



Industria y Comercio
SUPERINTENDENCIA

OK

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCION

21. EXPEDIENTE No. **06-55450**

54. TITULO **"DERIVADO DE OXAZOL DE TETRACICLINA"**

51. CLASIFICACION INTERNACIONAL **C07D 263/52**

AG 16 31/423

71. SOLICITANTE **WYETH** **AG 1P 31/04**

DOMICILIO **NUEVA JERSEY, ESTADOS UNIDOS**

74. APODERADO **ALVARO CORREA ORONDEZ**
T.P. 20.281

22. BOGOTA, D.C., **Junio 8, 2006**

PETITORIO

000001

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-058450-00000-0000
Fax: 2006-06-08 95:57:03 Dep. 2000 NUECREACIONES
Tel: 14 PATENTEMI
Cve: 276 FARMACIOMALI
Act: 411 PRESENTACION Fecha: '70

licación

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1

SOLICITUD DE :

☒ X

Patente de Invención

☐

Patente de Modelo de Utilidad

☒ X

Capítulo I.

☐

Capítulo II.

2

SOLICITANTE
(71)

Nombre: WYETH

Dirección: Five Glaxo Farms, Madison, NJ 07940 Estados Unidos de América

Nacionalidad o Domicilio: Nueva Jersey, Estados Unidos de América
Lugar de Constitución:

Teléfono:

Fax:

E-Mail:

IDENTIFICACION

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Cual

Número

3

REPRESENTANTE
O APODERADO

Nombre: ALVARO CORREA ORDOÑEZ

Dirección: Avenida 82 No. 10-02 Piso 6

Teléfono: 634 1500

Fax: 376 2211

E-Mail: office.bogota@bakernet.com

IDENTIFICACION

C.C.

☒ X

NIT

☐

C.E.

☐

Otro

☐

Cual

Número 79.103.281.464 TP 20.231

4

INVENTOR (ES)
(72)

Nombre: SUM, Phyllis-King; HOW, David Brian; HOPPER, Darrin William; VERA, Matthew Douglas; SABATINI, Joshua James

Dirección: 16 Chamberlain Court, Pomona, NY 10970 (US); 10 High Avenue, Nyack, NY 10960 (US); 201 West 101 St Street, Apt. 5A, New York, NY 10025 (US); 1201 Morgan Drive, Raystown, PA 15468 (PA); 3 Old Manumet Road, Apt. 5A, White Plains, NY 10605 (US)

Nacionalidad o Domicilio: Canadiense, canadiense, estadounidense, estadounidense y estadounidense, respectivamente

5

PCT (86)

Solicitud Internacional No. PCT/US2004/048830

Fecha 07-DIC-04

Publicación Internacional No. WO 2005/056538 A1

Fecha 23-JUN-05

6

Título (54)

DERIVADOS DE OXAZOL DE TETRACICLINA

7

Clasificación Internacional (51)

C07D 263/52, C07C 237/26, A61K 31/423, A61P 31/04

8

Prioridad

SI ☒ X

NO ☐

(33) País de Origen

US

US

(32) Fecha

08-DIC-03

01-JUL-04

(31) Número de Solicitud

68/527.928

68/514.823

9

Comprobante de pago No. 95-41395

Fecha 02-JUN-06

10

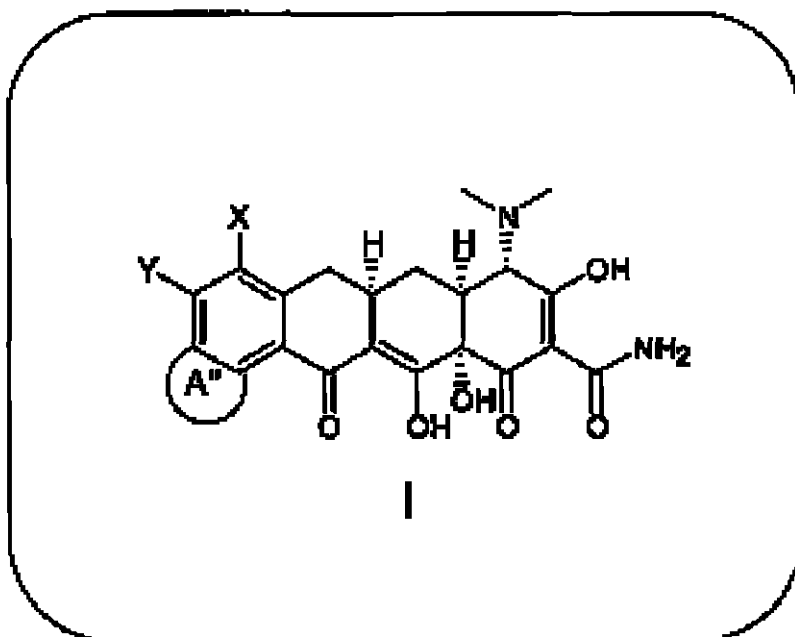
ANEXOS

2

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica
- ☐ Poderes, si fuere el caso
- ☒ 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, dibujos)
- ☐ 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 acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arta final 12 x 12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros: Extracción publicación, propietario y temático, reporte de búsqueda

11

FIGURA CARACTERÍSTICA



12

Solicito la concesión de la patente.

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 70.143.346 de Usaquén T.P. 20.281

Instrucciones para la presentación de los anexos, ver reverso de esta página

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 08-055450-00000-0000
Fec: 2008-08-08 15:57:03 Dep. 2020 NUECREACIONES
Tm. 11 PATENTEYS
Enc: 878 FASENACIONALI
Act: 411 PRESENTACION Folios: 70

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 41,393
FECHA : JUNIO 2 DE 2006

CONSIGNACION

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PBO	Vr. PAGO
RATSECK LARA RODRIGUEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	36559816	02/06/2006	30,657,000.00

CONCEPTO

CANT. CONTABILITICO	CONCEPTO	TOTAL CONCEPTO
1 30005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	443,000.00
	TOTAL :	443,000.00

SUM: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : 

TRADUCCIÓN OFICIAL No. 209/06 de un documento escrito en inglés, el cual para su identificación se sella con el sello del Traductor. Esta es una Traducción Oficial efectuada el día 5 de junio de 2006 por la Sra. María Teresa Lara, c.c. 41.568.055 de Bogotá, Traductora Oficial según Resolución No. 01016 del 2 de octubre de 1998, expedida por el Ministerio de Justicia.

=====

Declaración Juramentada (Affidavit) de WYETH respecto de solicitud de patente para "Derivados Oxazol de Tetraciclinas". Certificación notarial suscrita por Barbara A. Kiely, Notario Público del estado de Nueva Jersey, y legalizaciones subsiguientes.

AM101558 L1

DECLARACIÓN JURAMENTADA

Yo, Michelle L. McGowan, certifico por la presente que la copia adjunta ha sido comparada contra la Cesión original (expediente de Wyeth no. AM101558 L1 correspondiente a la U.S.S.N. 60/527,928, y cualquier equivalente legal de la misma en un país extranjero, para el invento titulado: "DERIVADOS OXAZOL DE TETRACICLINAS") fechada el 3 de diciembre de 2004 de Phaik-Eng Sum, David Brian How, Darrin William Hopper y Matthew Douglas Vera; y fechada el 4 de diciembre de 2003 de Joshua James Sabatini a Wyeth y que la citada copia es fiel copia del original.

Dado a los 8 días del mes de febrero de 2006, en Madison, Nueva Jersey, Estados Unidos de América.

(Fdo.) Michelle L. McGowan

Michelle L. McGowan

PARA USO EN COLOMBIA


 MARIA TERESA LARA R.
 TRADUCTORA OFICIAL
 RESOLUCION No. 01016
 DEL MINISTERIO DE JUSTICIA

RECONOCIMIENTO

Estado de Nueva Jersey)
)
Condado de Morris)

A los 8 días del mes de febrero de 2006, ante mí personalmente compareció Michelle L. McGowan, a quien conozco y de quien me consta que es la persona descrita en el instrumento anterior y quien lo suscribió, y reconoció ante mí haber suscrito el mismo.

(Fdo.) Barbara A. Kiely
Notario Público

(Sello notarial
en relieve)

[Sello] Barbara A. Kiely ID. 33893
 Notario Público de Nueva Jersey
 Mi comisión expira el 20 de junio de 2009

BARBARA TERESA IQUA R.
TRADUCTORA OFICIAL
RECONOCIDA POR EL ESTADO
DE NEW JERSEY

Expediente No: AM101558 L1
Patente

Para: ☒ Derechos en los E.U. y/o ☒ Extranjeros
Para: ☒ Solicitud en los E.U. o ☐ Patente de los E.U.

Cesión de Invento

En virtud del pago por la CESIONARIA al CEDENTE de contraprestación válida, el recibo de la cual se reconoce por el presente, el CEDENTE:

(1) Nombre Completo del Inventor: Phaik-Eng SUM
Residencia: 16 Chamberlain Court, Pomona, NY 10970
Ciudadanía: Canadiense

(2) Nombre Completo del Inventor: David Brian HOW
Residencia: 10 High Avenue, Nyack, NY 10960
Ciudadanía: Canadiense

(3) Nombre Completo del Inventor: Darrin William HOPPER
Residencia: 201 West 101st Street, Apt. 5A, New York, NY 10025
Ciudadanía: Estados Unidos de América

(4) Nombre Completo del Inventor: Matthew Douglas VERA
Residencia: 31 Kennedy Drive, West Haverstraw, NY 10993
Ciudadanía: Estados Unidos de América

(5) Nombre Completo del Inventor: Joshua James SABATINI
Residencia: 3 Old Mamaroneck Road, Apt. 5E, White Plains, NY 10605
Ciudadanía: Estados Unidos de América

por la presente vende, cede y traspasa a la CESIONARIA:

Wyeth
Five Giralda Farms
Madison, Nueva Jersey 07940

y los sucesores, cesionarios y representantes legales de la CESIONARIA, todo derecho, título e interés para los Estados Unidos y sus posesiones territoriales y en todos los países extranjeros, incluyendo todo los derechos a reclamar prioridad, en y sobre el invento titulado:

DERIVADOS OXAZOL DE TETRACICLINAS

e inventado por el CEDENTE y los siguientes inventores adicionales, en caso de haberlos:

y la cual se encuentra en

[marcar y completar (a), (b), (c), (d) o (e)]

- (a) ☐ solicitud de patente de los E.U. de igual fecha que la presente
(b) ☐ solicitud de patente de los E.U. suscrita el:

TRADUCCION OFICIAL
DE LA
"LAW OFFICE OF
JAMES M. LUDWIG"
"LAW OFFICE OF
JAMES M. LUDWIG"

(c) ☒ solicitud provisional de los E.U., no presentada aún, que nombra al(los) inventor(es) anterior(es) para el invento de la referencia

(d) ☐ ☒ etiqueta de correo expreso no.: EU673382117US
Solicitud de Patente de los E.U. No. presentada el:

(e) ☐ Patente de los E.U. No. expedida el:

[marcar también si se están cediendo solicitud(es) extranjera(s)]

(f) ☒ y cualquier equivalente legal de las mismas en un país extranjero,

Incluyendo el derecho a reclamar prioridad, incluidas todas y cada una de las mejoras allí divulgadas, y en y sobre todas las Patentes que hayan de obtenerse para dicho invento en virtud de la solicitud anterior o cualquier solicitud provisional, no provisional, de continuación, divisional, de renovación o sustituta de la misma posteriormente presentada, y respecto de Patentes cualquier reemisión o reexamen de las mismas.

El CEDENTE pacta por el presente que no se ha hecho ni se hará ni se realizará ninguna cesión, venta, acuerdo o gravamen que pudiese entrar en conflicto con esta cesión.

El CEDENTE autoriza a la CESIONARIA a presentar solicitudes y recibir Patentes para dicho invento en cualquiera de dichos países en su propio nombre, o en nombre de la CEDENTE, a su elección.

El CEDENTE pacta y acuerda suscribir u obtener cualquier garantía adicional necesaria del título sobre dicho invento y cualquier Patente que pueda emitirse para la misma, en cualquier momento, y a solicitud y por cuenta de la CESIONARIA entregar cualquier testimonio en cualquier interferencia, litigio o proceso relacionado con la misma y otorgar todos los

documentos que puedan ser necesarios o convenientes para perfeccionar el título sobre dicho invento o cualquier Patente que pueda otorgarse para la misma en la CESIONARIA, sus sucesores, cesionarios u otros representantes legales y que, en cualquier momento, a solicitud y por cuenta de la CESIONARIA suscriba cualquier continuación, continuación en parte, solicitud divisional, renovación o sustituta de la misma, y en cuanto a Patentes y reemisión o reexamen de las mismas, o cualquier otra solicitud adicional de Patente para dicho invento o cualquier parte del mismo, todas las cuales solicitudes y cualesquiera Patentes que se expidan sobre las mismas son por la presente cedidas a la CESIONARIA, y hará todo los juramentos o declaraciones lícitos, y realizará todo los actos lícitos requeridos para adquirir las mismas, sin otra compensación, pero por cuenta de la CESIONARIA, sus sucesores, cesionarios u otros representantes legales.

El CEDENTE autoriza y solicita al Comisionado de Patentes expedir todas y cada una de las Patentes de los Estados Unidos para dicho invento, resultantes de cualquiera de las anteriores solicitudes para su CESIONARIA.

(Fdo.) Phalk-Eng SUM
Phalk-Eng SUM

Diciembre 3, 2003
Fecha

RECONOCIMIENTO

Estado de Nueva York }
 ss:
Condado de Rockland }

A los 3 días del mes de diciembre de 2004, compareció personalmente ante mí Phalk-Eng SUM, a quien conozco como la misma persona descrita y que otorgó el instrumento anterior, y reconoció haber otorgado el mismo, por su propia voluntad y para los propósitos allí señalados.

ANNA TERESA IBAÑEZ R.
TRADUCTORA OFICIAL
RESOLUCION No. 2110
DE LA JUDICATURA

(Fdo.) Janice A. White
Notario Público

[Sello] JANICE A. WHITE
NOTARIO PÚBLICO-ESTADO DE NUEVA YORK
NO. 01-WH6052604
HABILITADA EN EL CONDADO DE ROCKLAND
MI COMISIÓN EXPIRA 12-26-2006

(Fdo.) David Brian HOW
David Brian HOW

Diciembre 3, 2003
Fecha

RECONOCIMIENTO

Estado de Nueva York }
ss:
Condado de Rockland }

A los 3 días del mes de diciembre de 2003, compareció personalmente ante mí David Brian HOW, a quien conozco como la misma persona descrita y que otorgó el Instrumento anterior, y reconoció haber otorgado el mismo, por su propia voluntad y para los propósitos allí señalados.

(Fdo.) Janice A. White
Notario Público

[Sello] JANICE A. WHITE
NOTARIO PÚBLICO-ESTADO DE NUEVA YORK
NO. 01-WH6052604
HABILITADA EN EL CONDADO DE ROCKLAND
MI COMISIÓN EXPIRA 12-26-2006

(Fdo.) Darrin William Hopper
Darrin William HOPPER

Diciembre 3, 2003
Fecha

RECONOCIMIENTO

TERESA LARA R.
TRADUCTORA OFICIAL
REGISTRADA EN EL ESTADO DE N.Y.
EN INSTRUMENTOS

Estado de Nueva York }
 ss:
Condado de Rockland }

A los 3 días del mes de diciembre de 2003, compareció personalmente ante mí
Darrín William HOPPER, a quien conozco como la misma persona descrita y
que otorgó el instrumento anterior, y reconoció haber otorgado el mismo, por
su propia voluntad y para los propósitos allí señalados.

(Fdo.) Janice A. White
Notario Público

[Sello] JANICE A. WHITE
NOTARIO PÚBLICO-ESTADO DE NUEVA YORK
NO. 01-WH8052604
HABILITADA EN EL CONDADO DE ROCKLAND
MI COMISIÓN EXPIRA 12-26-2006

(Fdo.) Matthew Douglas Vera
Matthew Douglas VERA

Diciembre 3, 2003
Fecha

RECONOCIMIENTO

Estado de New York }
 ss:
Condado de Rockland }

A los 3 días del mes de diciembre de 2003, compareció personalmente ante mí
Matthew Douglas VERA, a quien conozco como la misma persona descrita y
que otorgó el instrumento anterior, y reconoció haber otorgado el mismo, por
su propia voluntad y para los propósitos allí señalados.

(Fdo.) Janice A. White
Notario Público

[Sello] JANICE A. WHITE
NOTARIO PÚBLICO-ESTADO DE NUEVA YORK
NO. 01-WH6052604
HABILITADA EN EL CONDADO DE ROCKLAND
MI COMISIÓN EXPIRA 12-26-2006

TERESA LARA R.
TRADUCTORA OFICIAL
RECONOCIMIENTO No. 209/06
JULIO AGUIRRE

(Fdo.) Joshua James Sabatini
Joshua James SABATINI

Diciembre 4, 2004
Fecha

RECONOCIMIENTO

Estado de Nueva York }
 ss:
Condado de Rockland }

A los 4 días del mes de diciembre de 2003, compareció personalmente ante mí
Joshua James SABATINI, a quien conozco como la misma persona descrita y
que otorgó el instrumento anterior, y reconoció haber otorgado el mismo, por
su propia voluntad y para los propósitos allí señalados.

(Fdo.) Janice A. White
Notario Público

[Sello] JANICE A. WHITE
NOTARIO PÚBLICO-ESTADO DE NUEVA YORK
NO. 01-YMH6062804
HABILITADA EN EL CONDADO DE ROCKLAND
MI COMISIÓN EXPIRA 12-28-2006

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. País: Estados Unidos de América
2. Este documento público ha sido firmado por: Barbara A. Klely
3. actuando en calidad de: Notario Público de Nueva Jersey
4. lleva el sello/timbre de: Barbara A. Klely, Notario

CERTIFICADO

5. en Trenton, Nueva Jersey
6. el día 10 de febrero de 2006
7. por Bradley I. Abelow, TESORERO DE NUEVA JERSEY

...HA TERESA LIDA E.
TRADUCTORA OFICIAL
REGISTRADA EN EL
OFICIO DE NOTARÍA

8. No. A251417

9. Sello/Timbre:

(Sello del Estado
de Nueva Jersey)

10. Firma

(Fdo.) Bradley Abelow

=====

La anterior es traducción fiel y completa del documento en referencia, de la cual se deja copia en este archivo para su confrontación.



María Teresa Lara R.
c.c. 41.568.055 de Bogotá
Traductora Oficial según
Resolución No. 01016 del
2 de octubre de 1998, del
Ministerio de Justicia



MARÍA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCIÓN No. 01016
DE OCTUBRE DE 1998
DE JUSTICIA

APOSTILLE

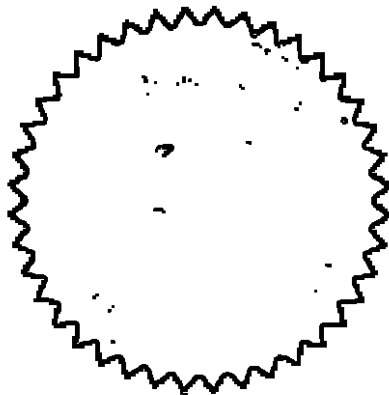
(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

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

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 10TH DAY OF FEBRUARY 2006
7. BY: Bradley I. Abelow, NEW JERSEY TREASURER
8. NO. A251417
9. SEAL/STAMP:
10. SIGNATURE

Bradley Abelow



Teresa Salas

TERESA SALAS R.
TRADUCTORA OFICIAL
REGISTRADA EN EL
DEPARTAMENTO

209/06

AM101558 L1

AFFIDAVIT

I, Michelle L. McGowan, do hereby certify that the attached copy has been compared with the original Assignment (Wyeth's docket no. AM101558 L1 corresponding to U.S.N. 60/527,928, and any legal equivalent thereof in a foreign country, for the invention entitled: "OXAZOLE DERIVATIVES OF TETRACYCLINES") dated December 3, 2004 from Phalk-Eng Sum, David Brian How, Darin William Hopper and Matthew Douglas Vera; and dated December 4, 2003 from Joshua James Sabatini to Wyeth and that the said copy is a true copy of the original.

Dated this 8th day of February, 2006, at Madison, New Jersey, United States of America.

Michelle L. McGowan
Michelle L. McGowan

TO BE USED IN COLOMBIA

ACKNOWLEDGMENT

State of New Jersey)
)
County of Morris)

On this 8th day of February, 2006, before me personally appeared Michelle L. McGowan, to me known and known to me to be the individual described in and who executed the foregoing instrument, and he acknowledged to me that he executed the same.

