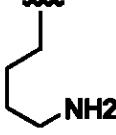
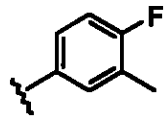
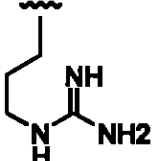
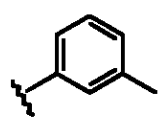
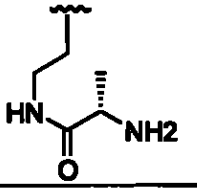
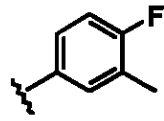
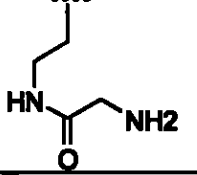
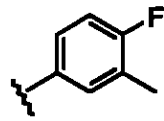
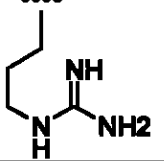
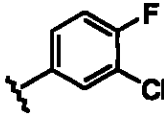
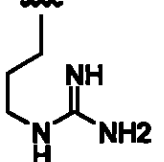
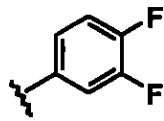
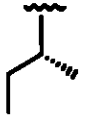
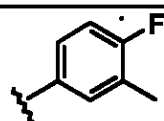
- 30 2. Un compuesto según la reivindicación 1 donde R es un heterocicloalquilo y todas las demás variables como se definieron originalmente.

3. Un compuesto según la reivindicación 1 donde R es un heteroaril y todas las demás variables como se definieron originalmente.
4. Un compuesto según la reivindicación 1 donde R¹ es un grupo fenil opcionalmente sustituido con de 1 a 3 grupos de R^a y R es un grupo heterocicloalquil, o heteroaril.
5. Un compuesto según la reivindicación 1 donde R¹ es un grupo fenil opcionalmente sustituido con de 1 a 3 grupos entre metoxi, halógeno, metil, etil, propil, butil, naftil, 5-(2-piridil)tiofen-2-il o una mezcla de ellos, y R un heterocicloalquilo o heteroarilo.
6. Un compuesto según la reivindicación 1 el cual es seleccionado del grupo consistente en:
- 15 N-t-butoxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida;
N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida;
N-t-butoxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-2-(4'-tetrahidropiranyl)-acetamida;
N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-2-(4'-tetrahidropiranyl)-acetamida;
- 20 N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-(S)-ciclopropilbutiramida; y de las tablas 1 y 2 siguientes

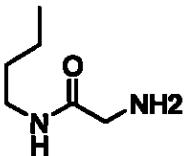
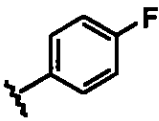
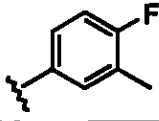
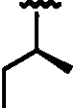
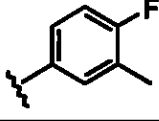
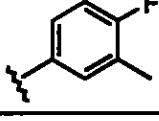
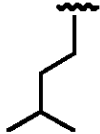
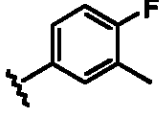
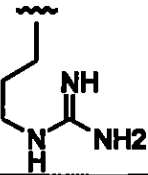
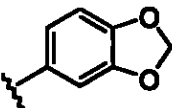
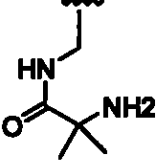
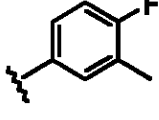
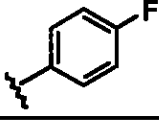
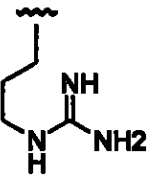
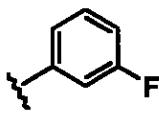
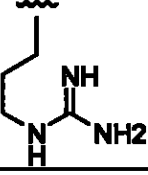
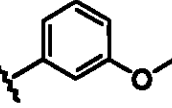
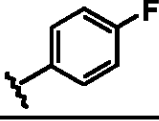