Barbara A. Kieley
Notary Public

Barbara A. Kieley ID. 33893
Notary Public of New Jersey
My Commission Expires June 20, 2009

For: ☒ U.S. and/or ☒ Foreign Rights
For: ☒ U.S. Application or ☐ U.S. Patent

Assignment of Invention

In consideration of the payment by ASSIGNEE to ASSIGNOR of good and valuable consideration, the receipt of which is hereby acknowledged,
ASSIGNOR:

(1) Full Name of Inventor: Phalk-Eng SUM
Residence: 16 Chamberlain Court, Pomona, NY 10970
Citizenship: Canadian

(2) Full Name of Inventor: David Brian HOW
Residence: 10 High Avenue, Nyack, NY 10960
Citizenship: Canadian

(3) Full Name of Inventor: Darrin William HOPPER
Residence: 201 West 101st Street, Apt. 5A, New York, NY 10026
Citizenship: United States of America

(4) Full Name of Inventor: Matthew Douglas VERA
Residence: 31 Kennedy Drive, West Haverstraw, NY 10993
Citizenship: United States of America

(5) Full Name of Inventor: Joshua James SABATINI
Residence: 3 Old Mamaroneck Road, Apt. 5E, White Plains, NY 10606
Citizenship: United States of America

(6) Full Name of Inventor:
Residence:
Citizenship:

hereby sells, assigns and transfers to ASSIGNEE:

Wyeth
Five Giralda Farms
Madison, New Jersey 07940

and the successors, assigns and legal representatives of the ASSIGNEE the entire right, title and interest for the United States and its territorial possessions and in all foreign countries, including all rights to claim priority, in and to the invention entitled:
OXAZOLE DERIVATIVES OF TETRACYCLINES

and invented by ASSIGNOR and the following additional inventors, if any:

and which is found in

[check and complete (a), (b), (c), (d) or (e)]

- (a) ☐ U.S. patent application executed on even date herewith.
 (b) ☐ U.S. patent application executed on:
 (c) ☒ U.S. provisional application, not yet filed, naming the above inventor(s) for the above-entitled invention
 ☒ Express mail label no.: EU673382117US
 (d) ☐ U.S. Patent Application No. filed on:
 (e) ☐ U.S. Patent No. issued on:

[also check (f) if foreign application(s) is(are) also being assigned]

- (f) ☒ and any legal equivalent thereof in a foreign country,

including the right to claim priority, including any and all improvements disclosed therein, and in and to all Letters Patent to be obtained for said invention by the above application or any subsequently filed provisional, nonprovisional, continuation, divisional, renewal, or substitute thereof, and as to Letters Patent any reissue or re-examination thereof.

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment.

ASSIGNOR authorizes ASSIGNEE to make applications for and to receive Letters patent for said invention in any of said countries in its own name, or in ASSIGNOR's name, at its election.

ASSIGNOR covenants and agrees to execute or procure any further necessary assurance of the title to said invention and any Letters Patent which may issue therefore and to, at any time, upon the request and at the expense of ASSIGNEE deliver any testimony in any interference, litigation or proceeding related thereto and execute all papers that may be necessary or desirable to perfect the title to said invention or any Letters Patent which may be granted therefore in ASSIGNEE, its successors, assigns or other legal representatives, and that to, at any time, upon the request and at the expense of ASSIGNEE execute any continuation, continuation-in-part, divisional, renewal or substitute thereof, and as to Letters Patent and reissue or re-examination thereof, or any other additional applications of Letters Patent for said invention or any part thereof, all of which applications and any Letters Patent issuing thereon are hereby assigned to ASSIGNEE, and will make all rightful oaths or declarations, and do all lawful acts requisite for procuring the same therein, without further compensation, but at the expense of ASSIGNEE, its successors, assigns or other legal representatives.

ASSIGNOR authorizes and requests the Commissioner of Patents to issue any and all Letters Patent of the United States for said Invention, resulting from any of the aforesaid applications to its ASSIGNEE.

Phalk-Eng SUM
Phalk-Eng SUM

Dec 3, 2003
Date

ACKNOWLEDGMENT

State of New York)
County of Rockland) ss:

On the 3rd day of December, 2003, Phalk-Eng SUM personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

JANICE A. WHITE
NOTARY PUBLIC - STATE OF NEW YORK
NO. 11-1440052004
QUALIFIED IN ROCKLAND COUNTY
MY COMMISSION EXPIRES 12-28-2006

Janice A. White
Notary Public

David Brian HOW
David Brian HOW

December 3, 2003
Date

ACKNOWLEDGMENT

State of New York)
County of Rockland) ss:

On the 3rd day of December, 2003, David Brian HOW personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

Janice A. White
Notary Public

JANICE A. WHITE
NOTARY PUBLIC - STATE OF NEW YORK
NO. 11-1440052004
QUALIFIED IN ROCKLAND COUNTY
MY COMMISSION EXPIRES 12-28-2006

Darin William Hopper
 Darin William HOPPER

12/3/03
 Date

ACKNOWLEDGMENT

State of New York)
) ss:
 County of Rockland)

On the 3rd day of December 2003, Darin William HOPPER personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

JANICE A. WHITE
 NOTARY PUBLIC - STATE OF NEW YORK
 NO. 01-WH052804
 QUALIFIED IN ROCKLAND COUNTY
 MY COMMISSION EXPIRES 12-26-2006

Janice A. White
 Notary Public

Matthew Douglas VERA
 Matthew Douglas VERA

December 3, 2003
 Date

ACKNOWLEDGMENT

State of New York)
) ss:
 County of Rockland)

On the 3rd day of December 2003, Matthew Douglas VERA personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

Janice A. White
 Notary Public

JANICE A. WHITE
 NOTARY PUBLIC - STATE OF NEW YORK
 NO. 01-WH052804
 QUALIFIED IN ROCKLAND COUNTY
 MY COMMISSION EXPIRES 12-26-2006

Joshua James SABATINI

12/4/03
Date

ACKNOWLEDGMENT

State of New York }
County of Rockland } ss:

On the 4th day of December 2003, Joshua James SABATINI personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

JANICE A. WHITE
NOTARY PUBLIC - STATE OF NEW YORK
NO. 01-1446152004
QUALIFIED IN ROCKLAND COUNTY
MY COMMISSION EXPIRES 12/31/2004

Janice A. White
Notary Public

Date

ACKNOWLEDGMENT

State of _____ }
County of _____ } ss:

On the _____ day of _____ 2003, _____ personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

Notary Public

TRADUCCIÓN OFICIAL No. 210/06 de un documento escrito en Inglés, el cual para su identificación se sella con el sello del Traductor. Esta es una Traducción Oficial efectuada el día 5 de junio de 2006 por la Sra. María Teresa Lara, c.c. 41.568.055 de Bogotá, Traductora Oficial según Resolución No. 01016 del 2 de octubre de 1998, expedida por el Ministerio de Justicia.

=====

Declaración Juramentada (Affidavit) de WYETH respecto de solicitud de patente para "Derivados Oxazol de Tetraciclinas". Certificación notarial suscrita por Barbara A. Klely, Notario Público del estado de Nueva Jersey, y legalizaciones subsiguientes.

AM101558 L2

DECLARACIÓN JURAMENTADA

Yo, Michelle L. McGowan, certifico por la presente que la copia adjunta ha sido comparada contra la Cesión original (para la U.S.S.N. 60/584,823, y cualquier equivalente legal de la misma en un país extranjero, para el invento titulado: "DERIVADOS OXAZOL DE TETRACICLINAS") fechada el 27 de julio de 2004 de Phaik-Eng Sum, David Brian How, Darrin William Hopper y Joshua James Sabatini; y fechada el 29 de julio de 2004 de Matthew Douglas Vera a Wyeth y que la citada copia es fiel copia del original.

Dado a los 8 días del mes de febrero de 2006, en Madison, Nueva Jersey, Estados Unidos de América.

Wyeth

(Fdo.) Michelle L. McGowan

Michelle L. McGowan

PARA USO EN COLOMBIA

MARIA TERESA LARA B.
TRADUCTORA OFICIAL
RESOLUCION 74.11613
DE BOGOTA

RECONOCIMIENTO

Estado de Nueva Jersey)
)
 Condado de Morris)

A los 8 días del mes de febrero de 2006, ante mí personalmente compareció Michelle L. McGowan, a quien conozco y de quien me consta que es la persona descrita en el instrumento anterior y quien lo suscribió, y reconoció ante mí haber suscrito el mismo.

(Fdo.) Barbara A. Klely
Notario Público

(Sello notarial
en relieve)

[Sello] Barbara A. Kleiy ID. 33893
Notario Público de Nueva Jersey
MI comisión expira el 20 de junio de 2009

Expediente No: AM101558 L2
Patente

Cesión de Inventario

En virtud del pago por la CESIONARIA al CEDENTE de contraprestación válida, el recibo de la cual se reconoce por el presente, el CEDENTE:

- (1) **Nombre Completo del Inventor:** Phalk-Eng SUM
Residencia: 16 Chamberlain Court, Pomona, NY 10970
Ciudadanía: Canadiense

- (2) Nombre Completo del Inventor: David Brian HOW
Residencia: 10 High Avenue, Nyack, NY 10960
Ciudadanía: Canadiense

(3) **Nombre Completo del Inventor: Darrin William HOPPER**
Residencia: 201 West 101st Street, Apt. 5A, New York, NY 10025
Ciudadanía: Estados Unidos de América

(4) **Nombre Completo del Inventor: Matthew Douglas VERA**
Residencia: 1201 Morgan Drive, Royersford, PA 19468
Ciudadanía: Estados Unidos de América

(5) **Nombre Completo del Inventor: Joshua James SABATINI**
Residencia: 3 Old Mamaroneck Road, Apt. 5E, White Plains, NY 10605
Ciudadanía: Estados Unidos de América

por la presente vende, cede y traspasa a la CESIONARIA:

Wyeth
Five Giralda Farms
Madison, Nueva Jersey 07940

y los sucesores, cesionarios y representantes legales de la CESIONARIA, todo derecho, título e Interés para los Estados Unidos y sus posesiones territoriales y en todos los países extranjeros, incluyendo todo los derechos a reclamar prioridad, en y sobre el invento titulado:

DERIVADOS OXAZOL DE TETRACICLINAS

e inventado por el CEDENTE y los siguientes inventores adicionales, en caso de haberlos:

y la cual se encuentra en la Solicitud Provisional de los E.U. No. 60/584,823 presentada el: 1 de julio de 2004

[marcar también si se están cediendo solicitud(es) extranjera(s)]

[X] y cualquier equivalente legal de las mismas en un país extranjero,

la fecha de presentación y número de solicitud de dicha solicitud de los Estados Unidos, al conocerse, deberá insertarse arriba, incluido el derecho a

TERESA IUBA R.
TRADUCTORA OFICIAL
REGISTRADA EN EL
MINISTERIO DE INTERIO

reclamar prioridad, incluyendo todas y cada una de las mejoras divulgadas en la misma, y en y sobre todas las Patentes que hayan de obtenerse para dicho invento mediante la anterior solicitud o cualquier solicitud provisional, no provisional, de continuación, divisional, de renovación o sustituta de la misma posteriormente presentada, y respecto de Patentes cualquier reemisión o reexamen de las mismas.

El CEDENTE pacta por el presente que no se ha hecho ni se hará ni se realizará ninguna cesión, venta, acuerdo o gravamen que pudiese entrar en conflicto con esta cesión.

El CEDENTE autoriza a la CESIONARIA a presentar solicitudes y recibir Patentes para dicho invento en cualquiera de dichos países en su propio nombre, o en nombre de la CEDENTE, a su elección.

El CEDENTE pacta y acuerda suscribir u obtener cualquier garantía adicional necesaria del título sobre dicho invento y cualquier Patente que pueda emitirse para la misma, en cualquier momento, y a solicitud y por cuenta de la CESIONARIA entregar cualquier testimonio en cualquier Interferencia, litigio o proceso relacionado con la misma y otorgar todos los documentos que puedan ser necesarios o convenientes para perfeccionar el título sobre dicho invento o cualquier Patente que pueda otorgarse para la misma en la CESIONARIA, sus sucesores, cesionarios u otros representantes legales y que, en cualquier momento, a solicitud y por cuenta de la CESIONARIA suscriba cualquier continuación, continuación en parte, solicitud divisional, renovación o sustituta de la misma, y en cuanto a Patentes y reemisión o reexamen de las mismas, o cualquier otra solicitud adicional de Patente para dicho invento o cualquier parte del mismo, todas las cuales solicitudes y cualesquiera Patentes que se explidan sobre las mismas son por

LA TERCERA PARTE DE
TRADUCCION OFICIAL
DE LA SOLUCION No. 210/06

la presente cedidas a la CESIONARIA, y hará todo los juramentos o declaraciones lícitos, y realizará todo los actos lícitos requeridos para adquirir las mismas, sin otra compensación, pero por cuenta de la CESIONARIA, sus sucesores, cesionarios u otros representantes legales.

El CEDENTE autoriza y solicita al Comisionado de Patentes expedir todas y cada una de las Patentes de los Estados Unidos para dicho Invento, resultantes de cualquiera de las anteriores solicitudes para su CESIONARIA.

(Fdo.) Phalk-Eng SUM
Phalk-Eng SUM

Julio 27, 2004
Fecha

RECONOCIMIENTO

Estado de Nueva York }
ss:
Condado de Rockland }

A los 27 días del mes de julio de 2004, compareció personalmente ante mí Phalk-Eng SUM, a quien conozco como la misma persona descrita y que otorgó el instrumento anterior, y reconoció haber otorgado el mismo, por su propia voluntad y para los propósitos allí señalados.

(Fdo.) Janice A. White
Notario Público

[Sello] JANICE A. WHITE
NOTARIO PÚBLICO-ESTADO DE NUEVA YORK
NO. 01-WH6052804
HABILITADA EN EL CONDADO DE ROCKLAND
MI COMISIÓN EXPIRA 12-26-2008

(Fdo.) David Brian HOW
David Brian HOW

Julio 27, 2004
Fecha

000018
25

RECONOCIMIENTO

Estado de Nueva York }
 ss:
Condado de Rockland }

A los 27 días del mes de julio de 2004, compareció personalmente ante mí David Brian HOW, a quien conozco como la misma persona descrita y que otorgó el instrumento anterior, y reconoció haber otorgado el mismo, por su propia voluntad y para los propósitos allí señalados.

(Fdo.) Janice A. White
Notario Público

[Sello] JANICE A. WHITE
NOTARIO PÚBLICO-ESTADO DE NUEVA YORK
NO. 01-WH6052604
HABILITADA EN EL CONDADO DE ROCKLAND
MI COMISIÓN EXPIRA 12-26-2006

TRADUCCIÓN PARA EL
GOBIERNO DE LOS
ESTADOS UNIDOS
DE AMÉRICA

(Fdo.) Darrin William Hopper
Darrin William HOPPER

Julio 27, 2004
Fecha

RECONOCIMIENTO

Estado de Nueva York }
 ss:
Condado de Rockland }

A los 27 días del mes de julio de 2004, compareció personalmente ante mí Darrin William HOPPER, a quien conozco como la misma persona descrita y que otorgó el instrumento anterior, y reconoció haber otorgado el mismo, por su propia voluntad y para los propósitos allí señalados.

(Fdo.) Janice A. White
Notario Público

000018
26

[Sello] JANICE A. WHITE
NOTARIO PÚBLICO-ESTADO DE NUEVA YORK
NO. 01-WH8052804
HABILITADA EN EL CONDADO DE ROCKLAND
MI COMISIÓN EXPIRA 12-26-2006

(Fdo.) Matthew Douglas Vera
Matthew Douglas VERA

Julio 29, 2004
Fecha

RECONOCIMIENTO

Estado de Pennsylvania }
ss:
Condado de Montgomery }

A los 29 días del mes de julio de 2004, compareció personalmente ante mí
Matthew Douglas VERA, a quien conozco como la misma persona descrita y
que otorgó el instrumento anterior, y reconoció haber otorgado el mismo, por
su propia voluntad y para los propósitos allí señalados.

(Fdo.) Cynthia J. Tagliaferi
Notario Público

[Sello] SELLO NOTARIAL
CYNTHIA J. TAGLIAFERI, Notario Público
Mplo. de Collegeville, Condado de Montgomery
MI comisión expira el 19 de septiembre de 2006

(Fdo.) Joshua James Sabatini
Joshua James SABATINI

Julio 27, 2004
Fecha

RECONOCIMIENTO

Estado de Nueva York }
ss:
Condado de Rockland }

A los 27 días del mes de julio de 2004, compareció personalmente ante mí
Joshua James SABATINI, a quien conozco como la misma persona descrita y



María Teresa Lara R.
c.c. 41.568.055 de Bogotá
Traductora Oficial según
Resolución No. 01016 del
2 de octubre de 1998, del
Ministerio de Justicia



MARIA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 01016
del 2 de octubre de 1998

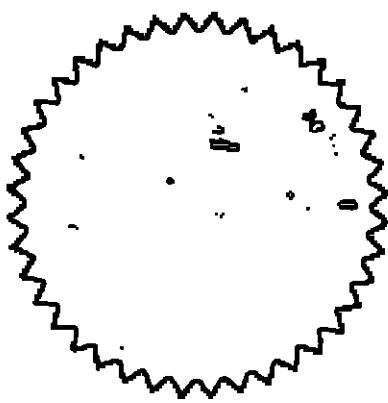
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

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

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 10TH DAY OF FEBRUARY 2006
7. BY: Bradley I. Abelow, NEW JERSEY TREASURER
8. NO. A251418
9. SEAL/STAMP:
10. SIGNATURE

Bradley Abelow

Disculpa.

MARIA TERESA LARA R.
TRADUCTORA CERTIF.
RESOLUCION N.º 21012
DE MINISTERIO

210/06

AM101558 L2

AFFIDAVIT

I, Michelle L. McGowan, do hereby certify that the attached copy has been compared with the original Assignment (For U.S.S.N. 60/584,823, and any legal equivalent thereof in a foreign country, for the invention entitled: "OXAZOLE DERIVATIVES OF TETRACYCLINES") dated July 27, 2004 from Phaik-Eng Sum, David Brian How, Darrin William Hopper and Joshua James Sabatini; and dated July 29, 2004 from Matthew Douglas Vera to Wyeth and that the said copy is a true copy of the original.

Dated this 8th day of February, 2006, at Madison, New Jersey, United States of America.

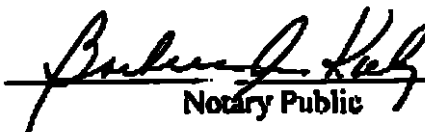

Michelle L. McGowan

TO BE USED IN COLOMBIA

ACKNOWLEDGMENT

State of New Jersey)
)
County of Morris)

On this 8th day of February, 2006, before me personally appeared Michelle L. McGowan, to me known and known to me to be the individual described in and who executed the foregoing instrument, and he acknowledged to me that he executed the same.


Notary Public

Barbara A. Kiely ID. 33893
Notary Public of New Jersey
My Commission Expires June 20, 2009

Assignment of Invention

In consideration of the payment by ASSIGNEE to ASSIGNOR of good and valuable consideration, the receipt of which is hereby acknowledged,
ASSIGNOR:

- (1) Full Name of Inventor: Phaik-Eng SUM
Residence: 18 Chamberlain Court, Pomona, NY 10970
Citizenship: Canadian
-
- (2) Full Name of Inventor: David Brian HOW
Residence: 10 High Avenue, Nyack, NY 10960
Citizenship: Canadian
-
- (3) Full Name of Inventor: Darrin William HOPPER
Residence: 201 West 101st Street, Apt. 5A, New York, NY 10025
Citizenship: United States of America
-
- (4) Full Name of Inventor: Matthew Douglas VERA
Residence: 1201 Morgan Drive, Royersford, PA 19468
Citizenship: United States of America
-
- (5) Full Name of Inventor: Joshua James SABATINI
Residence: 3 Old Mamaroneck Road, Apt. 5E, White Plains, NY 10605
Citizenship: United States of America
-
- (6) Full Name of Inventor:
Residence:
Citizenship:
-

hereby sells, assigns and transfers to ASSIGNEE:

Wyeth
Five Giralda Farms
Madison, New Jersey 07940

and the successors, assigns and legal representatives of the ASSIGNEE the entire right, title and interest for the United States and its territorial possessions and in all foreign countries, including all rights to claim priority, in and to the invention entitled:
OXAZOLE DERIVATIVES OF TETRACYCLINES

and invented by ASSIGNOR and the following additional inventors, if any:

and which is found in U.S. Provisional Application No. 60/584,823 filed on: July 1, 2004.

[also check if foreign application(s) is(are) also being assigned]

☒ and any legal equivalent thereof in a foreign country.

the date of filing and application number of said U.S. application when known, to be inserted above, including the right to claim priority, including any and all improvements disclosed therein, and in and to all Letters Patent to be obtained for said invention by the above application or any subsequently filed provisional, nonprovisional, continuation, divisional, renewal, or substitute thereof, and as to Letters Patent any reissue or re-examination thereof.

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment.

ASSIGNOR authorizes ASSIGNEE to make applications for and to receive Letters patent for said invention in any of said countries in its own name, or in ASSIGNOR's name, at its election.

ASSIGNOR covenants and agrees to execute or procure any further necessary assurance of the title to said invention and any Letters Patent which may issue therefore and to, at any time, upon the request and at the expense of ASSIGNEE deliver any testimony in any interference, litigation or proceeding related thereto and execute all papers that may be necessary or desirable to perfect the title to said invention or any Letters Patent which may be granted therefore in ASSIGNEE, its successors, assigns or other legal representatives, and that to, at any time, upon the request and at the expense of ASSIGNEE execute any continuation, continuation-in-part, divisional, renewal or substitute thereof, and as to Letters Patent and reissue or re-examination thereof, or any other additional applications of Letters Patent for said invention or any part thereof, all of which applications and any Letters Patent issuing thereon are hereby assigned to ASSIGNEE, and will make all rightful oaths or declarations, and do all lawful acts requisite for procuring the same therein, without further compensation, but at the expense of ASSIGNEE, its successors, assigns or other legal representatives.

ASSIGNOR authorizes and requests the Commissioner of Patents to issue any and all Letters Patent of the United States for said invention, resulting from any of the aforesaid applications to its ASSIGNEE.