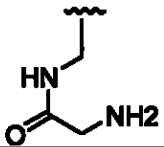
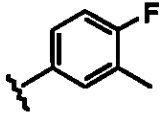
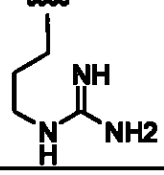
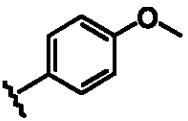
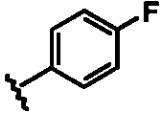
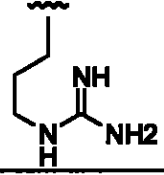
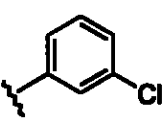
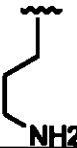
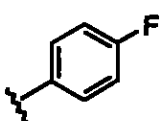
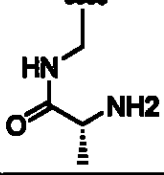
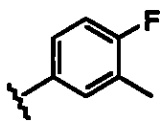
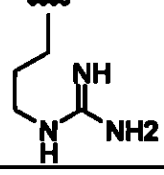
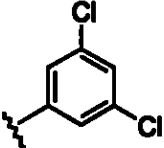
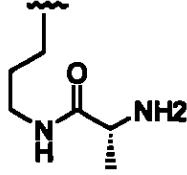
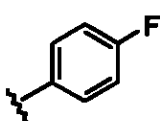
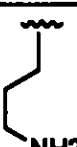
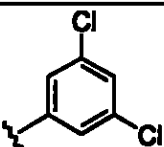
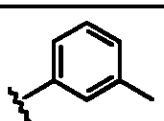
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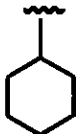
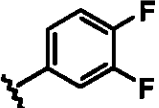
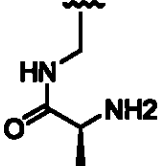
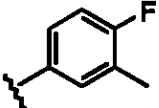
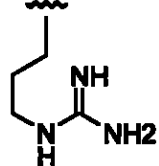
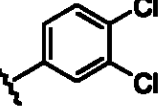
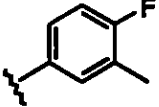
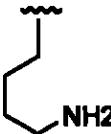
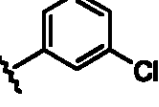
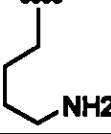
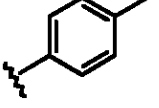
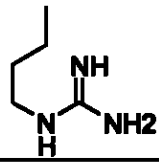
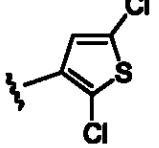
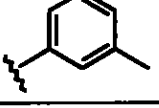
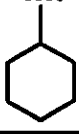
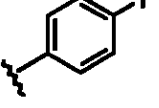
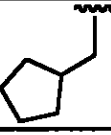
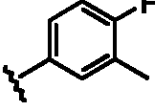
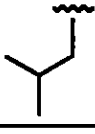
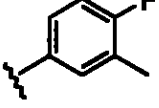
Ejemplo #	R1	R2
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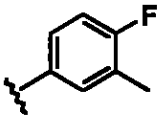
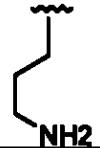
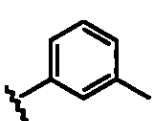
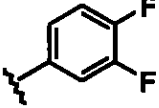
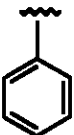
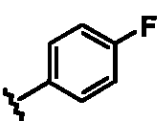
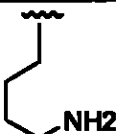
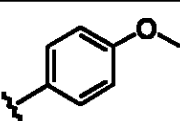
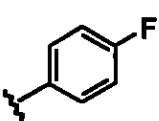
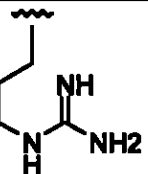
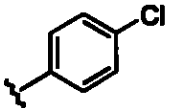
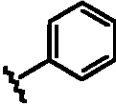
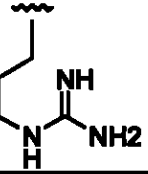
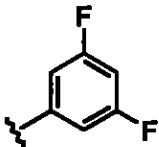
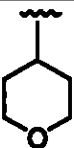
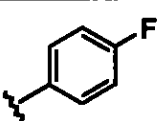