Phaik-Eng SUM July 27, 2004
Phaik-Eng SUM Date

ACKNOWLEDGMENT

State of New York }
County of Rockland } ss:

On the 27 day of July 2004, Phaik-Eng SUM personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

JANICE A. WHITE
NOTARY PUBLIC - STATE OF NEW YORK
NO. 01-WH8052804
QUALIFIED IN ROCKLAND COUNTY
MY COMMISSION EXPIRES 12-28-2006

Janice A. White
Notary Public

David Brian HOW July 27, 2004
David Brian HOW Date

ACKNOWLEDGMENT

State of New York }
County of Rockland } ss:

On the 27 day of July 2004, David Brian HOW personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

JANICE A. WHITE
NOTARY PUBLIC - STATE OF NEW YORK
NO. 01-WH8052804
QUALIFIED IN ROCKLAND COUNTY
MY COMMISSION EXPIRES 12-28-2006

Janice A. White
Notary Public

Darrin William Hopper

Darrin William HOPPER

7/27/04

Date

ACKNOWLEDGMENTState of New York }
ss:
County of Rockland }

On the 27 day of July 2004, Darrin William HOPPER personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

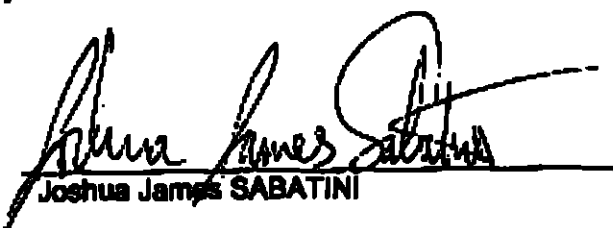
JANICE A. WHITE
NOTARY PUBLIC - STATE OF NEW YORK
NO. 01-WH062804
QUALIFIED IN ROCKLAND COUNTY
MY COMMISSION EXPIRES 12-28-2006

Janice A. White
Notary PublicMatthew Douglas VERA
Matthew Douglas VERAJuly 29, 2004
DateACKNOWLEDGMENTState of Pennsylvania }
ss:
County of Montgomery }

On the 29th day of July 2004, Matthew Douglas VERA personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

Cynthia J. Tagliaferri
Notary Public

NOTARIAL SEAL
CYNTHIA J. TAGLIAFERRI Notary Public
Collegiate Boro Montgomery County
My Commission Expires September 19, 2006


Joshua James SABATINI

7/27/04
Date

ACKNOWLEDGMENT

State of New York)
County of Rockland) ss:

On the 27 day of July 2004, Joshua James SABATINI personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

JANICE A. WHITE
NOTARY PUBLIC - STATE OF NEW YORK
NO. 01-WH8082804
QUALIFIED IN ROCKLAND COUNTY
MY COMMISSION EXPIRES 12-28-2006


Notary Public

Date

ACKNOWLEDGMENT

State of _____)
County of _____) ss:

On the _____ day of _____ 2004, _____ personally appeared before me, known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he/she executed the same, of his/her own free will and for the purposes set forth.

Notary Public

From the INTERNATIONAL BUREAU

000022
36

PCT

NOTIFICATION CONCERNING
TRANSMITTAL OF COPY OF INTERNATIONAL
APPLICATION AS PUBLISHED OR REPUBLISHED

To:

CALNAN, William, H.
Wyeth
Patent Law Department
Five Gilets Farm
Madison, NJ 07940
ETATS-UNIS D'AMERIQUE

JUL 01 2005

AM 77-05

Date of mailing (day/month/year) 23 June 2005 (23.06.2005)		IMPORTANT NOTICE	
Applicant's or agent's file reference AM101558			
International application No. PCT/US2004/040850	International filing date (day/month/year) 07 December 2004 (07.12.2004)	Priority date (day/month/year) 08 December 2003 (08.12.2003)	
Applicant WYETH et al			

The International Bureau transmits herewith the following documents:

- ☒ copy of the international application as published by the International Bureau on 23 June 2005 (23.06.2005) under No. WO 2005/056639
- ☐ copy of international application as republished by the International Bureau on under No. WO
For an explanation as to the reason for this republication of the international application, reference is made to INID circle (15), (48) or (82) (or the case may be) on the front page of the attached document.

CC: PEARL RIVER

CC: TAPLOW

DUCKETED

DUE DATE

STAT DATE

BY: 44-77-05

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Philippe Becamel

Facsimile No. 41 22 740 14 33

Facsimile No. 41 22 338 70 40

Form PCT/IB/311 (January 2004)

7-6-05

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



PCT

(43) International Publication Date
23 June 2005 (23.06.2005)

PCT

(10) International Publication Number
WO 2005/056538 A1

(51) International Patent Classification: C07D 263/52,
C07C 237/26, A61K 31/423, A61P 31/04

(21) International Application Number:
PCT/US2004/00850

(22) International Filing Date: 7 December 2004 (07.12.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Date:
60/527,928 8 December 2003 (08.12.2003) US
60/594,823 1 July 2004 (01.07.2004) US

(71) Applicant (for all designated States except US): WYETH
(US/US): Hoechst Pharmaceuticals, Madison, NJ 07940 (US).

(72) Inventors: and

(75) Inventors/Applicants (for US only): SUM, Phaik-Eng
(CA/US): 16 Chamberlain Court, Pomona, NY 10970
(US): HOW, David, Brian (CA/US): 10 High Avenue,
Nyack, NY 10960 (US); HOPPER, Darrin, William
(US/US): 301 West 101st Street, Apt. 5A, New York, NY
10025 (US); VERA, Matthew; Douglas (US/US): 1201
Morgan Drive, Ryeckford, PA 19468 (US); SARATINI,
Joshua, James (US/US): 3 Old Mamaroneck Road, Apt.
511, White Plains, NY 10605 (US).

(74) Agents: CALNAN, William, H. et al.; Wyeth, Patent Law
Department, Hoechst Pharmaceuticals, Madison, NJ 07940 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AI, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EG, ES, FI,
GB, GD, GE, GR, GT, GU, HK, HU, ID, IL, IN, IS, JP,
KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, MY, NA, NI, NO, NZ, OM,
PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,

ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LI, LU, MC, NL, PL, PT, RO,
SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, NG, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(I)) for the following designations AE,
AG, AI, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ,
CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EG,
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TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM,
ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA,
SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,
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IE, IS, IT, LI, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR),
OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
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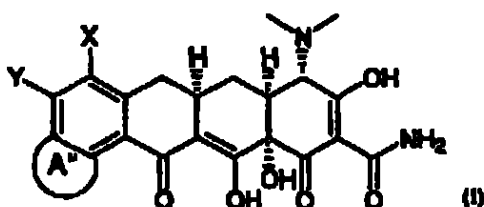
— as to the applicant's entitlement to claim the priority of the
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EC, EG, ES, FI, GB, GD, GE, GR, GM, GU, HU, ID,
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NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM,
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(54) Title: OXAZOLINE DERIVATIVES OF TETRACYCLINES



(57) Abstract: This invention provides compounds of the formula: wherein A⁺, X and Y are defined in the specification. These compounds are useful as antibacterial agents.

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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.

OXAZOLE DERIVATIVES OF TETRACYCLINES

FIELD OF THE INVENTION

5 The present invention relates to novel oxazole derivatives of tetracyclines which are useful as antibiotic agents and exhibit antibacterial activity against a wide spectrum of organisms including organisms which are resistant to tetracyclines and other antibiotics. This invention also relates to novel tetracycline intermediates useful for making the novel compounds and novel methods for producing the novel

10 compounds and the intermediate compounds.

BACKGROUND OF THE INVENTION

15 Since 1947 a variety of tetracycline antibiotics have been synthesized and described for the treatment of infectious diseases in man and animals. Tetracyclines inhibit protein synthesis by binding to the 30S subunit of the bacterial ribosome preventing binding of aminoacyl RNA (Chopra, Handbook of Experimental Pharmacology, Vol. 78, 317-392, Springer-Verlag, 1985). Resistance to tetracyclines has emerged among many clinically important microorganisms which limit the utility of these

20 antibiotics. There are two major mechanisms of bacterial resistance to tetracyclines: a) energy-dependant efflux of the antibiotic mediated by proteins located in the cytoplasmic membrane which prevents intracellular accumulation of tetracycline (S. B. Levy, et al., Antimicrob. Agents Chemotherapy 33, 1373-1374 (1989); and b) ribosomal protection mediated by a cytoplasmic protein which interacts with the

25 ribosome such that tetracycline no longer binds or inhibits protein synthesis (A. A. Salyers, B. S. Speers and N. B. Shoemaker, Mol. Microbiol. 4:151-156, 1990). The efflux mechanism of resistance is encoded by resistance determinants designated tetA-tetL. They are common in many Gram-negative bacteria (resistance genes Class A-E), such as Enterobacteriaceae, Pseudomonas, Haemophilus and

30 Aeromonas, and in Gram-positive bacteria (resistance genes Class K and L), such as Staphylococcus, Bacillus and Streptococcus. The ribosomal protection mechanism of resistance is encoded by resistance determinants designated TetM, N and O, and is common in Staphylococcus, Streptococcus, Campylobacter,

Gardnerella, Haemophilus and Mycoplasma (A. A. Bayers, B. S. Speers and N. B. Shoemaker, Mol. Microbiol, 4:151-156 1990).

A particularly useful tetracycline compound is 7-(dimethylamino)- 6-demethyl-6-deoxytetracycline, known as minocycline (see U.S. Pat. No. 3,148,212, U.S. Pat. No. RE 28,253 and U.S. Pat. No. 3,226,436 discussed below). However, strains harboring the tetB (efflux in gram-negative bacteria) mechanism, but not tetK (efflux in Staphylococcus) are resistant to minocycline. Also, strains carrying tetM (ribosomal protection) are resistant to minocycline. This invention describes the synthesis of novel tetracycline compounds which demonstrate significant in vitro and in vivo activity vs. tetracycline and minocycline susceptible strains and some tetracycline and minocycline resistant strains, that is, those harboring the tetM (ribosomal protection) resistance determinants.

Dugger, U.S. Pat. No. 2,482,053, discloses the preparation of Aureomycin-ATM by fermentation which have antibacterial activity. Growich et al., U.S. Pat. No.

3,007,965, discloses improvements to the fermentation preparation. Beersboom et al., U.S. Pat. No. 3,043,875 discloses tetracycline derivatives Boothe et al., U.S. Pat. No. 3,148,212, released as U.S. Pat. No. RE 28,253, and Pettai et al., U.S. Pat. No. 3,226,436, discloses tetracycline derivatives which are useful for treating bacterial infections. Blackwood et al., U.S. Pat. No. 3,200,149 discloses tetracycline derivatives which possess microbiological activity. Pettai et al., U.S. Pat. No. 3,338,963 discloses tetracycline compounds which have broad-spectrum antibacterial activity. Bitha et al., U.S. Pat. No. 3,341,585 discloses tetracycline compounds which have broad-spectrum antibacterial activity. Shu, U.S. Pat. No. 3,380,557 discloses 9- hydroxytetracyclines which have been found to possess antibacterial activity. Zambrano, U.S. Pat. No. 3,380,581 discloses a process for preparing 9-nitrotetracyclines. Martell et al., U.S. Pat. No. 3,518,308 discloses tetracyclines which possess in vivo antibacterial activity.

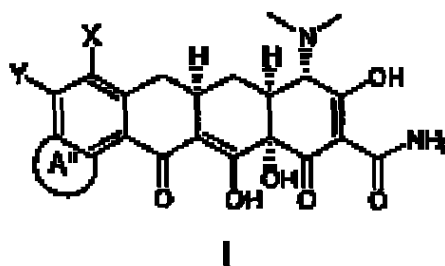
In U.S. Pat. No. 5,021,407 a method of overcoming the resistance of tetracycline resistant bacteria is disclosed. The method involves utilizing a blocking agent compound in conjunction with a tetracycline type antibiotic. This patent does not disclose novel tetracycline compounds which themselves have activity against resistant organisms. Described in U.S. Pat. No. 5,494,903 are 7-substituted-9-

substituted amino-8-dimethyl-8-deoxytetracyclines which have broad spectrum antibacterial activity.

In summary, none of the above patents teach or suggest the novel compounds of this application. In addition, none of the above patents teach or suggest novel tetracycline compounds of the invention having activity against tetracycline and minocycline resistant strains as well as strains which are normally susceptible to tetracyclines.

SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided compounds represented by Formula (I);



wherein:

X is selected from hydrogen, amino, $\text{NR}^{\text{R1}}\text{R}^{\text{R2}}$, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

A' is a moiety selected from the group:



R^{R1} and R^{R2} are each independently H or alkyl of 1 to 12 carbon atoms or

R^{11} and R^{12} when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

5 Y is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted, vinyl, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

10 R is selected from alkyl of 1 to 12 carbon atoms optionally substituted, alkenyl of 2 to 12 carbon atoms optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted, $-CH_2NR^1R^2$, aryl of 6, 10 or 14 carbon atoms optionally substituted, aralkyl of 7 to 16 carbon atoms optionally substituted, aroyl of 7 to 15 carbon atoms optionally substituted, SR^3 , heteroaryl of 5 or 6 ring atoms optionally substituted, containing 1 to 4 heteroatoms which may be the same or different, independently
15 selected from nitrogen, oxygen and sulfur, and heteroarylcarbonyl of 5 or 6 ring atoms optionally substituted containing 1 to 4 heteroatoms which may be the same or different, independently selected from nitrogen, oxygen and sulfur;

20 R^1 and R^2 are each independently H or alkyl of 1 to 12 carbon atoms or R^1 and R^2 when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

25 R^3 is alkyl of 1 to 12 carbon atoms optionally substituted, $-CH_2$ -aryl optionally substituted, aralkyl of 7 to 16 carbon atoms optionally substituted, aroyl, $-CH_2(CO)OCH_2$ -aryl optionally substituted, $-CH_2$ -alkenyl of 2 to 12 carbon atoms optionally substituted, and $-CH_2$ -alkynyl of 2 to 12 carbon atoms optionally substituted;

30 with the proviso that when X is NR^1R^2 and R^1 is hydrogen, then R^2 is methyl, ethyl, n-propyl, n-butyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; and that when R^1 is methyl or ethyl then R^2 is methyl, ethyl, n-propyl, 1-methylethyl, n-propyl, 1-methylpropyl, or 2-methylpropyl; or a tautomer or pharmaceutically acceptable salts thereof.

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5 Definitions

The term alkyl as a group or part of a group means a straight or branched alkyl moiety of 1 to 12 carbon atoms which can be optionally independently substituted with 1 to 3 substituents selected from the group halogen, amino, cyano, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon atoms, aryl optionally substituted, phenyl, hydroxyl, alkoxy of 1 to 12 carbon atoms, NH-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon atoms, NH-(alkyl of 1 to 12 carbon atoms)-aryl optionally substituted and heterocyclyl of 3 to 6 membered ring. In some embodiments of the invention alkyl is a moiety of 1 to 8 carbon atoms. In other embodiments of the invention alkyl is a moiety of 1 to 3 carbon atoms. In other embodiments alkyl is substituted by heterocyclyl of 4 to 7 ring members (e.g. pyrrolidinyl)

The term alkenyl means a straight or branched carbon chain of 2 to 12 carbon atoms having at least one site of unsaturation optionally independently substituted with 1 to 3 substituents selected from the group optionally substituted aryl, phenyl, heteroaryl, halogen, amino, cyano, alkyl of 1 to 12 carbon atoms, hydroxyl, and alkoxy of 1 to 12 carbon atoms.

The term vinyl means a moiety $\text{CH}_2=\text{CH}-$.

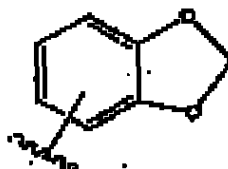
As used herein the term alkoxy as a group or part of a group refers to alkyl-O- wherein alkyl is hereinbefore defined.

As used herein the term aryl as a group or part of a group, e.g., aralkyl, aracyl, means an aromatic moiety having 6, 10 or 14 carbon atoms preferably 6 to 10 carbon atoms, which can be optionally substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, benzoyloxy, amino, alkylamino, dialkylamino, carboxyl, alkoxy carbonyl, methylenedioxy and

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phenyl. In particular, aryl is phenyl or naphthyl optionally substituted with 1 to 3 substituents. Substituted phenyl may optionally be the moiety



5

The term aralkyl as used herein of 7 to 18 carbon atoms means an alkyl substituted with an aryl group in which the aryl and alkyl group are previously defined. Non-limiting exemplary aralkyl groups include benzyl and phenethyl and the like.

10 Phenyl as used herein refers to a 6-membered carbon aromatic ring.

As used herein the term alkynyl includes both straight chain and branched moieties containing 2 to 12 carbon atoms having at least one carbon to carbon triple bond optionally substituted with 1 to 3 substituents independently selected from the group
15 halogen, amino, cyano, alkyl of 1 to 12 carbon atoms, hydroxyl, and alkoxy of 1 to 12 carbon atoms.

As used herein the term halogen or halo means F, Cl, Br or I.

20 As used herein the term cycloalkyl means a saturated monocyclic ring having from 3 to 6 carbon atoms. Exemplary cycloalkyl rings include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. In an embodiment of the invention cycloalkyl is a moiety of 5 or 6 carbon atoms.

25 As used herein, R¹ and R² and R¹¹ and R¹² when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring, where a non-limiting example is pyrrolidinyl,



The term **aroyl** means an aryl-C(O)- group in which the aryl group is as previously defined. Non-limiting examples include benzoyl and naphthoyl.

- 5 The term **heteroaryl** means an aromatic heterocyclic, monocyclic ring of 5 or 6 ring atoms containing 1 to 4 heteroatoms independently selected from O, N and S. Heteroaryl rings may optionally be substituted with 1 to 3 substituents selected from the group halogen, cyano, nitro, hydroxy, amino, alkylamino, dialkylamino, alkoxy, aryloxy, -CH₂OC(O)CH₃ and carboxy. Non-limiting heteroaryl moieties optionally
- 10 substituted include: furanyl, thienyl, pyridyl, tetrazolyl, imidazo, thiazolyl and the like. Further included are benzofuranyl, benzothienyl and quinoliny.

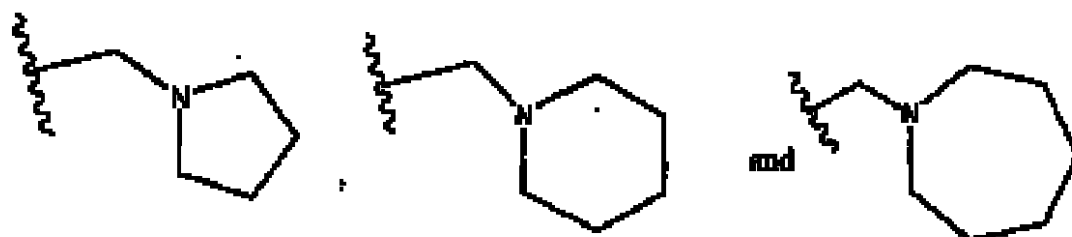
The term **heteroarylcarbonyl** means a heteroaryl-C(O)- group in which the heteroaryl group is as previously defined.

15

The term **heterocyclyl** as used herein represents a saturated 3 to 8 membered ring containing one to three heteroatoms selected from nitrogen, oxygen and sulfur. Representative examples are pyrrolidyl, piperidyl, piperazinyl, morpholiny, thiomorpholiny, aziridinyl, tetrahydrofuranyl and the like.