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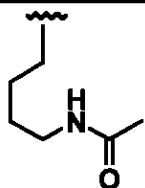
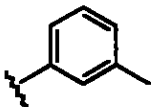
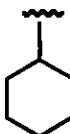
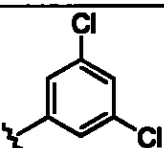
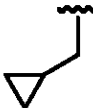
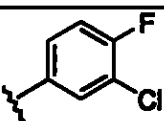
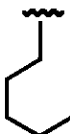
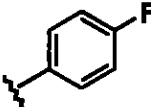
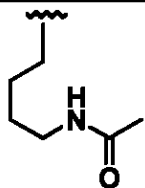
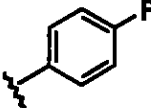
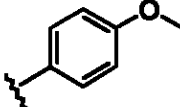
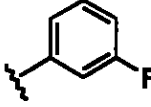
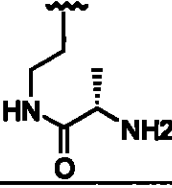
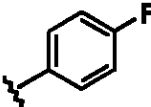
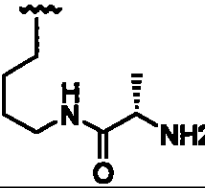
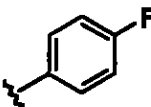
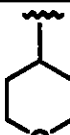
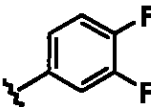
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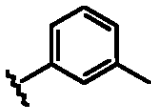
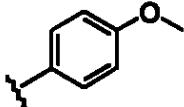
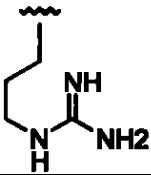
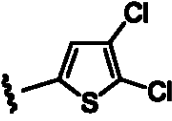
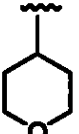
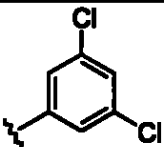
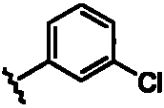
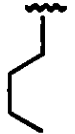
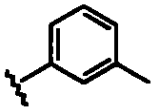
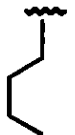
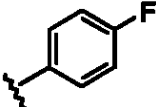
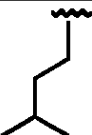
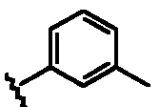
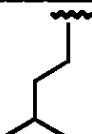
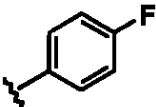
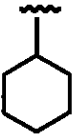
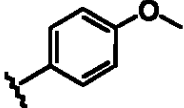
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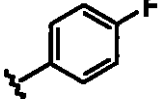
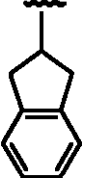
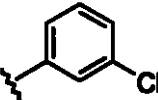
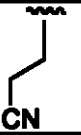
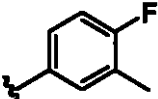
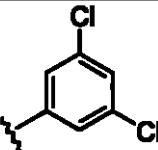
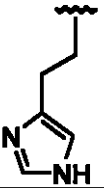
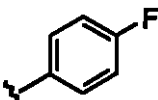
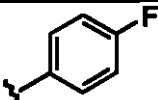
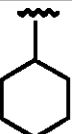
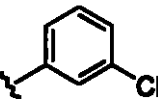
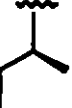
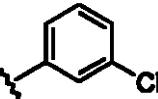
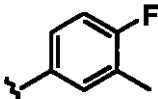
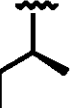
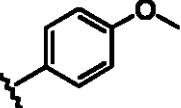
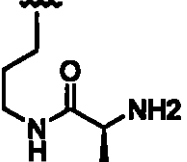
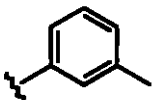
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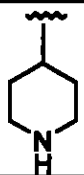
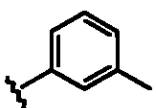
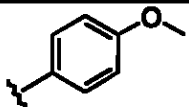
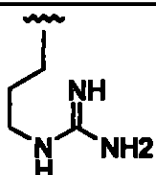
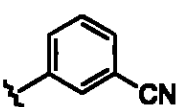
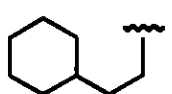
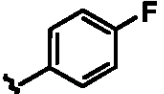
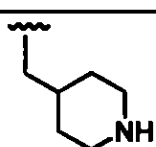
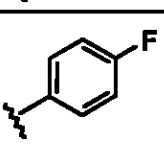
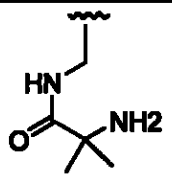
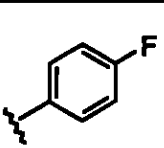
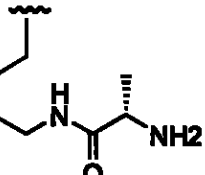
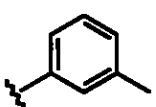
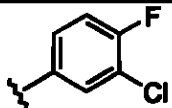
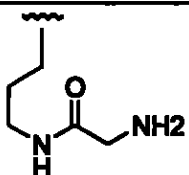
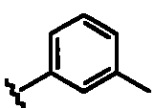
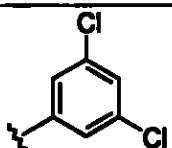
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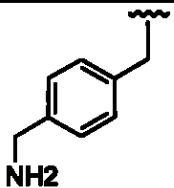
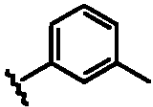
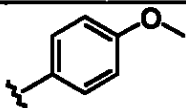
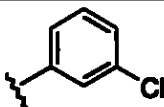
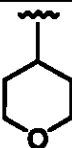
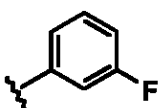
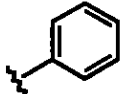
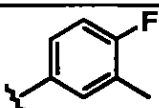
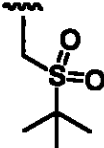
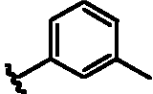
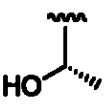
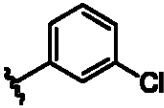
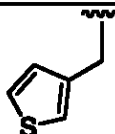
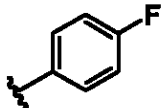
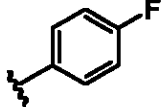
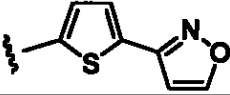
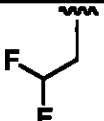
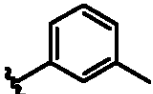
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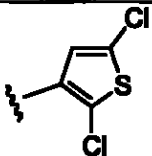
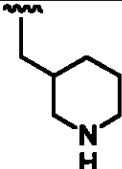
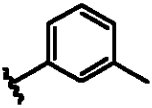
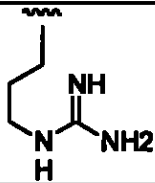
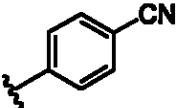
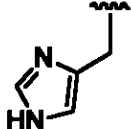
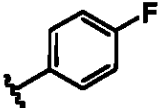
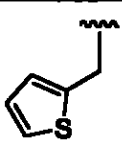
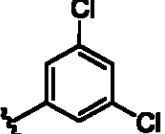
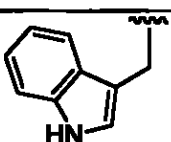
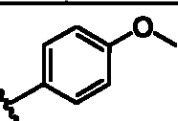
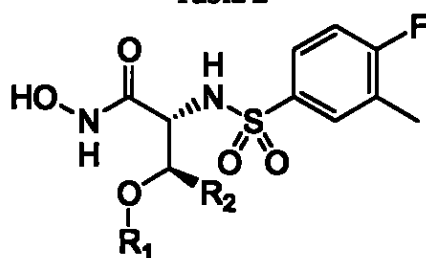
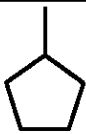
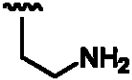
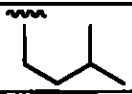
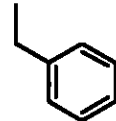
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Tabla 2