20

The term **alkylheterocyclyl** means an alkyl-heterocyclyl group in which the alkyl and heterocyclyl group are previously defined. Non-limiting exemplary alkylheterocyclyl groups include moieties of the formulas:

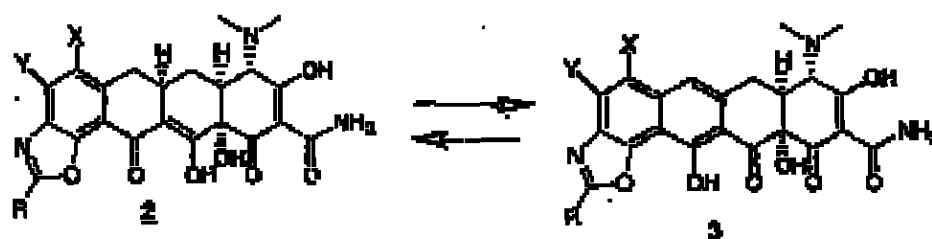


Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be

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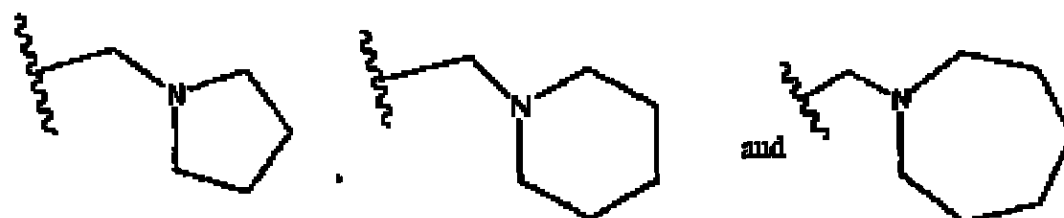
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Included within the scope of the present invention. For instance, compounds of formula (I) which exist as tautomers are depicted below:



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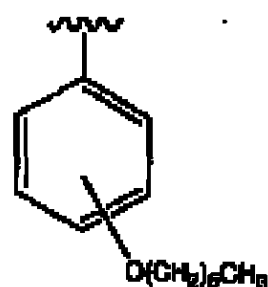
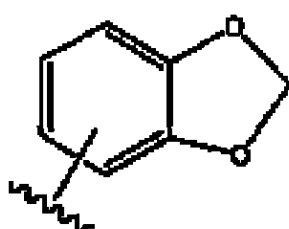
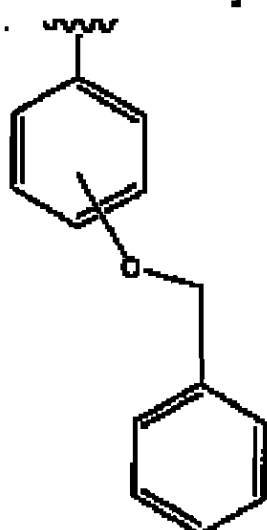
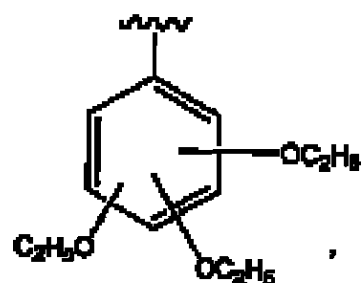
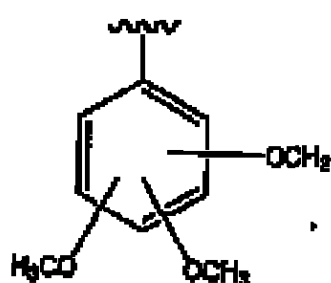
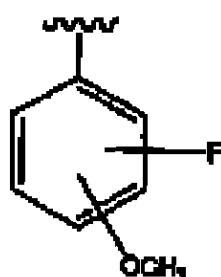
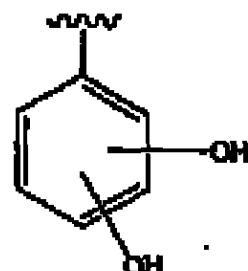
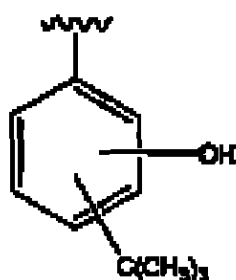
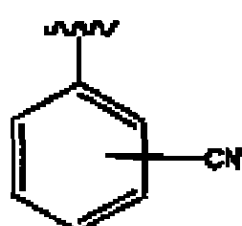
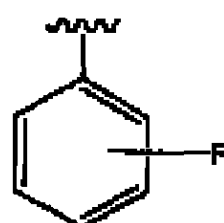
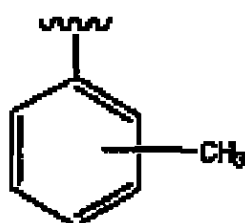
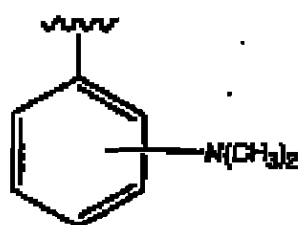
One embodiment of this invention is where R of Formula (I) is selected from the group alkyl of 1 to 8 carbon atoms, alkenyl of 2 to 8 carbon atoms, and alkyl- (heterocyclyl) selected from moieties of the group



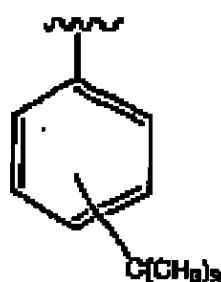
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Another embodiment of the invention is where R of Formula (I) is phenyl optionally substituted with 1 to 3 substituents. In a preferred embodiment R is selected from moieties of the group

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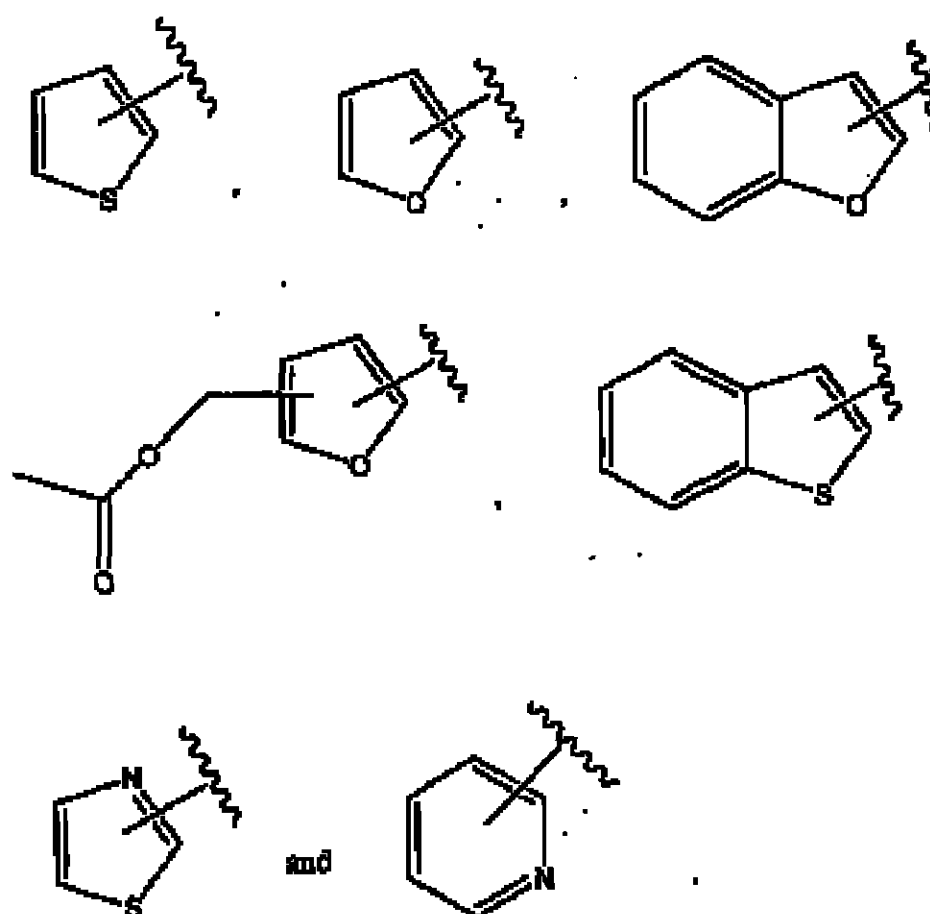
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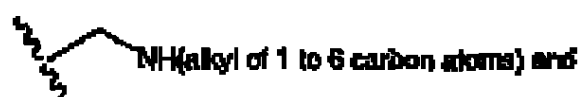
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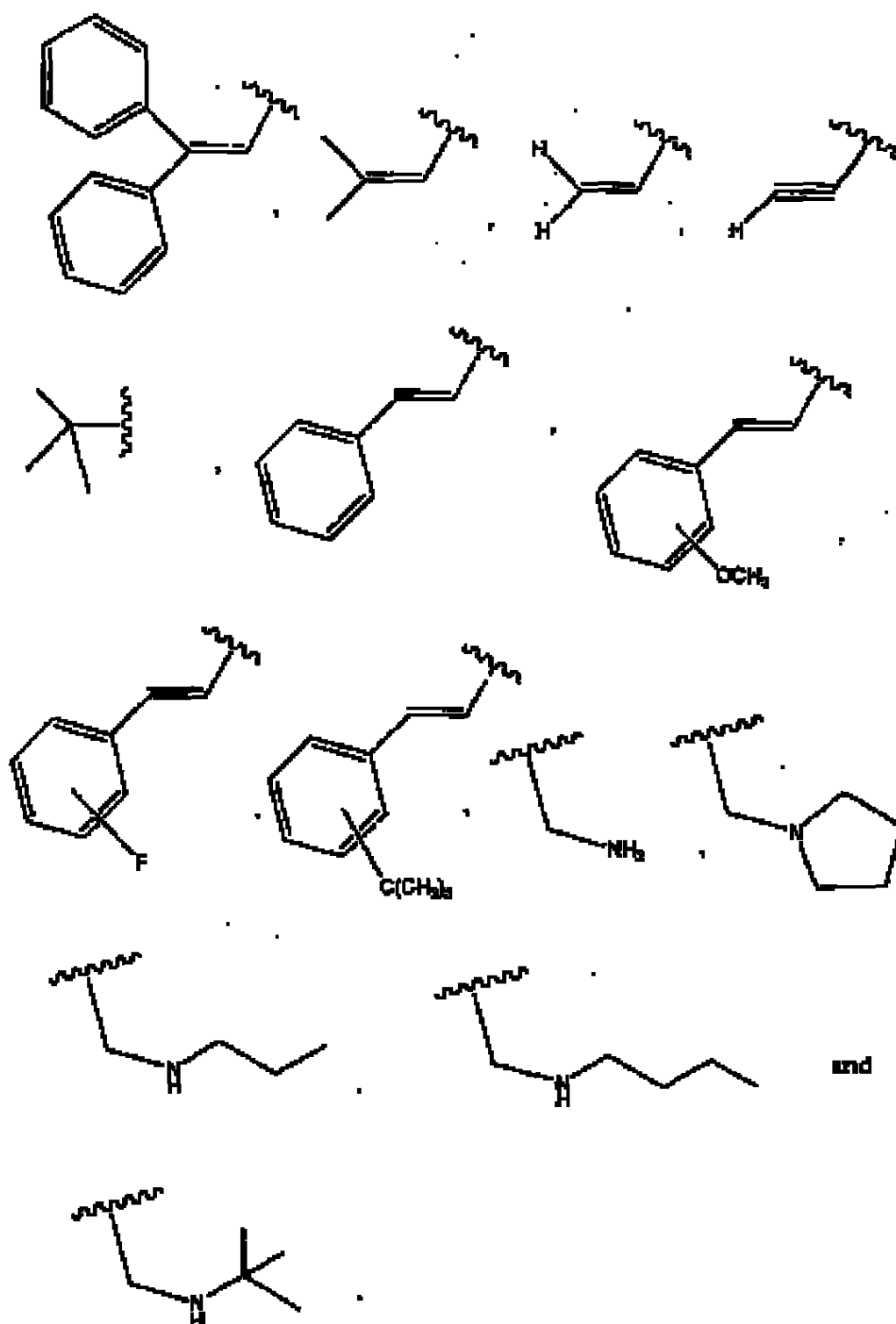
- A further preferred embodiment of the invention is where R is heteroaryl. In a
5 preferred embodiment R is selected from moieties of the group



- 10 An additional embodiment of the invention is where R is alkyl of 1 to 6 carbon atoms optionally substituted, alkenyl of 2 to 6 carbon atoms optionally substituted,

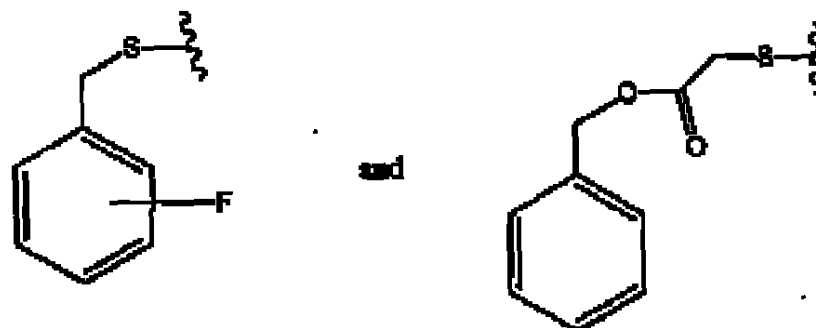


In a preferred embodiment R is selected from moieties of the group



An additional embodiment of the invention is where R of Formula (I) is S-alkyl of 1 to 12 carbon atoms, S-CH₂-aryl optionally substituted and S-CH₂(CO)OCH₂-aryl

optionally substituted. In a preferred embodiment R is selected from moieties of the group



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Preferred compounds of the invention include those selected from the group:

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(2,2-diphenylvinyl)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

10

(7aS,8S,11aS)-8-(dimethylamino)-9,11a,13-trihydroxy-2-(2-methyl-1-propenyl)-11,12-dioxo-7,7a,8,11,11a,12-hexahydronaphthaceno[2,1-d][1,3]oxazole-10-carboxamide,

15

(6aR,7aS,8S,11aS)-2-*tert*-butyl-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

20

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(*E*)-2-(2-furyl)ethenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

25

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-[(*E*)-2-phenylethenyl]-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-[(E)-2-(4-methoxyphenyl)ethenyl]-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 5 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-[(E)-2-(3-methoxyphenyl)ethenyl]-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 10 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-[(E)-2-(2-methoxyphenyl)ethenyl]-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 15 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(E)-2-(4-fluorophenyl)ethenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 20 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(E)-2-(2-fluorophenyl)ethenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 25 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(dimethylamino)methyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 30 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(pyrrolidin-1-ylmethyl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-
 [(propylamino)methyl]-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-
 10-carboxamide,
- 5 (6aR,7aS,8S,11aS)-2-[(butylamino)methyl]-5,8-bis(dimethylamino)-9,11a,12-
 trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-
 10-carboxamide,
- 10 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-
 [(propylamino)methyl]-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-
 10-carboxamide and
- 15 (6aR,7aS,8S,11aS)-2-[(tert-butylamino)methyl]-5,8-bis(dimethylamino)-9,11a,12-
 trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-
 10-carboxamide.
- Preferred compounds of the invention include those selected from the group:
- 20 (7aS,8S,11aS)-8-(dimethylamino)-2-[4-(dimethylamino)phenyl]-9,11a,13-trihydroxy-
 11,12-dioxo-7,7a,8,11,11a,12-hexahydronaphthaceno[2,1-d][1,3]oxazole-10-
 carboxamide,
- 25 (6aR,7aS,8S,11aS)-2-tert-butyl-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-
 dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-(4-methylphenyl)-
 11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-
 carboxamide,
- 30 (7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(3-fluorophenyl)-9,11a,13-trihydroxy-11,12-
 dioxo-7,7a,8,11,11a,12-hexahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

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- (6aR,7aS,8S,11aS)-2-(4-cyanophenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 5 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[4-(dimethylamino)phenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 10 (6aR,7aS,8S,11aS)-2-(5-tert-butyl-2-hydroxyphenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 15 (6aR,7aS,8S,11aS)-2-[4-(benzyloxy)phenyl]-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 20 (6aR,7aS,8S,11aS)-2-(2,4-dihydroxyphenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(3-fluoro-4-methoxyphenyl)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 25 (6aR,7aS,8S,11aS)-2-(1,3-benzodioxol-5-yl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 30 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(2,4,6-trimethoxyphenyl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(2,4,5-trifluorophenyl)-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- 5 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-(1-methyl-1H-indol-2-yl)-11,13-dioxo-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- 10 (6aR,7aS,8S,11aS)-2-(4-tert-butylphenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide and

- 15 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[4-(hexyloxy)phenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide.

Preferred compounds include those selected from the group:

- 20 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-thien-3-yl-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- 25 (6aR,7aS,8S,11aS)-2-(1-benzofuran-2-yl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(2-furyl)-9,11a,12-trihydroxy-11,13-dioxo-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- 30 (5-[(6aR,7aS,8S,11aS)-10-(aminocarbonyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazol-2-yl]-2-furyl)methyl acetate,

(6aR,7aS,8S,11aR)-2-(1-benzothien-3-yl)-5,8-bis(dimethylamino)-9,11a,12-

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trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

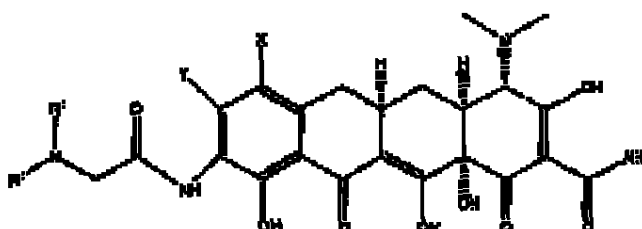
(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(1,3-thiazol-2-yl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-pyridin-4-yl-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide and

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-pyridin-3-yl-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide.

15

An additional embodiment of the invention is a process for the preparation of a compound of the formula



or a pharmaceutically acceptable salt thereof

wherein:

X is selected from hydrogen, amino, NR^1R^2 , alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

R^1 and R^2 are each independently H or alkyl of 1 to 12 carbon atoms or

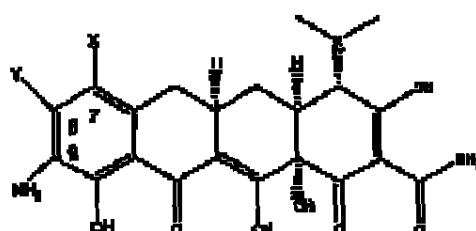
R^1 and R^2 when optionally taken together with the nitrogen atom to which each is attached form a 5 to 7 membered saturated hydrocarbon ring;

- Y is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, alkenyl of 2 to 12 carbon atoms optionally substituted, vinyl, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

comprising the steps:

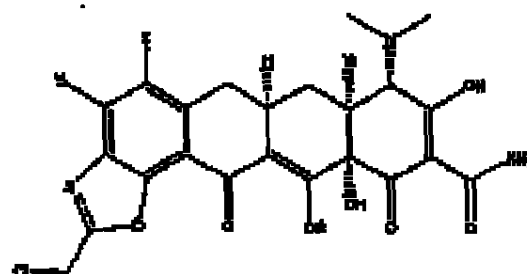
10

- a. reacting 7-(substituted)-8-(substituted)-8-amino-6-demethyl-8-deoxytetracycline of the formula

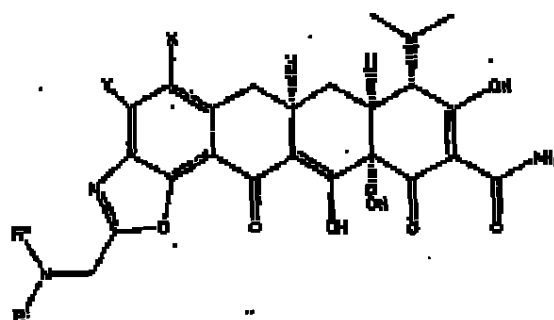


or a pharmaceutically acceptable salt thereof

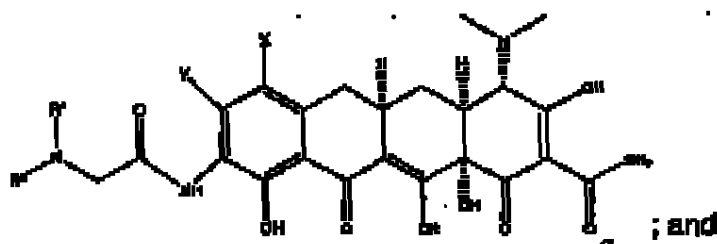
- 15 with 2-chlorotrimethoxyethane in an aprotic solvent to afford a chloro compound of the formula



- 20 b. reacting the chloro compound with an amine R^1R^2NH to form a substituted amine of the formula



- c. hydrolyzing the substituted amine with acid to give a compound of the formula



5

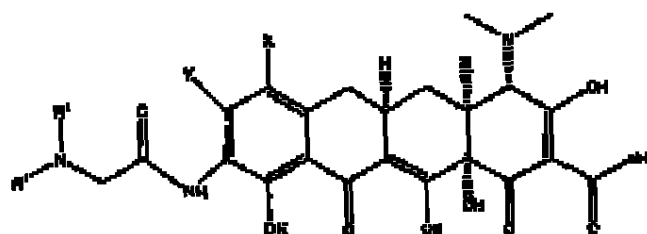
- d. isolating the compound or a pharmaceutically acceptable salt thereof.

10 In a preferred embodiment of the process X is $N(CH_3)_2$ and the amine R^1R^2NH is 1-butyl amine.

In a preferred embodiment of the process the compound [4S-(4 α ,4 α ,5 α ,12 α)]-4,7-Bis(dimethylamino)-8-[2-(1,1-dimethylethylamino)acetylamino]-1,4,4 α ,5,5 α ,8,11,12 α -octahydro-3,10,12,12 α -tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide or a pharmaceutically acceptable salt thereof is prepared.

15

A further embodiment of the invention is a process for the preparation of a compound of the formula



20

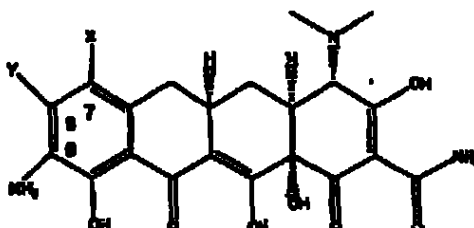
wherein:

5 X is selected from hydrogen, amino, NR^1R^2 , alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl, optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

10 R^1 and R^2 are each independently H or alkyl of 1 to 12 carbon atoms or R^1 and R^2 when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

15 Y is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, alkenyl of 2 to 12 carbon atoms optionally substituted, vinyl, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;
or a pharmaceutically acceptable salt thereof
comprising the steps:

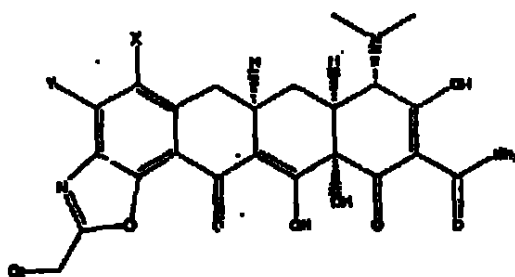
20 a. reacting 7-(substituted)-8-(substituted)-9-amino-6-demethyl-8-deoxytetracycline of the formula



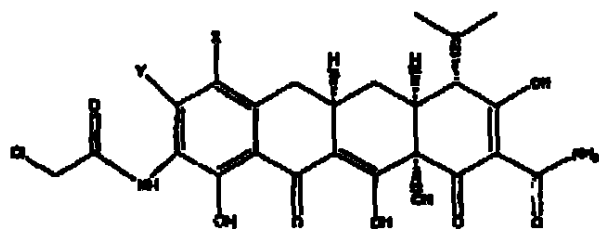
or a pharmaceutically acceptable salt thereof
with 2-chlorobis(methoxy)ethane in an aprotic solvent to afford a chloro compound of
the formula

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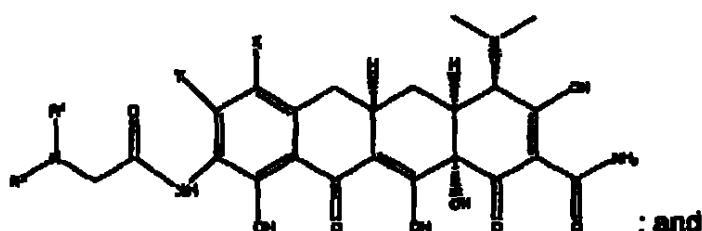
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- b. reacting the chloro compound with acid to give 9-(2-chloromethylcarbonylamino)substituted-6-demethyl-6-deoxytetracycline of the formula



- c. reacting the 9-(2-chloromethylcarbonylamino)substituted-6-demethyl-6-deoxytetracycline with amine R^1R^2NH to give a compound of the formula



- d. isolating the compound or a pharmaceutically acceptable salt thereof.