Ejemplo #	R1	R2
146		Me
147		Me

148		Me
149		H
150		Me
151		Me
152		Me
153		Me

y sales farmacéuticamente aceptables, enantiómeros, diastereómeros o ésteres hidrolizables in vivo o mezclas de ellos.

7. Un compuesto de acuerdo con la reivindicación 6 el cual se selecciona del grupo consistente en:
- 5 N-t-butoxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida;
 N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida;
 N-t-butoxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-2-(4'-tetrahidropiranyl)-acetamida;
- 10 N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-2-(4'-tetrahidropiranyl)-acetamida;
 N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-(S)-ciclopropilbutiramida; y
 sales farmacéuticamente aceptables, enantiómeros, diastereómeros o ésteres hidrolizables in vivo o mezclas de ellos.

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8. Un compuesto de acuerdo con la reivindicación 7 el cual es:
 N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-3-metilbutiramida; o
 N-hidroxi-2(R)-[(4-fluoro-3-metilfenilsulfonil)]amino-2-(4'-tetrahidropiranyl)-acetamida; o sales farmacéuticamente aceptables, enantiómeros, diastereómeros o
 20 ésteres hidrolizables in vivo o mezclas de ellos.

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9. Una composición de acuerdo con la reivindicación 1, que comprende un compuesto de fórmula I y un transportador farmacéuticamente aceptable.

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TRADUCCION OFICIAL No.2004-11-05-528 de un documento escrito en Inglés, la cual para efectos del presente lleva el sello personal de **Martha Lucia Arciniegas M.**, Traductora e Intérprete Oficial en virtud de la Res 1523 /88 del Ministerio de Justicia.

APOSTILLA

(Convención de La Haya del 5 de octubre de 1961)

1. País: Estados Unidos de América
2. Este documento público ha sido firmado por:
Cristy L. Craig
3. actuando en calidad de:
Notaria Pública de New Jersey
4. lleva el sello/estampilla de:
Cristy L. Craig, Notaria

Certificado

5. en Trenton, New Jersey
6. el día 28 de Octubre 2004
7. por: John E McCormac, CPA, Tesorero de New Jersey
8. No. **A211636**
9. Sello/estampilla:
Hay un sello dorado
10. Firma
(ilegible)

Según mi leal saber y entender, esta es una traducción fiel y completa de su original en inglés de la cual se deja copia para futuras referencias.

Martha Lucia Arciniegas
MARTHA LUCIA ARCINIEGAS M.
 TRADUCTORA E INTERPRETE OFICIAL
 RESOLUCION 1523/88 MINJUSTICIA

142

MINISTERIO DE
RELACIONES EXTERIORES

282320
Cuya firma aparece en el
documento de senpena
las funciones indicadas

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2004 NOV -9 A 8 45

LIB
JEFE DE LEGALIZACIONES
BOGOTA D.C.

Yo, **MARGARET M. DOUGHERTY**, en virtud del presente certifico bajo juramento que la fotocopia anexa de la Cesión y Acuerdo de Estados Unidos, Caso No. 21111Y intitulada: "COMPUESTOS UTILES EN EL TRATAMIENTO DE ANTRAX E INHIBIDOR DEL FACTOR LETAL" es una copia auténtica, correcta y completa del documento original sobre el cual tengo responsabilidad de custodia.

(fdo)

MARGARET M. DOUGHERTY

Socia del Grupo Senior

Suscrito y presentado bajo juramento a los 21 días de Septiembre del 2004

(fdo)

NOTARIA PUBLICA

Cristy L. Craig

Notaria Pública de New Jersey

La comisión vence el 4 Septiembre, 2006

Caso Extranjero No. 21111Y

2
144

PATENTE

No. Expediente Abogado No. 21111Y

No Serial _____

Fecha de Registro _____

CESION Y ACUERDO

Por el valor recibido, nosotros Yusheng Xiong, Kevin Chapman, Suresh Singh, Jian Guo, y Arthur A. Patchett

**de 60 Bradford Lane, Plainsboro, New Jersey 08536;
1974 Duncan Drive, Scotch Plains, New Jersey 07076;
4 Adams Road, Kendall Park, New Jersey 08824;
2128 Cheyenne Way, Scotch Plains, New Jersey, 07076; y
1090 Minisink Way, Westfield, New Jersey 07090; respectivamente**

en virtud del presente, vendemos, cedemos y transferimos a MERCK & CO, Inc. una corporación del Estado de New Jersey, con oficina en Lincoln Avenue, Ciudad de Rahway, Estado de New Jersey, y sus sucesores, cesionarios y representantes legales, todo el derecho, título e interés, para todos los países en y para ciertas invenciones relacionadas con:

W. J.

147

**COMPUESTOS UTILES EN EL TRATAMIENTO DE ANTRAX E INHIBIDOR DEL
FACTOR LETAL**

descrita en una solicitud de Patentes, que tiene el Número de Expediente de Abogado Número 21111PV y la (s) solicitud (es) No. Serial 60/383,998 registrada en 05/29/2002; No Serial _____ registrada en _____ No. Serial _____ registrada en _____ (si es aplicable)

y todos los derechos y privilegios, incluyendo cualquier y todos los beneficios bajo la Convención Internacional para la Protección de Propiedad Industrial, bajo cualquiera y todas las Patentes que puedan en consecuencia ser otorgadas y bajo cualquiera y todas las extensiones, divisiones y continuaciones de las mencionadas solicitudes de Patentes, incluyendo cualquier solicitud extranjera que se derive de allí, equivalente al mismo o que reivindique prioridad del mismo.

Nosotros solicitamos que cualquier y todas las Patentes para las mencionadas invenciones sean emitidas al mencionado cesionario, sus cesionarios y representantes legales, o a aquellos nominados, que pudieran ser designados.

Nosotros acordamos que a solicitud, sin cargo para el mencionado cesionario, firmaremos todos los documentos, tomaremos todos los juramentos de

rigor, realizaremos todos los actos que consideren necesarios, deseables o convenientes para la seguridad y mantenimiento de las Patentes para dichas invenciones en cualquiera y todos los países y para conferir el derecho al mismo título en el mencionado cesionario, sus sucesores, designados y representantes legales o nominados.

Acordamos con dicho cesionario, sus sucesores, cesionarios y representantes legales, que los derechos y propiedad por el presente transferida están libres de todo gravamen y que tenemos todo el derecho de traspasar el mismo como se expresa por el presente.

Por el presente autorizamos a nuestra apoderada Sylvia A. Ayler o a un Abogado con poder en esta solicitud de la mencionada Merck & CO., Inc para insertar el No. Serial y la Fecha de Presentación de dicha solicitud cuando se conozca.

Firmado en Rahway, NJ, este 24 de marzo, 2003 .

(firma ilegible)

Yusheng Xiong

· · ·

(firma ilegible)

Jiant Guo

(firma ilegible)

Arthur A. Patchett

CESION Y ACUERDOS

ESTADO DE NEW JERSEY)
) ss:
Condado de Union)

Comparecieron personalmente ante mí, los anteriormente nombrados
Yusheng Xiong, Jian Guo, Arthur A. Patchett

a quienes conozco y quien sé que es (son) la(s) persona(s) que ejecutaron el documento anterior y reconocieron que dicho instrumento era su propio acto y escritura libre, este día 24 de marzo, 2003.

(firma ilegible)

Notario Público de New Jersey

DAVIO R. HOOKER

La comisión vence el 12/29/2004

151

Firmado en Rahway, New Jersey, este 28 de marzo del 2003.

(firma ilegible)
Suresh Singh

ESTADO DE NEW JERSEY)
) ss:
Condado de Union)

Comparecieron personalmente ante mí, Suresh Singh
a quien conozco y quien sé que es la persona que ejecutó el documento anterior
y reconoció que dicho instrumento era su propio acto y escritura libre, este día 28
de marzo, 2003.