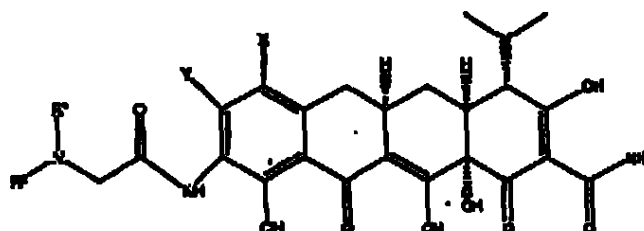
In a preferred embodiment of the process X is $N(CH_3)_2$ and the amine R^1R^2NH is t-butyl amine.

In a preferred embodiment of the process the compound [4S-(4 α ,4 α ,5 α ,12 α)]-4,7-Bis(dimethylamino)-9-[2-(1,1-dimethylethylamino)acetylaminol-

1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide or a pharmaceutically acceptable salt thereof is prepared.

An additional embodiment of the invention is a compound of the formula

5



or a pharmaceutically acceptable salt thereof

wherein:

10

X is selected from hydrogen, amino, NR^1R^2 , alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

15

R^1 and R^2 are each independently H or alkyl of 1 to 12 carbon atoms or R^1 and R^2 when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

20

Y is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, alkenyl of 2 to 12 carbon atoms optionally substituted, vinyl, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

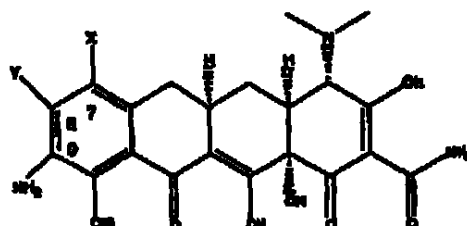
produced by the process comprising the steps:

25

a. reacting 7-(substituted)-8-(substituted)-8-amino-6-demethyl-8-deoxytetracycline of the formula

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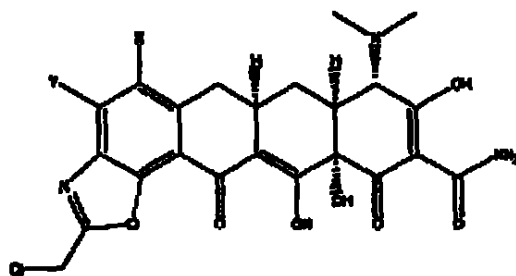
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or a pharmaceutically acceptable salt thereof

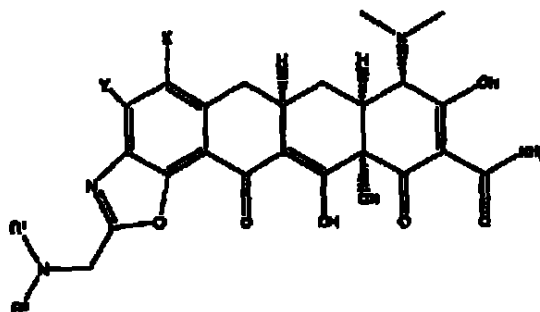
with 2-chlorotrimethoxyethane in an aprotic solvent to afford a chloro compound of the formula

5

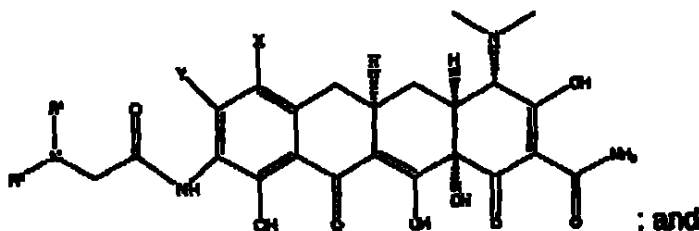


b. reacting the chloro compound with an amine R^1R^2NH to form a substituted amine of the formula

10



c. hydrolyzing the substituted amine with acid to give a compound of the formula



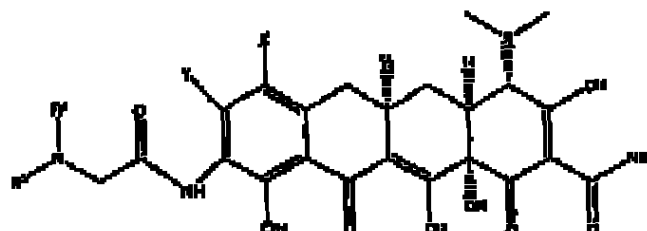
15

d. isolating the compound or a pharmaceutically acceptable salt thereof.

In a preferred embodiment of the process X is $N(CH_3)_2$ and the amine R^1R^2NH is t-butyl amine.

In a preferred embodiment of the process the compound [4S-(4a,4ax,5ax,12ax)]-4,7-Bis(dimethylamino)-9-[2-(1,1-dimethylethylamino)acetylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-9-carboxamide or a pharmaceutically acceptable salt thereof is prepared.

In an additional embodiment of the invention a compound of the formula



wherein:

X is selected from hydrogen, amino, NR^1R^2 , alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

R^1 and R^2 are each independently H or alkyl of 1 to 12 carbon atoms or when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

Y is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, alkynyl of 2 to 12 carbon atoms

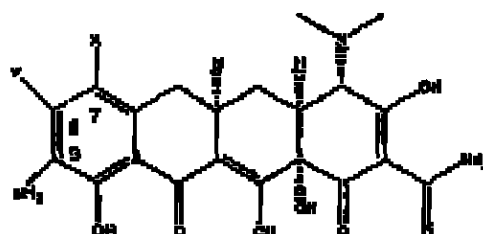
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optionally substituted, vinyl, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;
or a pharmaceutically acceptable salt thereof
produced by the process comprising the steps:

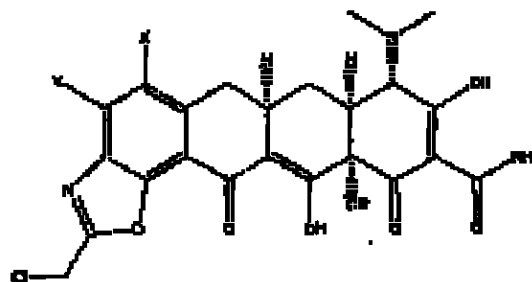
5

a. reacting 7-(substituted)-8-(substituted)-9-amino-6-demethyl-8-deoxytetracycline of the formula



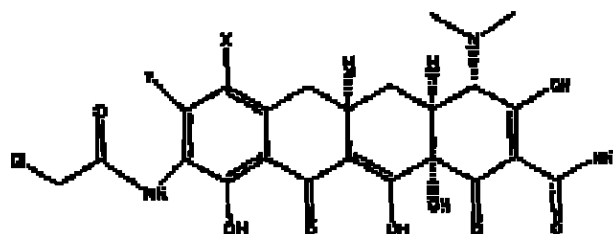
or a pharmaceutically acceptable salt thereof

10 with 2-chlorotrimethoxyethane in an aprotic solvent to afford a chloro compound of the formula



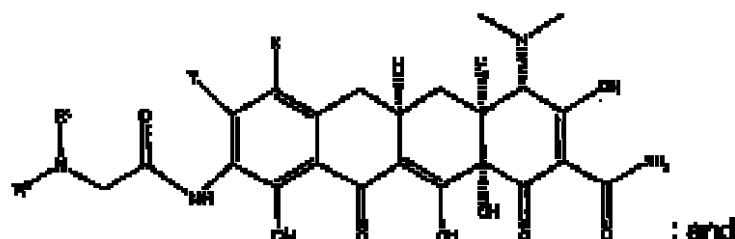
b. reacting the chloro compound with acid to give 9-(2-chloromethylcarbonylamino)substituted-6-demethyl-8-deoxytetracycline of the formula

15



c. reacting the 9-(2-chloromethylcarbonylamino)substituted-6-demethyl-8-deoxytetracycline with amine R^1R^2NH to give a compound of the formula

20



- 5 d. isolating the compound or a pharmaceutically acceptable salt thereof.

In a preferred embodiment of the process X is $N(CH_3)_2$ and the amine R^1R^2NH is t-butyl amine.

- 10 In a preferred embodiment the compound [4S-(4a,4a α ,5a α ,12a α)]-4,7-Bis(dimethylamino)-8-[2-(1,1-dimethylethylamino)acetylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide or a pharmaceutically acceptable salt thereof is prepared by the process.

15

20

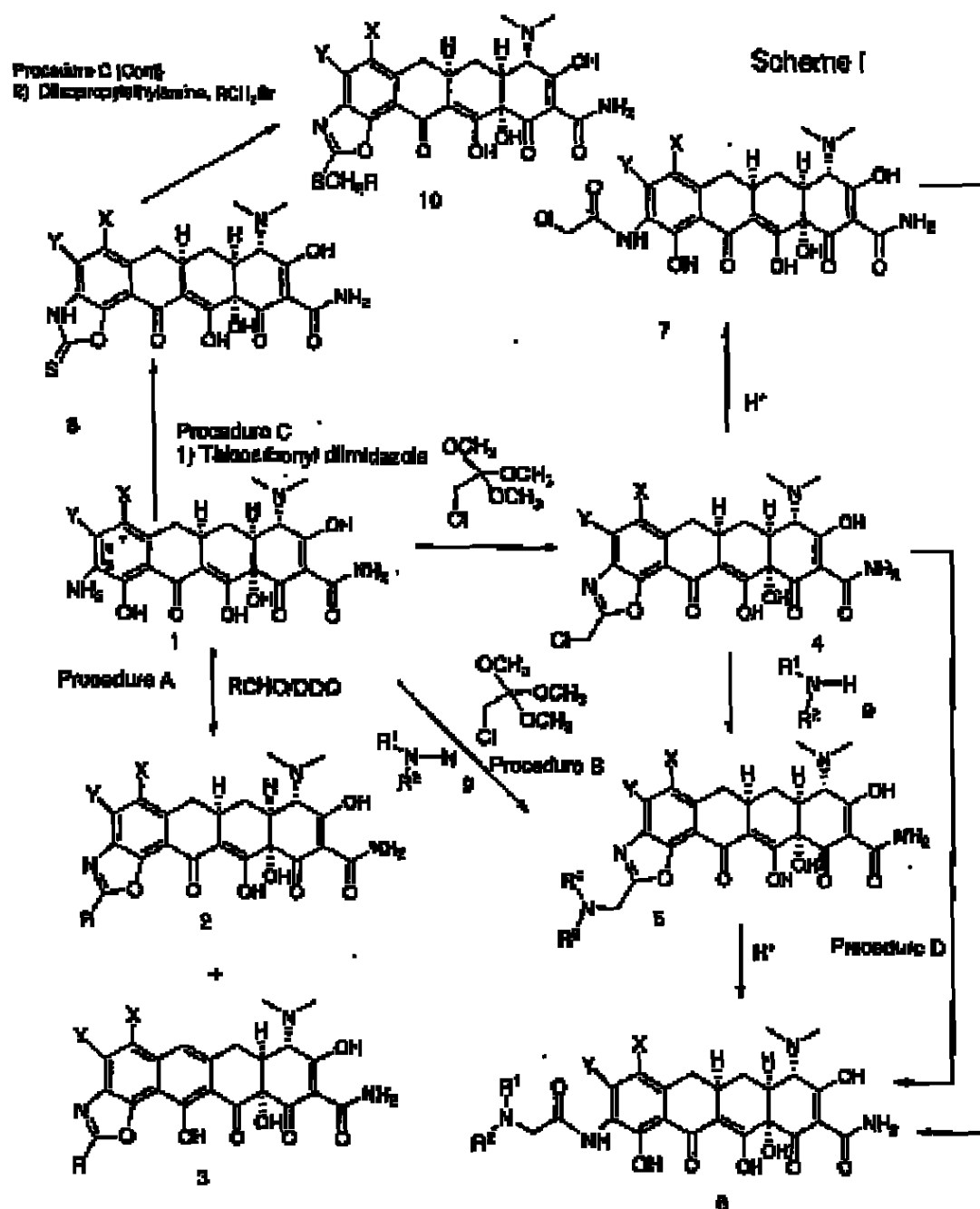
DESCRIPTION OF THE PREFERRED EMBODIMENTS.

- 5 The novel compounds of the present invention may be readily prepared in accordance with the following Scheme I.

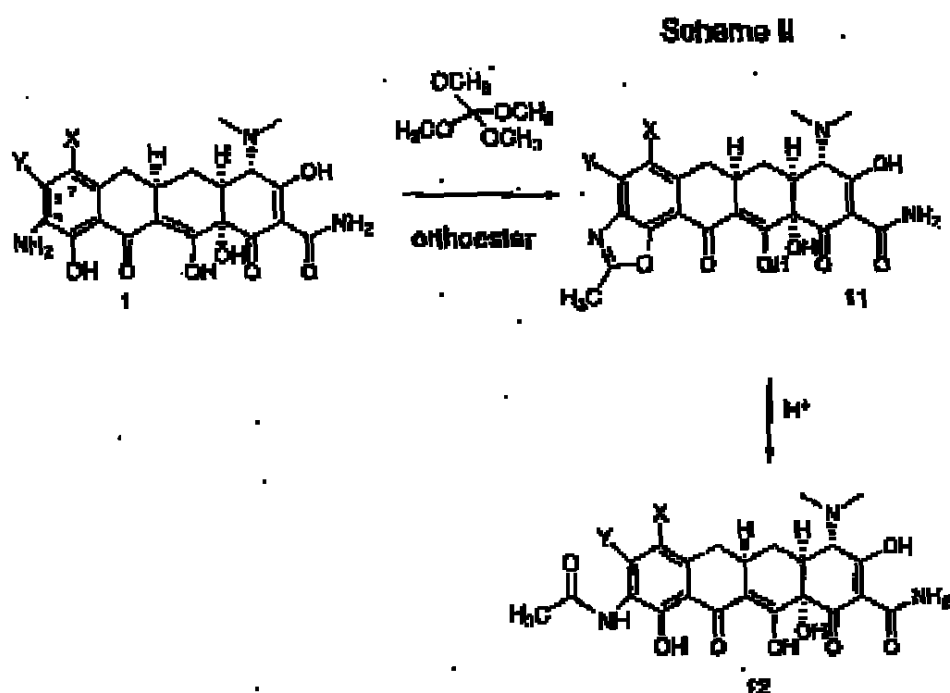
The starting 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-deoxytetracyclines
1 or pharmaceutically acceptable salts thereof where X and Y are hereinbefore
10 defined are reacted with aldehyde $RCHO$ in the presence of 2,2-dichloro-5,5-
dicyano-1,4-benzoquinone (DDQ) to afford benzoxazole 2 and 3 (Procedure A). As
further described, reaction of 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-
deoxytetracyclines 1 or pharmaceutically acceptable salts thereof where X and Y are
hereinbefore defined are reacted with 2-chloro-1,1,1-trimethoxy-ethane in an aprotic
15 solvent such as N,N-dimethylformamide (DMF) to give chloromethyl-benzoxazole 4,
optionally isolated, then converted to substituted amine 5 by further reaction with an
amine 9 (Procedure B). Hydrolysis of amine 5 affords 9-(2-substituted aminomethyl
carbonylamino)substituted-6-dimethyl-6-deoxytetracycline 6 (Procedure D).
Hydrolysis of chloromethylbenzoxazole 4 gives 9-(2-chloromethylcarbonyl-
20 amino)substituted-6-demethyl-6-deoxytetracycline 7 which may be further reacted
with amine 9 to give 9-(2-substituted aminomethyl carbonylamino)substituted-6-
dimethyl-6-deoxytetracycline 8.

25 Additionally, reaction of 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-
deoxytetracyclines 1 or pharmaceutically acceptable salts thereof with
thiocarbonyldiimidazole provides thio 8 followed by alkylation with RCH_2Br in the
presence of an amine which includes N,N-diisopropylethylamine affords oxazole 10
(Procedure C).

30 Preferably, amine 9 in the preparation of 9-(2-substituted aminomethyl
carbonylamino)substituted-6-dimethyl-6-deoxytetracycline 8, in Scheme I is t-
butylamine.



As shown in Scheme II, the starting 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-deoxytetracyclines 1 or pharmaceutically acceptable salts thereof where X and Y are hereinbefore defined are reacted with a methyl orthoester to afford methyl benzoxazole derivative 11. Acid hydrolysis of methyl benzoxazole derivative 11 affords N-acetyl derivative 12.



Reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformation being effected. It is understood by those skilled in the art of organic synthesis that the various functionalities present on the molecule must be consistent with the chemical transformations proposed. This may necessitate judgment as to the order of synthetic steps, protecting groups, if required, and deprotection conditions. Substituents on the starting materials may be incompatible with some of the reaction conditions. Such restrictions to the substituents which are compatible with the reaction conditions will be apparent to one skilled in the art.

Some of the compounds of the hereinbefore described schemes have center of asymmetry. The compounds may, therefore, exist in at least two and often more stereoisomeric forms. The present invention encompasses all stereoisomers of the compounds whether free from other stereoisomers or admixed with other stereoisomers in any proportion and thus includes, for instance, racemic mixture of enantiomers as well as the diastereomeric mixture of isomers. The absolute configuration of any compound may be determined by conventional X-ray crystallography.

Pharmaceutically acceptable salts of the compounds of the invention may be obtained as metal complexes such as aluminum, calcium, iron, magnesium, manganese and complex salts; inorganic and organic salts and corresponding Mannich base adducts using methods known to those skilled in the art (Richard C. Larock, Comprehensive Organic Transformations, VCH Publishers, 411-415, 1989). Preferably, the compounds of the invention are obtained as inorganic salts such as hydrochloric, hydrobromic, hydroiodic, phosphoric, nitric or sulfate; or organic salts such as acetate, benzoate, citrate, cysteine or other amino acids, fumarate, glycolate, maleate, succinate, tartrate alkylsulfonate or arylsulfonate. The salt formation preferentially occurs with the C(4)-dimethylamino group when forming inorganic salts. The salts are preferred for oral and parenteral administration.

Standard Pharmacological Test Procedures

5 Methods for in Vitro Antibacterial Evaluation

The minimum inhibitory concentration (MIC)

Antimicrobial susceptibility testing. The in vitro activities of the antibiotics are
10 determined by the broth microdilution method as recommended by the National
Committee for Clinical Laboratory Standards (NCCLS) (1). Mueller-Hinton II broth
(MHBII) (BBL Cockeysville, MD) is the medium employed in the testing procedures.
Microtiter plates containing serial dilutions of each antimicrobial agent are inoculated
with each organism to yield the appropriate density (10^5 CFU/ml) in a 100 μ l final
15 volume. The plates are incubated for 18 – 22 hours at 35°C in ambient air. The
minimal inhibitory concentration for all isolates is defined as the lowest concentration
of antimicrobial agent that completely inhibits the growth of the organism as detected
by the unaided eye.

- 20 1. NCCLS. 2000. Methods for Dilution Antimicrobial Susceptibility Tests for
Bacteria That Grow Aerobically; Approved Standards: M7-A5, vol. 20.
National Committee for Clinical Laboratory Standards, Wayne, PA.

TABLE I
ANTIBACTERIAL ACTIVITY OF (7-SUBSTITUTED)-8-(SUBSTITUTED)-9-(SUBSTITUTED)-TETRACYCLINES
MIC (μ g/ml) COMPOUND

	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6
1 E coli GC2270 (tet(M))	>64	>64	>64	>64	>64	>64
2 E coli GC4558 (parent GC4560)	>64	>64	>64	>64	>64	>64
3 E coli GC4560 (IMP mutant)	32	8	16	16	4	8
4 E coli GC2268 (ATCC Control)	>64	>64	>64	>64	>64	>64
5 E coli GC1073 (tet(B))	>64	>64	>64	>64	>64	>64
6 S. aureus GC1131 (Clinical)	16	8	2	16	4	4
7 S. aureus GC6486 (tet(M))	32	8	2	32	4	4
8 S. aureus GC6467 (tet(M)+K)	32	8	2	32	4	4
9 S. aureus GC1079 (tet(K))	16	8	1	16	4	4
10 S. aureus GC4538 (Smith MP -In Vivo)	16	8	2	32	4	4
11 S. aureus GC2216 (ATCC Control)	16	8	2	32	4	8
12 E faecalis GC4565 (ATCC Control)	32	8	2	32	4	8
13 E faecalis GC2267 (tet(L)+M)+S)	32	8	2	32	4	4
14 E faecalis GC2242 (Van-resistant)	16	8	2	32	4	4
15 S pneumoniae* GC4485 (Clinical)	16	8	2	16	16	16
16 S pneumoniae* GC1894 (Clinical)	8			32	8	16
17 S pyogenes* GC4863 (Clinical)	8	8	8	16	16	16
18 M catarrhalis* GC8907 (Clinical)	>64			18	18	32
19 H. influenzae<-> GC8998 (ATCC Control)	>64			>64	>64	>64
20 C. albicans GC3086 ATCC (Control)	>64	>64	>64	>64	>64	>64

TABLE II
ANTIBACTERIAL ACTIVITY OF (7-SUBSTITUTED)-8-(8-SUBSTITUTED)-8-SUBSTITUTED)-TETRACYCLINES
MIC ($\mu\text{g/ml}$) COMPOUND

	Example 7	Example 8	Example 10	Example 11
1 E coli GC2270 (tet(M))	>64	>64	>64	>64
2 E coli GC4559 (parent GC4560)	>64	>64	>64	>64
3 E. coli GC4560 (IMP mutant)	8	16	32	>64
4 E coli GC2203 (ATCC Control)	>64	>64	>64	>64
5 E coli GC1078 (tet(B))	>64	>64	>64	>64
6 S aureus GC1131 (Clinical)	8	8	8	32
7 S aureus GC8486 (tet(M))	8	16	16	64
8 S aureus GC8487 (tet(M)+(K))	8	8	16	32
9 S aureus GC1079 (tet(K))	8	16	16	64
10 S. aureus GC4536 (Smith MP -In Vivo)	8	16	16	64
11 S. aureus GC2216 (ATCC Control)	8	8	16	64
12 E. faecalis GC4555 (ATCC Control)	8	32	16	64
13 E. faecalis GC2267 (tet(L)+(M)+(S))	8	16	16	>64
14 E. faecalis GC2242 (Van-resistant)	8	8	8	64
15 S. pneumoniae* GC4465 (Clinical)	8	32	16	32
16 S. pneumoniae* GC1894 (Clinical)	16	16	8	32
17 S. pyogenes* GC4563 (Clinical)	8	16	16	32
18 M. catarrhalis* GC6907 (Clinical)	4	64	>64	32
19 H influenzae-> GC6896 (ATCC Control)	64	>64	>64	>64
20 C. albicans GC3066 ATCC (Control)	>64	>64	>64	>64

TABLE III
ANTIBACTERIAL ACTIVITY OF (7-SUBSTITUTED)-6-(SUBSTITUTED)-9-(SUBSTITUTED)-TETRACYCLINES
MIC (µg/ml) COMPOUND

	Example 12	Example 13	Example 14	Example 15	Example 16
1 <i>E. coli</i> GC2270 (tet(M))	>64	>64	>64	>64	>64
2 <i>E. coli</i> GC4566 (parent GC4560)	>64	>64	>64	>64	>64
3 <i>E. coli</i> GC4590 (IMP mutant)	4	4	16	32	16
4 <i>E. coli</i> GC2203 (ATCC Control)	32	>64	>64	>64	>64
5 <i>E. coli</i> GC1073 (tet(B))	>64	>64	>64	>64	>64
6 <i>S. aureus</i> GC1131 (Clinical)	4	4	4	64	16
7 <i>S. aureus</i> GC6456 (tet(M))	8	4	4	64	16
8 <i>S. aureus</i> GC6467 (tet(M)+K)	8	8	8	64	16
9 <i>S. aureus</i> GC1079 (tet(K))	8	4	4	64	16
10 <i>S. aureus</i> GC4536 (Smith MP -in Vivo)	8	8	4	64	16
11 <i>S. aureus</i> GC2216 (ATCC Control)	4	4	4	64	16
12 <i>E. faecalis</i> GC4556 (ATCC Control)	8	8	8	64	16
13 <i>E. faecalis</i> GC2267 (tet(L)+M)+S)	8	8	8	64	16
14 <i>E. faecalis</i> GC2242 (Van-resistant)	8	8	4	64	16
15 <i>S. pneumoniae</i> * GC4465 (Clinical)	8	32	16	>64	>64
16 <i>S. pneumoniae</i> * GC1894 (Clinical)	8	16	16	>64	>64
17 <i>S. pyogenes</i> * GC4563 (Clinical)	4	16	16	>64	64
18 <i>M. catenhalis</i> * GC6907 (Clinical)	4	16	4	64	>64
19 <i>H. influenzae</i> GC6896 (ATCC Control)	16	>64	>64	>64	>64
20 <i>C. albicans</i> GC3066 ATCC (Control)	>64	>64	>64	>64	>64

TABLE IV
ANTIBACTERIAL ACTIVITY OF (7-SUBSTITUTED)-8-(SUBSTITUTED)-9-(SUBSTITUTED)-TETRACYCLINES
MIC (μ g/ml) COMPOUND

	Example 17	Example 18	Example 19	Example 20	Example 21
1 E coli GC2270 (tet(M))	>64	>64	>64	>64	>64
2 E coli GC4559 (parent GC4560)	>64	>64	>64	>64	>64
3 E coli GC4560 (IMP mutant)	4	4	4	32	>64
4 E coli GC2203 (ATCC Control)	>64	>64	>64	>64	>64
5 E coli GC1073 (tet(B))	>64	>64	>64	>64	>64
6 S aureus GC1131 (Clinical)	8	4	4	32	64
7 S aureus GC8488 (tet(M))	8	4	4	32	32
8 S aureus GC8487 (tet(M)+(K))	8	4	4	32	32
9 S aureus GC1079 (tet(K))	8	4	4	32	32
10 S aureus GC4539 (Smith IMP -In Vivo)	8	4	8	64	64
11 S aureus GC2216 (ATCC Control)	8	4	4	32	32
12 E faecalis GC4555 (ATCC Control)	8	4	8	64	>64
13 E faecalis GC2267 (tet(L)+(M)+(S))	16	4	8	64	64
14 E faecalis GC2242 (Van-resistant)	8	4	4	32	32
15 S pneumoniae* GC4485 (Clinical)	32	16	4	>64	>64
16 S pneumoniae* GC1894 (Clinical)	32	16	4	64	>64
17 S. pyogenes* GC4868 (Clinical)	16	16	8	32	>64
18 M catarrhalis* GC8907 (Clinical)	16	8	16	32	>64
19 H. influenzae< GC8896 (ATCC Control)	>64	>64	>64	>64	>64
20 C. albicans GC3068 ATCC (Control)	>64	>64	>64	>64	>64

TABLE V
ANTIBACTERIAL ACTIVITY OF (7-SUBSTITUTED)-8-(SUBSTITUTED)-9-(SUBSTITUTED)-TETRACYCLINES
MIC (μg/ml) COMPOUND

	Example 22	Example 24	Example 25	Example 26
1 E. coli GC2270 (tet(M))	>64	>64	>64	>64
2 E. coli GC4559 (parent GC4560)	>64	>64	>64	>64
3 E. coli GC4560 (IMP mutant)	8	32	8	32
4 E. coli GC2203 (ATCC Control)	>64	>64	>64	>64
5 E. coli GC1073 (tet(B))	>64	>64	>64	>64
6 S. aureus GC1131 (Clinical)	8	32	8	16
7 S. aureus GC8466 (tet(M))	8	32	4	16
8 S. aureus GC6467 (tet(M)+(K))	8	32	8	16
9 S. aureus GC1079 (tet(K))	8	32	4	32
10 S. aureus GC4536 (Smith MP -In Vivo)	8	32	8	32
11 S. aureus GC2216 (ATCC Control)	8	64	4	16
12 E. faecalis GC4555 (ATCC Control)	8	32	8	32
13 E. faecalis GC2267 (tet(L)+(M)+(S))	8	32	4	16
14 E. faecalis GC2242 (Van-resistant)	8	32	4	16
15 S. pneumoniae* GC4465 (Clinical)	32	64	32	>64
16 S. pneumoniae* GC1894 (Clinical)	32	64	32	>64
17 S. pyogenes* GC4563 (Clinical)	16	32	16	64
18 M. catarrhalis* GC6907 (Clinical)	16	>64	16	>64
19 H. influenzae- GC6896 (ATCC Control)	>64	>64	>64	>64
20 C. albicans GC3066 ATCC (Control)	>64	>64	>64	>64

TABLE VI
ANTIBACTERIAL ACTIVITY OF (7-SUBSTITUTED)-8-(SUBSTITUTED)-9-(SUBSTITUTED)-TETRACYCLINES
MIC (μg/ml) COMPOUND

	Example 27	Example 28	Example 29	Example 30	Example 31
1 E. coli GC2270 (tet(M))	>64	>64	>64	>64	>64
2 E. coli GC4559 (parent GC4560)	>64	>64	>64	>64	>64
3 E. coli GC4560 (IMP mutant)	32	16	8	8	4
4 E. coli GC2203 (ATCC Control)	>64	>64	>64	>64	>64
5 E. coli GC1073 (tet(B))	>64	>64	>64	>64	>64
6 S. aureus GC1131 (Clinical)	8	8	8	4	8
7 S. aureus GC8466 (tet(M))	16	8	8	8	4
8 S. aureus GC8487 (tet(M)+(K))	8	8	8	8	8
9 S. aureus GC1079 (tet(K))	8	16	8	8	8
10 S. aureus GC4536 (Smith MP -In Vivo)	16	16	8	8	8
11 S. aureus GC2216 (ATCC Control)	8	8	8	4	8
12 E. faecalis GC4556 (ATCC Control)	16	16	8	8	8
13 E. faecalis GC2267 (tet(L)+(M)+(S))	8	8	8	4	8
14 E. faecalis GC2242 (Van-resistant)	8	8	8	4	8
15 S. pneumoniae* GC4465 (Clinical)	64	32	32	16	8
16 S. pneumoniae* GC1884 (Clinical)	64	64	32	16	8
17 S. pyogenes* GC4563 (Clinical)	64	16	16	16	8
18 M. catarrhalis* GC6807 (Clinical)	>64	64	16	32	16
19 H. influenzae<-> GC6896 (ATCC Control)	>64	>64	>64	>64	>64
20 C. albicans GC3086 ATCC (Control)	>64	>64	>64	>64	>64

TABLE VII
ANTIBACTERIAL ACTIVITY OF (7-SUBSTITUTED)-8-(SUBSTITUTED)-4-(SUBSTITUTED)-TETRACYCLINES
MIC (μg/ml) COMPOUND

	Example 32	Example 33	Example 34	Example 35	Example 36
1 <i>E. coli</i> GC2270 (tet(M))	>64	>64	>64	16	4
2 <i>E. coli</i> GC4559 (parent GC4580)	>64	>64	>64	8	4
3 <i>E. coli</i> GC4580 (OMP mutant)	>64	16	32	0.50	1
4 <i>E. coli</i> GC2203 (ATCC Control)	>64	64	>64	4	2
5 <i>E. coli</i> GC1079 (tet(B))	>64	>64	>64	32	4
6 <i>S. aureus</i> GC1131 (Clinical)	>64	16	32	0.50	4
7 <i>S. aureus</i> GC8466 (tet(M))	>64	32	64	1	4
8 <i>S. aureus</i> GC8467 (tet(M)+(K))	>64	32	64	8	16
9 <i>S. aureus</i> GC1078 (tet(K))	>64	16	32	4	4
10 <i>S. aureus</i> GC4536 (Smith MP -in vivo)	>64	16	64	1	4
11 <i>S. aureus</i> GC2216 (ATCC Control)	>64	16	32	0.50	2
12 <i>E. faecalis</i> GC4555 (ATCC Control)	64	16	32	1	4
13 <i>E. faecalis</i> GC2267 (tet(L)+(M)+(S))	>64	16	32	4	4
14 <i>E. faecalis</i> GC2242 (Van-resistant)	64	16	32	1	4
15 <i>S. pneumoniae</i> * GC4465 (Clinical)	16	16	32	0.50	1
16 <i>S. pneumoniae</i> * GC1894 (Clinical)	8	32	64	0.25	1
17 <i>S. pyogenes</i> * GC4583 (Clinical)	16	8	32	0.25	1
18 <i>M. catarrhalis</i> * GC6907 (Clinical)	32	8	16	0.50	1
19 <i>H. influenzae</i> ↔ GC6806 (ATCC Control)	>64	32	>64	2	4
20 <i>C. albicans</i> GC3068 ATCC (Control)	>64	>64	>64	>64	>64

TABLE VIII
ANTIBACTERIAL ACTIVITY OF (7-SUBSTITUTED)-8-(SUBSTITUTED)-9-(SUBSTITUTED)-
TETRACYCLINES
MIC (μg/ml) COMPOUND

	Example 37	Example 38	Example 39
1 E coli GC2270 (tet(M))	4	32	32
2 E coli GC4569 (parent GC4560)	2	32	32
3 E coli GC4560 (IMP mutant)	1	8	8
4 E coli GC2269 (ATCC Control)	2	32	32
5 E coli GC1073 (tet(S))	2	32	32
6 S aureus GC1131 (Clinical)	4	32	32
7 S. aureus GC6466 (tet(M))	4	32	32
8 S aureus GC6467 (tet(M)+(K))	8	>64	>64
9 S aureus GC1079 (tet(K))	4	64	64
10 S aureus GC4536 (Smith MP -In Vivo)	4	16	32
11 S aureus GC2216 (ATCC Control)	4	32	32
12 E faecalis GC4568 (ATCC Control)	2	16	32
13 E faecalis GC2267 (tet(L)+(M)+(S))	4	64	64
14 E faecalis GC2242 (Van-resistant)	2	16	32
15 S pneumoniae* GC4465 (Clinical)	1	4	8
16 S pneumoniae* GC1894 (Clinical)	1	4	8
17 S pyogenes* GC4563 (Clinical)	1	4	8
18 M. catarrhalis* GC6907 (Clinical)	1	4	8
19 H influenzae* GC6696 (ATCC Control)	4	64	64
20 C. albicans GC3066 ATCC (Control)	>64	>64	>64

When the compounds of the invention are employed as antibacterials, they can be combined with one or more pharmaceutically acceptable carriers, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 25 to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

An effective amount of compound from about 2.0 mg/kg of body weight to about 100.0 mg/kg of body weight may be administered one to five times per day via any typical route of administration including but not limited to oral, parenteral (including subcutaneous, intravenous, intramuscular, intrasternal injection or infusion techniques), topical or rectal, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

These active compounds may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

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The preferred pharmaceutical compositions of compounds of the invention from the standpoint of ease of preparation and administration are solid compositions, particularly tablet and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

- 5 These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid, polyethylene glycols and mixtures thereof in oils. Under ordinary
[0 conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

- The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and
15 must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacterial and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethy(ene glycol), suitable mixtures
20 thereof, and vegetable oil.

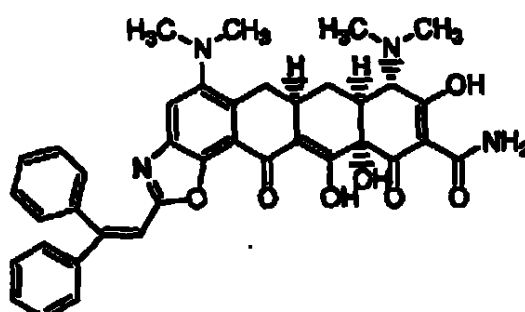
The invention will be more fully described in conjunction with the following specific examples which are not to be construed as limiting the scope of the invention.

5 Example of Procedure A

EXAMPLE 1

(8aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(2,2-diphenylvinyl)-9,11a,12-trihydroxy-11,13-dioxo-8,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

10



15

9-aminominoxyline sulfate salt (0.500g, 0.748 mmol) is dissolved in anhydrous DMF and treated with β -phenylcinnamaldehyde (0.779g, 3.74 mmol, 5 equivalents). The solution is then treated with DDQ (0.085 g, 0.374 mmol, 0.5 equivalents) and stirred at room temperature for 5 min. ES+ mass spectrometry showed a 1:1 ratio of product and starting material. A second portion of DDQ (0.088 g, 0.300 mmol, 0.4 equivalents) is added. After approximately 5 minutes, acetonitrile (7.5 mL) is added, and the entire reaction mixture is poured slowly into ether (750 mL). The pink solid is removed by filtration and washed with fresh ether to yield 0.480g of the crude product. This material is dissolved in water (75 mL) to give a solution at pH 2.2, which is extracted with dichloromethane (2 X 100 mL). The pH of the aqueous layer is raised to 3.0 with aqueous ammonia, and the solution is again

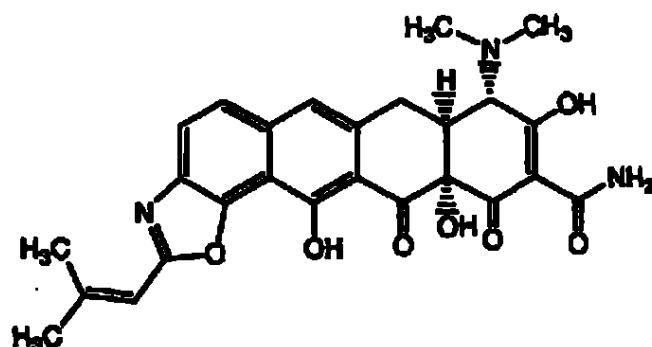
extracted with dichloromethane (2 X 100 mL.) The four organic extracts are dried (Na₂SO₄), filtered and concentrated to a volume of about 2 mL. A small portion of methanol (1 mL) is added, and the concentrated solution is treated dropwise with 1M HCl in ether. The solid precipitate is filtered, washed with fresh ether and dried under vacuum the product as its HCl salt.

Selected ¹H NMR signals: δ 4.26 (s, 1H), 7.13 (s, 1H), 7.26-7.45 (m, 8H), 7.63 (s, 1H); 9.08 (s, 1H), 9.54 (s, 1H).

- 10 The compounds of this invention listed below in Examples 2 to 37 are prepared substantially following the method described in detail hereinabove in Example 1 using procedure A.

EXAMPLE 2

- 15 (7a*S*,8*S*,11a*S*)-8-(dimethylamino)-9,11a,13-trihydroxy-2-(2-methyl-1-propenyl)-11,12-dioxo-7,7a,8,11,11a,12-hexahydronaphthaceno[2,1-*d*][1,3]oxazole-10-carboxamide

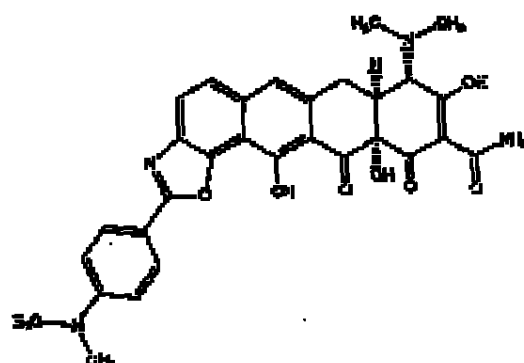


MS *m/z* 492 (*M*+*H*)

- 25 HRMS: calcd for C₂₈H₂₈N₂O₇, 491.16925; found (ESI+), 492.1765

EXAMPLE 3

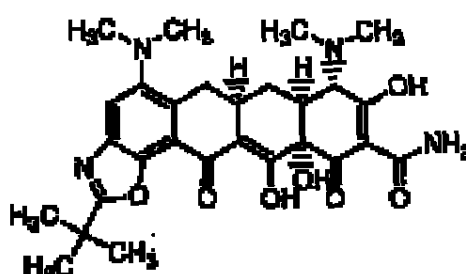
(7aS,8S,11aS)-8-(dimethylamino)-2-[4-(dimethylamino)phenyl]-9,11a,13-trihydroxy-11,12-dioxo-7,7a,8,11,11a,12-hexahydronaphthaceno[2,1-d][1,3]oxazole-10-carboxamide



HRMS: calcd for $C_{30}H_{30}N_4O_7$, 568.1958; found (ESI⁺), 557.2030

EXAMPLE 4

(6aR,7aS,8S,11aS)-2-tert-butyl-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,8]oxazole-10-carboxamide



MS (ESI) m/z 539.3 (M+H⁺);

MS (ESI) m/z 270.4 (M+2H⁺);

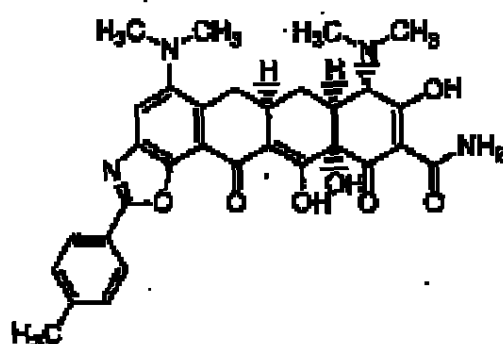
HRMS: calcd for $C_{30}H_{34}N_4O_7 \cdot HCl$, 574.2194; found (ESI⁺), 537.23482;

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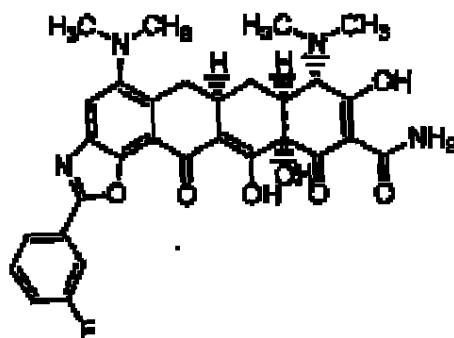
EXAMPLE 5

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-(4-methylphenyl)-
11,13-dioxo-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-
carboxamide

MS (ESI) m/z 573.3 ($M+H$);MS (ESI) m/z 287 ($M+2H$);HRMS: calcd for $C_{31}H_{38}N_4O_7 \cdot HCl$, 808.2098; found (ESI-), 571.2195;