(firma ilegible)
Notario Público de New Jersey
DAVIO R. HOOKER
La comisión vence el 12/29/2004

Firmado en Rahway, New Jersey, este 25 de marzo del 2003.

(firma ilegible)
Kevin Chapman

ESTADO DE NEW JERSEY)
) ss:
Condado de Union)

Comparecieron personalmente ante mí, Kevin Chapman

a quien conozco y quien sé que es la persona que ejecutó el documento anterior y
reconoció que dicho instrumento era su propio acto y escritura libre, este día 25 de
marzo, 2003.

(firma ilegible)
Notario Público de New Jersey
DAVIO R. HOOKER
la comisión vence el 12/29/2004

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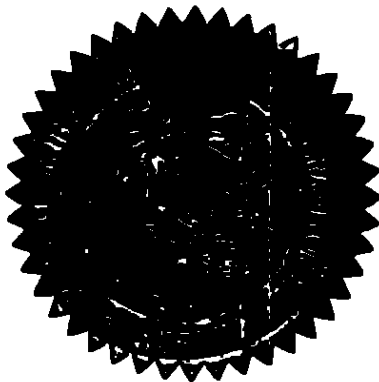
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
CRISTY L CRAIG
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
CRISTY L CRAIG, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 28TH DAY OF OCTOBER 2004
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER
8. NO. A211636
9. SEAL/STAMP:
10. SIGNATURE



John E McCormac

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I, MARGARET M. DOUGHERTY, hereby swear that the attached photocopy of:
U.S. Assignment and Agreement, Case No. 21111Y, entitled "COMPOUNDS USEFUL IN THE
TREATMENT OF ANTHRAX AND INHIBITING LETHAL FACTOR", is a true, correct, and complete
copy of the original document for which I have custodial responsibility.

Margaret M. Dougherty
MARGARET M. DOUGHERTY
SENIOR STAFF ASSOCIATE

Subscribed and sworn to before me this 21ST day of September, 2004.

Cristy L. Craig
NOTARY PUBLIC
CRISTY L. CRAIG
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires Sept. 4, 2006

Foreign Case No.: 21111Y



ASSIGNMENT AND AGREEMENT

For value received, we, Yusheng Xiong, Kevin Chapman, Suresh Singh, Jian Guo, and Arthur A. Patchett

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of 60 Bradford Lane, Plainsboro, New Jersey 08536;
 1974 Duncan Drive, Scotch Plains, New Jersey 07076;
 4 Adams Road, Kendall Park, New Jersey 08824;
 2128 Cheyenne Way, Scotch Plains, New Jersey 07076; and
 1090 Minilink Way, Westfield, New Jersey 07090; respectively

hereby sell, assign and transfer to MERCK & CO., Inc., a corporation of the State of New Jersey, having an office at Lincoln Avenue,
 City of Rahway, State of New Jersey, and its successors, assigns and legal representatives, our entire right, title and interest, for all
 countries, in and to certain inventions relating to

COMPOUNDS USEFUL IN THE TREATMENT OF ANTHRAX AND INHIBITING LETHAL FACTOR

described in an application for Patents having Attorney Docket Number 21111PV and in application(s) Serial No. 60/383,996
 filed on 05/29/2002 ; Serial No. _____ filed on _____ ; Serial No. _____ filed on _____ (if applicable),

and all our rights and privileges, including any and all benefits under the International Convention for the Protection of Industrial
 Property, under any and all Patents which may be granted therefor, and under any and all extensions, divisionals, reissues and
 continuations of said application for Patents, including any foreign applications derived therefrom, equivalent thereto or claiming
 priority thereof.

We request that any and all Patents for said inventions be issued to said assignee, its successor, assigns and legal
 representatives, or to such nominees as it may designate.

We agree that, when requested, we will, without charge to said assignee but at its expense, sign all papers, take all rightful
 oaths, and do all acts which may be necessary, desirable or convenient for securing and maintaining Patents for said inventions in any
 and all countries and for vesting title thereto in said assignee, its successors, assigns and legal representatives or nominees.