EXAMPLE 6

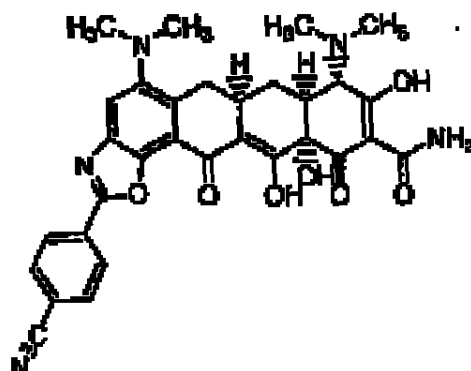
(7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(3-fluorophenyl)-9,11a,13-trihydroxy-11,12-
dioxo-7,7a,8,11,11a,12-hexahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide



EXAMPLE 7

(6aR,7aS,8S,11aS)-2-(4-cyanophenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-8,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

5



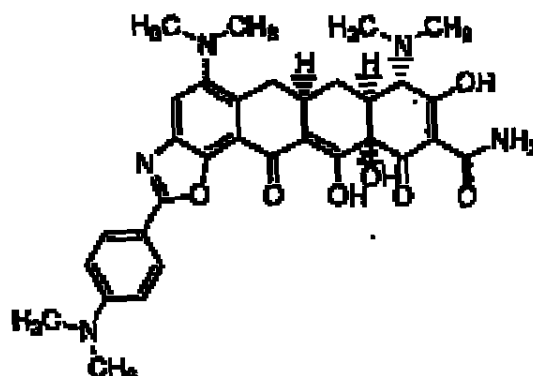
MS (ESI) m/z 584.4 ($M+H$);

HRMS: calcd for $C_{28}H_{29}N_5O_7 \cdot HCl$, 619.1834; found (ESI-), 682.19617;

10

EXAMPLE 8

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[4-(dimethylamino)phenyl]-9,11a,12-trihydroxy-11,13-dioxo-8,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide



15

MS (ESI) m/z 602.2 ($M+H$);

MS (ESI) m/z 301.8 ($M+2H$);

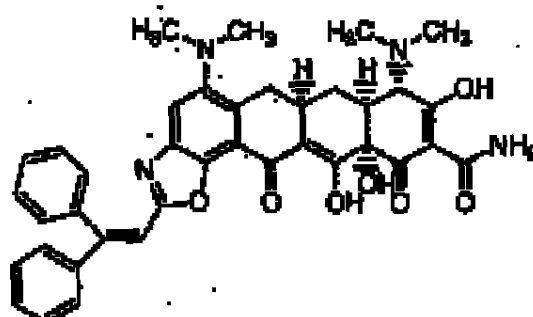
HRMS: calcd for $C_{32}H_{33}N_7O_7 \cdot HCl$, 637.2303; found (ESI-), 600.24521;

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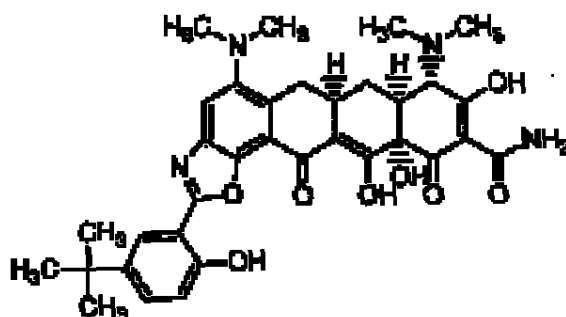
EXAMPLE 9

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(2,2-diphenylvinyl)-9,11a,12-trihydroxy-11,13-dioxo-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

MS (ESI) m/z 681.3 (M+H);MS (ESI) m/z 331.3 (M+2H);HRMS: calcd for $C_{35}H_{34}N_4O_7 \cdot HCl$, 686.2351; found (ESI-), 686.24957;

EXAMPLE 10

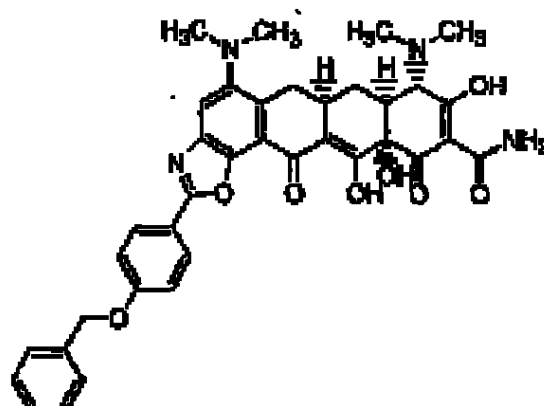
(6aR,7aS,8S,11aS)-2-(5-tert-butyl-2-hydroxyphenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

MS (ESI) m/z 631.4 (M+H);HRMS: calcd for $C_{34}H_{32}N_4O_8 \cdot HCl$, 666.2458; found (ESI+), 631.27753;

EXAMPLE 11

(6aR,7aS,8S,11aS)-2-[4-(benzyloxy)phenyl]-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

5

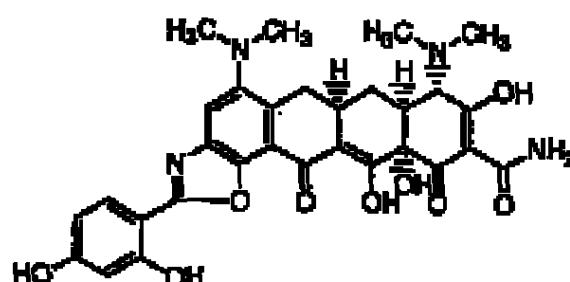
MS (ESI) m/z 865.2 (M+H);HRMS: calcd for $C_{27}H_{30}N_4O_8 \cdot HCl$, 700.2300; found (ESI+), 865.28096;

10

EXAMPLE 12

(6aR,7aS,8S,11aS)-2-(2,4-dihydroxyphenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

15

MS (ESI) m/z 591.2 (M+H);HRMS: calcd for $C_{21}H_{20}N_4O_8 \cdot HCl$, 626.1790; found (ESI+), 589.1927;

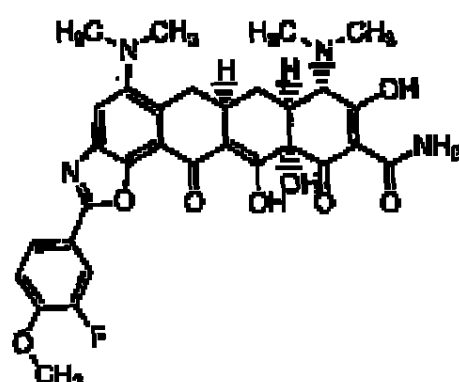
20

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EXAMPLE 13

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(3-fluoro-4-methoxyphenyl)-9,11a,12-trihydroxy-11,13-dioxo-8,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide



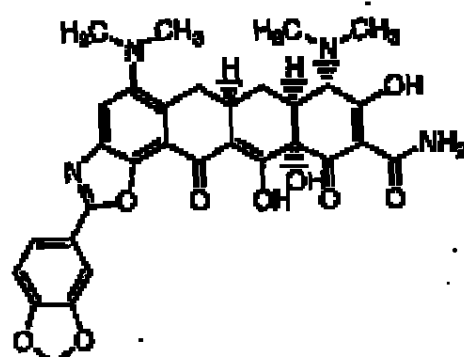
MS (ESI) m/z 607.3 (M+H);

MS (ESI) m/z 304 (M+2H);

HRMS: calcd for $C_{27}H_{31}FN_4O_5 \cdot HCl$, 642.1893; found (ESI+), 605.20519;

EXAMPLE 14

(6aR,7aS,8S,11aS)-2-(1,3-benzodioxol-5-yl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-8,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide



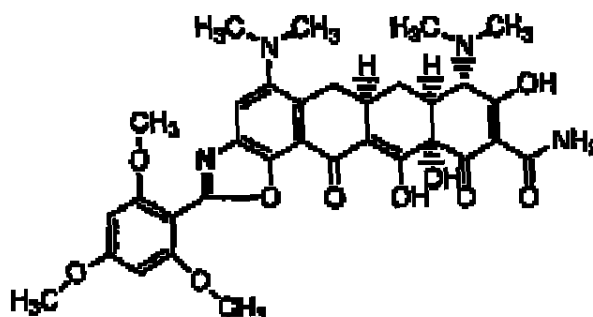
MS (ESI) m/z 603.3 (M+H);

MS (ESI) m/z 302.1 (M+2H);

HRMS: calcd for $C_{27}H_{33}N_4O_6 \cdot HCl$, 638.1780; found (ESI+), 603.20959;

EXAMPLE 15

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(2,4,6-trimethoxyphenyl)-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

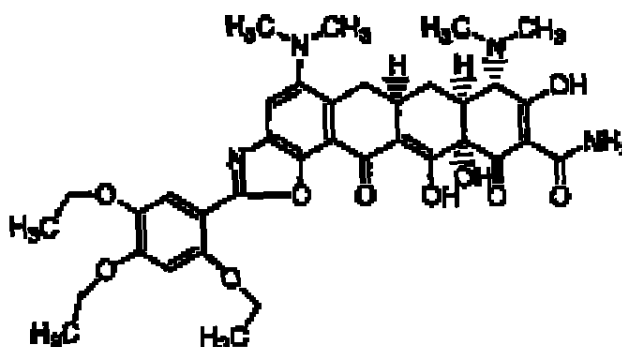


MS (ESI) m/z 649.2 ($M+H$);

HRMS: calcd for $C_{31}H_{38}N_4O_{10} \cdot HCl$, 684.2198; found (ESI⁺), 647.23441;

EXAMPLE 16

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(2,4,6-triethoxyphenyl)-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide



MS (ESI) m/z 691.3 ($M+H$);

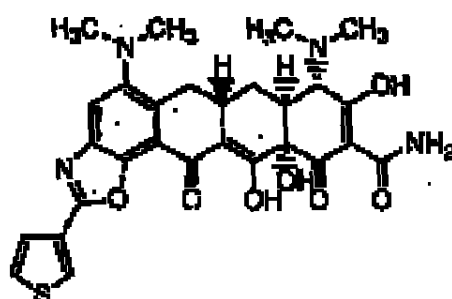
HRMS: calcd for $C_{35}H_{46}N_4O_{10} \cdot HCl$, 726.2668; found (ESI⁺), 691.29817;

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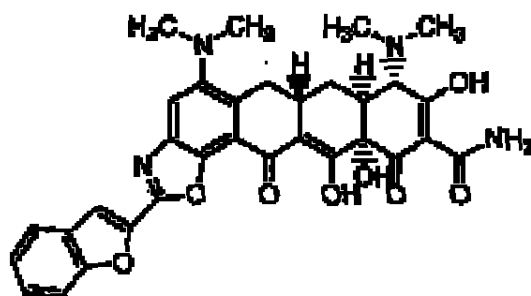
EXAMPLE 17

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-thien-3-yl-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

MS (ESI) m/z 585.2 (M+H);MS (ESI) m/z 283.4 (M+2H);HRMS: calcd for $C_{28}H_{29}N_4O_7S \cdot HCl$, 600.1445; found (ESI-), 583.15992;

EXAMPLE 18

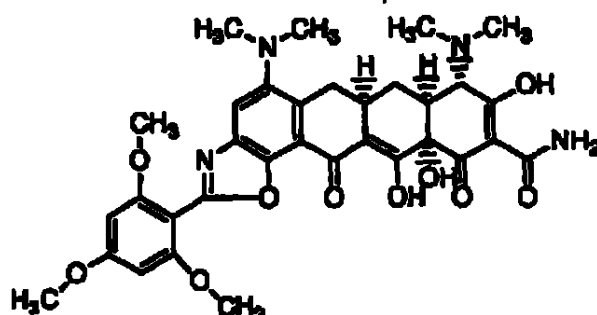
(6aR,7aS,8S,11aS)-2-(1-benzofuran-2-yl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

MS (ESI) m/z 609.3 (M+H);HRMS: calcd for $C_{32}H_{31}N_4O_8 \cdot HCl$, 634.1830; found (ESI-), 597.19811;

EXAMPLE 19

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-(1-methyl-1H-indol-2-yl)-11,13-dioxo-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

5



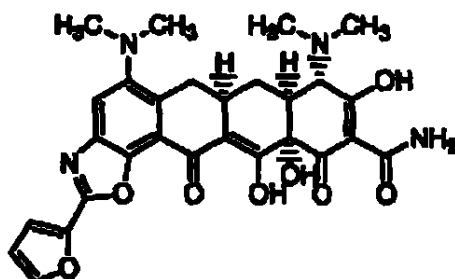
10

MS (ESI) m/z 612.2 (M+H);HRMS: calcd for $C_{33}H_{33}N_5O_7 \cdot HCl$, 647.2147; found (ESI+), 612.24406;

EXAMPLE 20

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(2-furyl)-9,11a,12-trihydroxy-11,13-dioxo-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

15

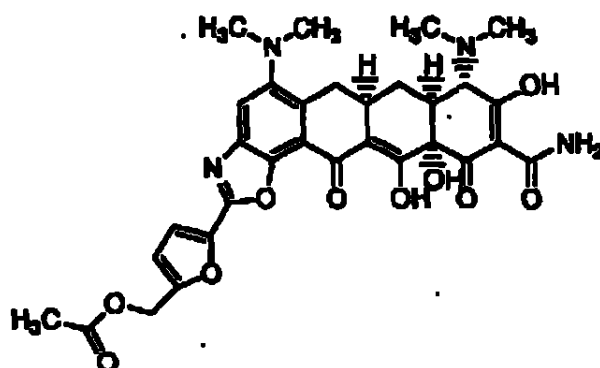


20

MS (ESI) m/z 549.3 (M+H);HRMS: calcd for $C_{29}H_{29}N_5O_8 \cdot HCl$, 584.1674; found (ESI-), 547.1822;

EXAMPLE 21

{5-[(6aR,7aS,8S,11aS)-10-(aminocarbonyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazol-2-yl]-2-furyl)methyl acetate

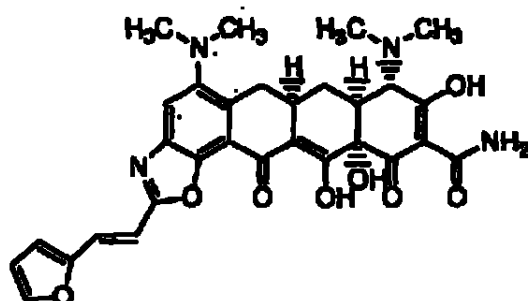


MS (ESI) m/z 621.2 (M+H);

HRMS: calcd for $C_{27}H_{32}N_4O_{10} \cdot HCl$, 656.1885; found (ESI+), 621.21807;

EXAMPLE 22

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(E)-2-(2-furyl)ethenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide



MS (ESI) m/z 575.2 (M+H);

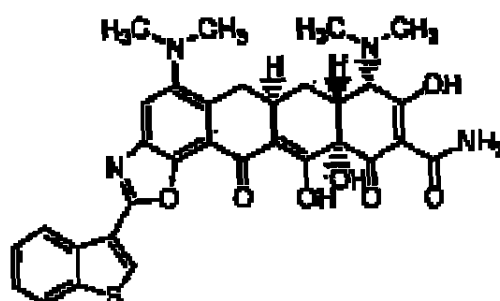
MS (ESI) m/z 288.3 (M+2H);

HRMS: calcd for $C_{30}H_{32}N_4O_8 \cdot HCl$, 610.1830; found (ESI+), 573.1985;

EXAMPLE 23

(6aR,7aS,8S,11aS)-2-(1-benzothien-3-yl)-5,8-bis(dimethylamino)-8,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

5



MS (ESI+) m/z 615.1 ((M+H)+);

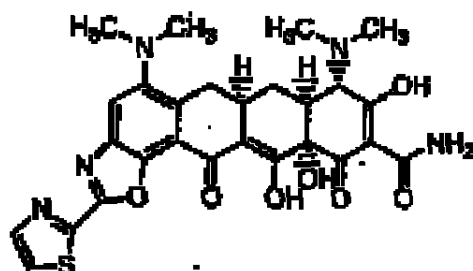
10

HRMS: calcd for $C_{33}H_{30}N_4O_7S \cdot HCl$, 650.1602; found (ESI+), 615.1909;

EXAMPLE 24

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-8,11a,12-trihydroxy-11,13-dioxo-2-(1,3-thiazol-2-yl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

15



20

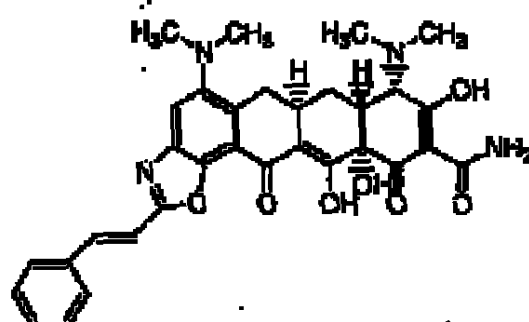
MS (ESI) m/z 566.4 (M+H);

MS (ESI) m/z 283.6 (M+2H);

HRMS: calcd for $C_{27}H_{26}N_4O_7S \cdot HCl$, 601.1398; found (ESI+), 566.1697;

EXAMPLE 25

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-[(E)-2-phenylathenyl]-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide



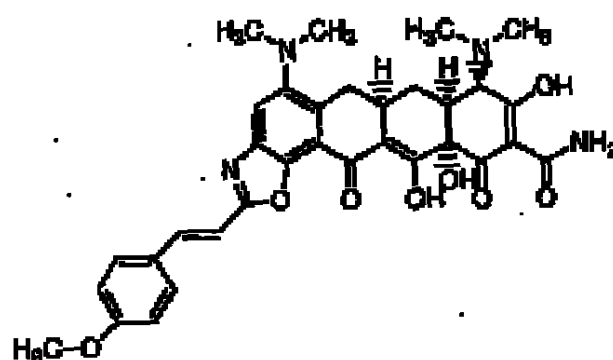
MS (ESI) m/z 585.4 (M+H);

MS (ESI) m/z 293.3 (M+2H);

HRMS: calcd for $C_{22}H_{22}N_4O_7 \cdot HCl$, 620.2038; found (ESI+), 585.2929;

EXAMPLE 26

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-[(E)-2-(4-methoxyphenyl)ethenyl]-11,13-dioxo-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide



MS (ESI) m/z 615.3 (M+H);

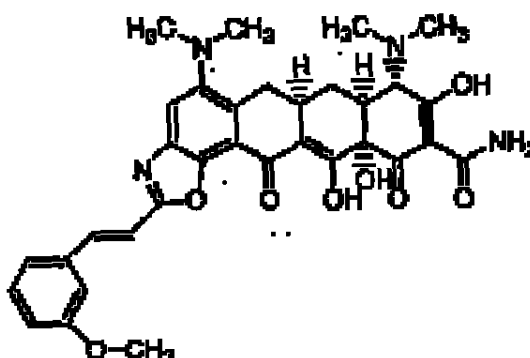
MS (ESI) m/z 308.3 (M+2H);

HRMS: calcd for $C_{23}H_{24}N_4O_8 \cdot HCl$, 650.2143; found (ESI+), 615.24413;

EXAMPLE 27

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-[(E)-2-(3-methoxyphenyl)ethenyl]-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

5



MS (ESI) m/z 815.4 (M+H);

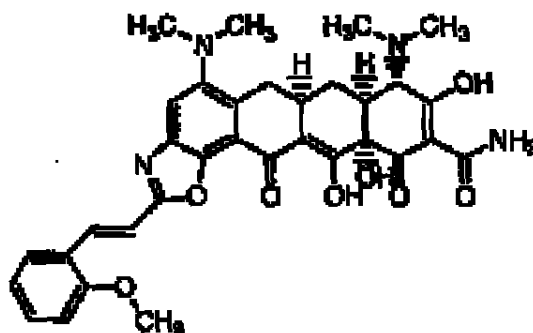
MS (ESI) m/z 308.3 (M+2H);

10 HRMS: calcd for $C_{35}H_{39}N_4O_5 \cdot HCl$, 850.2143; found (ESI+), 815.24419;

EXAMPLE 28

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-[(E)-2-(2-methoxyphenyl)ethenyl]-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

15



MS (ESI) m/z 815.3 (M+H);

MS (ESI) m/z 308.3 (M+2H);

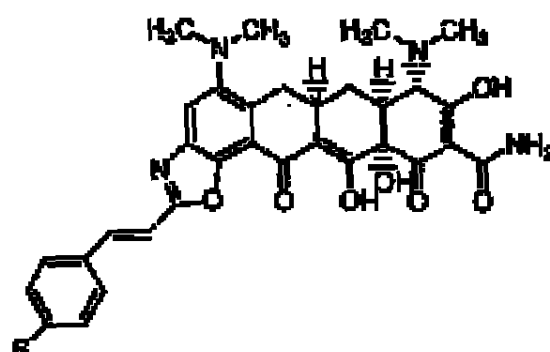
20 HRMS: calcd for $C_{35}H_{39}N_4O_5 \cdot HCl$, 850.2143; found (ESI+), 815.24408;

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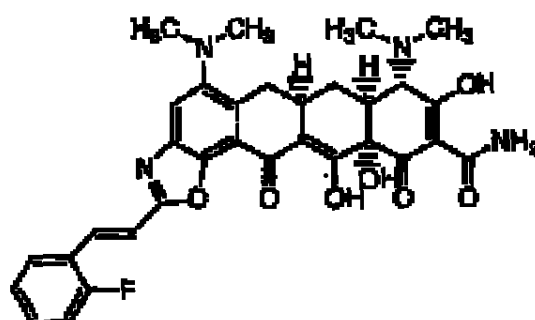
EXAMPLE 29

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(E)-2-(4-fluorophenyl)ethenyl]-
8,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-
d][1,3]oxazole-10-carboxamide

MS (ESI) m/z 603.2 (M+H);MS (ESI) m/z 302.3 (M+2H);HRMS: calcd for $C_{38}H_{31}FN_4O_7 \cdot HCl$, 639.1944; found (ESI+), 603.22476;

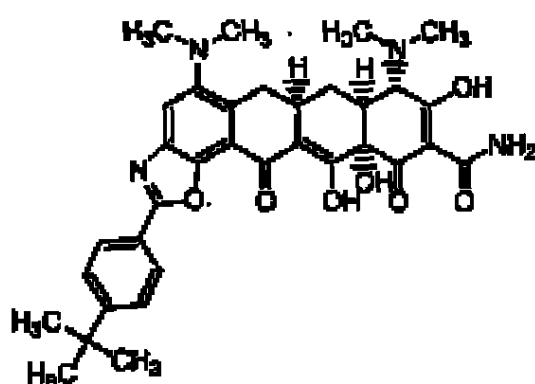
EXAMPLE 30

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(E)-2-(2-fluorophenyl)ethenyl]-
8,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-
d][1,3]oxazole-10-carboxamide

MS (ESI) m/z 603.2 (M+H);MS (ESI) m/z 302.3 (M+2H);HRMS: calcd for $C_{32}H_{25}FN_4O_7 \cdot HCl$, 639.1944; found (ESI+), 603.22469;

5

10-carboxamide



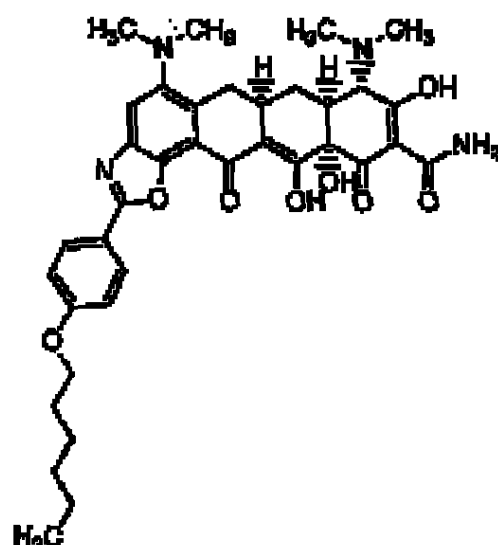
HRMS: calcd for $C_{24}H_{27}N_4O_7 \cdot HCl$, 650.2607; found (ESI+), 616.28057.