We covenant with said assignee, its successors, assigns and legal representatives, that the rights and property herein conveyed
 are free and clear of any encumbrance, and that we have full right to convey the same as herein expressed.

We hereby authorize our attorney, Sylvia A. Ayler or an attorney with Power of Attorney in this application,
 of the said MERCK & CO., Inc., to insert Serial No., (s) and Filing Date(s) of said application(s) when known.

Signed at Rahway, New Jersey this 24th day of March, 2003.

Yusheng Xiong
 Yusheng Xiong

Kevin Chapman
 Kevin Chapman

Jian Guo
 Jian Guo

Arthur A. Patchett
 Arthur A. Patchett

ASSIGNMENT AND AGREEMENT

STATE OF NEW JERSEY

County of UNION

SS.

Personally appeared before me the above-named Yusheng Xiong ~~Kevin Chapman~~ Jian Guo

Arthur A. Patchett

to me known and known to me to be the person(s) who executed the foregoing instrument and acknowledged said instrument to be their free act and deed this 24th day of March, 2003.

David R. Hogker
DAVID R. HOGKER Public
 NOTARY PUBLIC OF NEW JERSEY
 Commission Expires 12/29/2004

Signed at Rahway, New Jersey this 28th day of March, 2003.

Suresh B. Singh
 Suresh Singh

STATE OF NEW JERSEY

County of UNION

SS.

Personally appeared before me the above-named Suresh Singh

to me known and known to me to be the person(s) who executed the foregoing instrument and acknowledged said instrument to be their free act and deed this 28th day of March, 2003.

David R. Hogker
 Notary Public
DAVID R. HOGKER
 NOTARY PUBLIC OF NEW JERSEY
 Commission Expires 12/29/2004

ASSIGNMENT AND AGREEMENT

Signed at Rahway, New Jersey this 25th day of March, 2003.

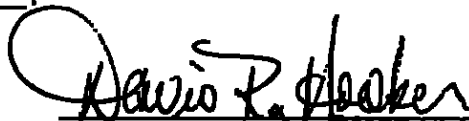
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Kevin Chapman

STATE OF NEW JERSEY }
County of UNION } SS.

Personally appeared before me the above-named Kevin Chapman

to me known and known to me to be the person(s) who executed the foregoing instrument and acknowledged said instrument to be
their free act and deed this 25th day of March, 2003.


David R. Hooker
DAVID R. HOOKER, Public
NOTARY PUBLIC OF NEW JERSEY
Commission Expires 12/28/2004

Signed at _____ this _____ day of _____, _____.

County of _____ } SS.

Personally appeared before me the above-named

to me known and known to me to be the person(s) who executed the foregoing instrument and acknowledged said instrument to be
their free act and deed this _____ day of _____, _____.

Notary Public

158

**REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT**

PATENTE DE INVENCION [x]

MODELO DE UTILIDAD []

- ◆ Indicación de que se solicita la concesión de una patente [x] 1
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud [x] 1
- ◆ Descripción de la invención [x] 92
- ◆ Dibujos de ser estos pertinentes []
- ◆ Comprobante de pago de las tasas establecidas [x] 2

COMPLETA [x]

INCOMPLETA []

DISEÑO INDUSTRIAL []

- ◆ Indicación de que se solicita el registro de Diseño Industrial []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

ESQUEMA DE TRAZADO []

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica del esquema trazado []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

Firma Responsable 

Fecha _____

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

2020
Bogotá D C

Doctor(a)
ALICIA LLOREDA RICAURTE
Apoderado(a)
MERCK & CO., INC.

REFERENCIA:	Radicación N°	04-18236
	Solicitud internacional	PCT/US03/016336
	Fecha inicio fase nacional	29/12/2004
	Trámite	011
	Evento	379
	Actuación	416
	Oficio N°	1777
	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 Decisión 486.

Cúmplase
Dado en Bogotá D C, **03 DIC. 2004**


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe División de Nuevas Creaciones.

202044