25

EXAMPLE 82

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[4-(hexyloxy)phenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

5

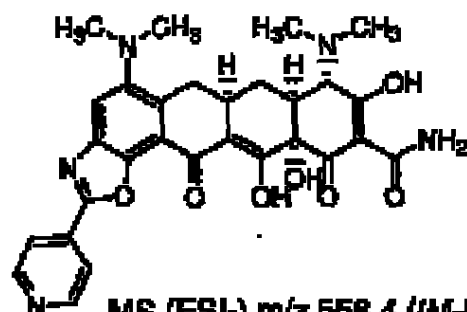
MS (ESI) m/z 659.4 ($M+H$);MS (ESI) m/z 390.4 ($M+2H$);HRMS: calcd for $C_{35}H_{42}N_4O_7 \cdot HCl$, 694.2769; found (ESI+), 659.3069;

10

EXAMPLE 83

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-pyridin-4-yl-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

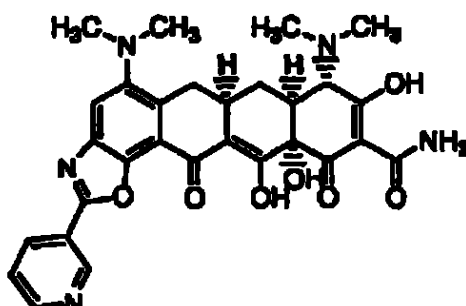
15

MS (ESI-) m/z 558.4 ($(M-H)^-$);

EXAMPLE 34

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-pyridin-3-yl-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

5



MS (ESI) m/z 560.3 (M+H);

10

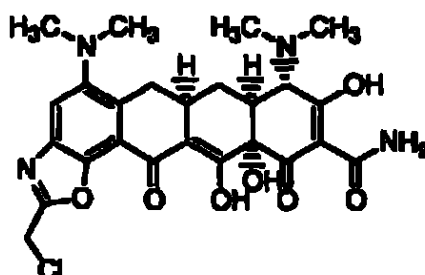
MS (ESI) m/z 280.7 (M+2H);

HRMS: calcd for $C_{28}H_{29}N_5O_7 \cdot HCl$, 595.1834; found (ESI+), 560.21353;

EXAMPLE 35

(6aR,7aS,8S,11aS)-2-(chloromethyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

15



20

MS (ESI) m/z 531.2 (M+H);

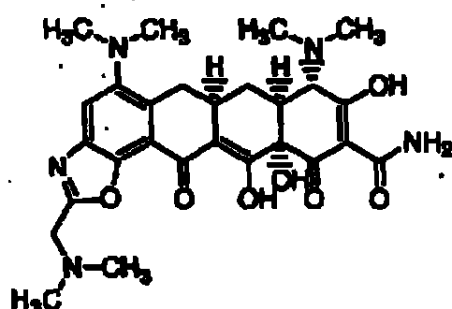
MS (ESI) m/z 266.3 (M+2H);

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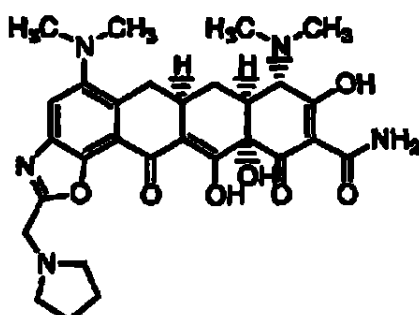
EXAMPLE 36

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(dimethylamino)methyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

MS (ESI) m/z 540.4 (M+H);MS (ESI) m/z 270.7 (M+2H);HRMS: calcd for $C_{27}H_{33}N_5O_7 \cdot HCl$, 575.2147; found (ESI+), 540.24506;

EXAMPLE 37

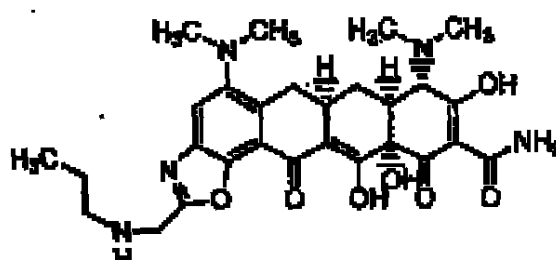
(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(pyrrolidin-1-ylmethyl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

MS (ESI) m/z 566.4 (M+H);MS (ESI) m/z 283.9 (M+2H);HRMS: calcd for $C_{28}H_{35}N_5O_7 \cdot HCl$, 601.2303; found (ESI+), 566.26066;

Example of Procedure B

EXAMPLE 38

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-
 5 [(propylamino)methyl]-8,8a,7,7a,8,11,11a,13-octahydroisotraceno[2,1-d][1,3]oxazole-
 10-carboxamide



10

9-aminominoocycline sulfate salt (1.0 g, 1.50 mmol) is dissolved in DMF (50 mL) and
 treated with a solution of 2-chloro-1,1,1-trimethoxyethane (0.489 g, 3.00 mmol, 2
 equivalents). The reaction is stirred at room temperature until mass spectrometry
 15 shows conversion to the chloromethylbenzoxazole derivative. The solution is then
 treated with *n*-propylamine (10 mL, excess) and stirred until mass spectrometry
 shows conversion to the *n*-propylaminomethyl benzoxazole. The mixture is
 concentrated under reduced pressure to remove excess *n*-propylamine, and then
 poured slowly into ether (1 L) and HCl/ether is added to precipitate the salt. The solid
 20 is rinsed with fresh ether and dried under vacuum. The crude solid is dissolved in
 water (100 mL) giving a solution at pH 2. The pH is raised successively by 0.5 units
 with aqueous ammonia, and extracted with dichloromethane. The fractions extracted
 at pH 4-4.5 are combined, dried (Na₂SO₄), filtered and concentrated nearly to
 dryness. A small volume of methanol is added and the solution is treated with 1M
 25 HCl in ether. The precipitated solid is collected by filtration, washed with fresh ether
 and dried under vacuum to yield 0.057 g of the product as its HCl salt.

Selected ¹H NMR signals: δ 0.94 (t, 3H), 1.73 (m, 2H), 4.31 (s, 1H), 4.65 (s, 2H),
 7.78 (s, 1H), 9.15 (s, 1H), 9.87 (s, 1H).

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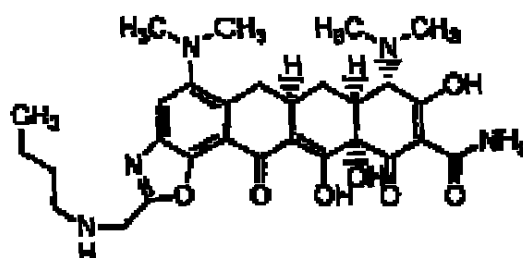
PCT/US2004/010250

The compounds of this invention listed below in Examples 38 to 41 are prepared substantially following the method described in detail hereinabove in Example 36 using procedure B.

(prepared from Procedure B)

EXAMPLE 39

(6aR,7aS,8S,11aS)-2-((butylamino)methyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-8,9a,7,7a,8,11,11a,13-octahydrotetraeno[2,1-d][1,3]oxazole-10-carboxamide



MS (ESI) m/z 568.3 (M+H);

MS (ESI) m/z 284.8 (M+2H);

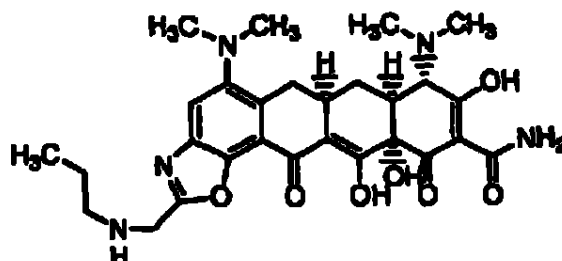
MS (ESI) m/z 305.2 (M+ACN+2H);

HRMS: calcd for $C_{22}H_{27}N_5O_7 \cdot HCl$, 603.2450; found (ESI+), 568.27616;

(Procedure B)

EXAMPLE 40

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-
[(propylamino)methyl]-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-
10-carboxamide



MS (ESI) m/z 554.3 (M+H);

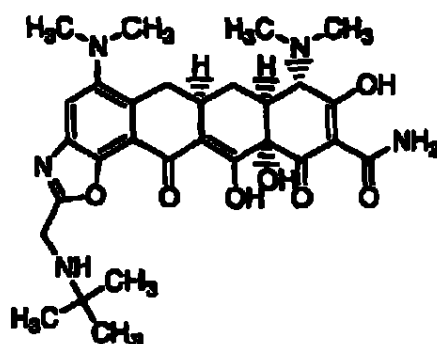
MS (ESI) m/z 277.7 (M+2H);

HRMS: calcd for $C_{28}H_{35}N_5O_7 \cdot HCl$, 589.2803; found (ESI+), 554.2804;

(Procedure B)

EXAMPLE 41

(6aR,7aS,8S,11aS)-2-[(*tert*-butylamino)methyl]-5,8-bis(dimethylamino)-9,11a,12-
trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-
10-carboxamide



9-amininocycline sulfate salt (1.0 g, 1.50 mmol) is dissolved DMF (20 mL) and treated with a solution of 2-chlorotrimethoxyethane (0.35 g, 2.2 mmol, 1.46 equivalents). The reaction is stirred at room temperature until mass spectrometry showed conversion to the chloromethylbenzoxazole derivative. The solution is then
5 treated with *t*-butylamine (7.3 mL, excess) and stirred until mass spectrometry showed conversion to the *t*-butylaminomethyl benzoxazole. The mixture is concentrated under reduced pressure to remove excess *t*-butylamine, and then poured slowly into ether (1 L) and HCl/ether is added to precipitate the salt. The solid is rinsed with fresh ether and dried under vacuum. The crude solid is dissolved in
10 water (100 mL) giving a solution at pH 2. The pH is raised successively by 0.5 units with aqueous ammonia, and extracted with dichloromethane. The fractions extracted at pH 4-4.5 are combined, dried (Na₂SO₄), filtered and concentrated nearly to dryness. A small volume of methanol is added and the solution is treated with 1M HCl in ether. The precipitated solid is collected by filtration, washed with fresh ether
15 and dried under vacuum to give the product as its HCl salt.

MS (ESI+) m/z 568.4 ((M+H)⁺);

MS (ESI+) m/z 284.9 ((M+2H)²⁺);

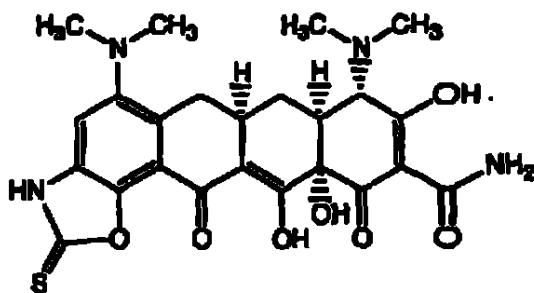
MS (ESI+) m/z 146.3 ((M⁺+H)⁺);

20 HRMS: calcd for C₂₉H₃₇N₅O₇ · HCl, 603.2460; found (ESI-), 586.26087;

Example of Procedure C

EXAMPLE 42

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-
25 thioxo-2,3,6,8a,7,7a,8,11,11a,13-decahydrotetracen-2-yl-1,3-oxazole-10-carboxamide



To a solution of 9-amino-mino disulfate (0.668 g, 1 mmol) in DMSO (30 mL) is added 2 equivalents of 1,1-thiocarbonyldiimidazole. The reaction is then stirred at room temperature for 2 to 12 hr (followed by MS(ES)). The mixture then trifurated with diethyl ether and the solid collected. Material is used in the next step without further purification.

MS (ESI) m/z 515.2 (M+H);

HRMS: calcd for $C_{24}H_{28}N_4O_7S \cdot H_2SO_4$, 812.1198; found (ESI+), 515.15934;

10

The compounds of this invention listed below in Examples 43 to 44 are prepared substantially following the method described in detail hereinabove in Example 42 using procedure C.

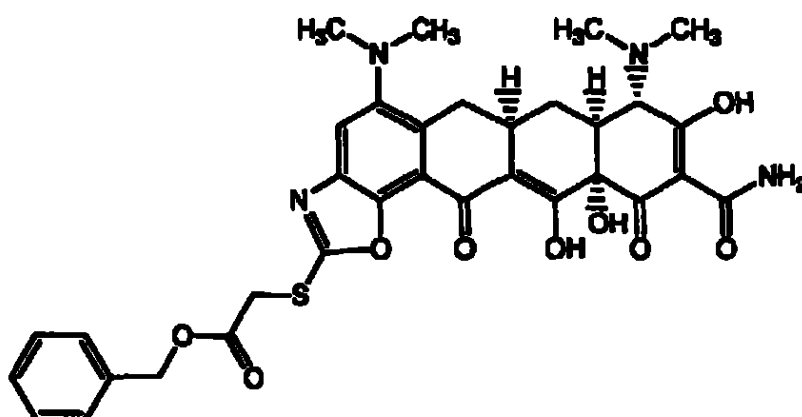
15

Example of procedure C

(Procedure C)

EXAMPLE 43

20 benzyl [[[6aR,7aS,8S,11aS)-10-(aminocarbonyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-8,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazol-2-yl]thio]acetate



25

To a solution of (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-thioxo-2,3,6,8a,7,7a,8,11,11a,13-decahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide (Example 42) in N,N-dimethylformamide (DMF) is added 2 equivalents of diisopropylethylamine, after stirring for 5 min. 1.2 equivalent of benzyl-2-bromoacetate is added. The reaction mixture is stirred for 1 hr and mixture triturated with diethyl ether and solid is collected. It is purified by extraction.

MS (ESI) m/z 663.2 (M+H);

MS (ESI) m/z 332.1 (M+2H);

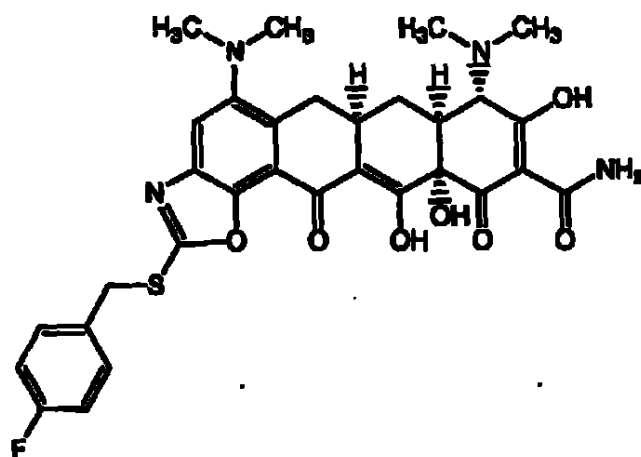
HRMS: calcd for $C_{28}H_{34}N_4O_8S \cdot HCl$, 666.1813; found (ESI+), 663.2115;

10

EXAMPLE 44

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(4-fluorobenzyl)thio]-9,11a,12-trihydroxy-11,13-dioxo-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

15



20

The compound of the example is prepared using procedure D in Example 43 using 4-fluorobenzylbromide.

MS (ESI) m/z 622.9 (M+H);

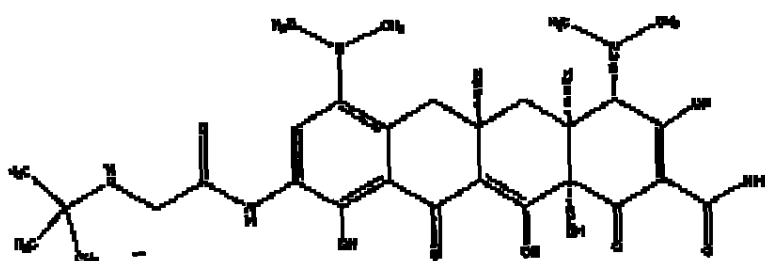
HRMS: calcd for $C_{21}H_{21}FN_4O_7S \cdot HCl$, 656.1664; found (ESI+), 623.18689;

25

Example of Procedure D (Compound 1 to 4 to 8)

Example 45

5 [4S-(4 α ,4a α ,5 α ,12 α)]-4,7-Bis(dimethylamino)-9-[2-(1,1-dimethylethylamino)acetylaminol-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide,
(mono HCl); (free base)



10

9-aminomincycline sulfate salt (1.0 g, 1.50 mmol) is dissolved DMF (20 mL) and treated with a solution of 2-chloromethoxyethane (0.35 g, 2.2 mmol, 1.47
15 equivalents). The reaction is stirred at room temperature until mass spectrometry showed conversion to the chloromethylbenzoxazole derivative. The solution is then treated with *t*-butylamine (7.3 mL, excess) and stirred until mass spectrometry showed conversion to the *t*-butylaminomethyl benzoxazole. The mixture is concentrated under reduced pressure to remove excess *t*-butylamine, and then
20 poured slowly into ether (1 L) and HCl/ether is added to precipitate the salt. The solid is rinsed with fresh ether and dried under vacuum. The crude solid is dissolved in water (100 mL) giving a solution at pH 2. The pH is raised successively by 0.5 units with aqueous ammonia, and extracted with dichloromethane. The fractions extracted at pH 4-4.5 are combined, dried (Na₂SO₄), filtered and concentrated nearly to
25 dryness. A small volume of methanol is added and the solution is treated with 1M HCl in ether. The precipitated solid is collected by filtration, washed with fresh ether and dried under vacuum to give the product as its HCl salt.

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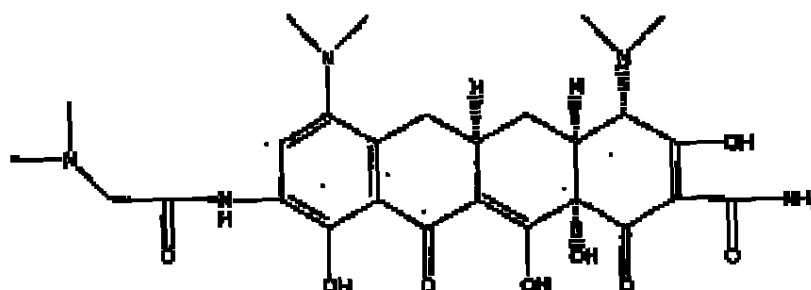
Product from example 41 is treated with aqueous acid for one hour to 24 hour to give mono HCL salt of example 45

MS (ESI+) m/z 568.4 ((M+H)+;

- 5 The following examples are prepared using similar method described in procedure D.

Example 46

[4S-(4 α ,4a α ,5a α ,12a α)]-4,7-Bis(dimethylamino)-9-[(dimethylamino)acetylamino]-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
10 naphthacenecarboxamide.

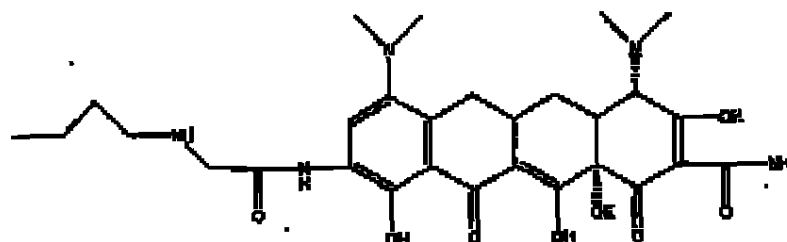


MS (FAB) m/z 568 ((M+H)+;

15

Example 47

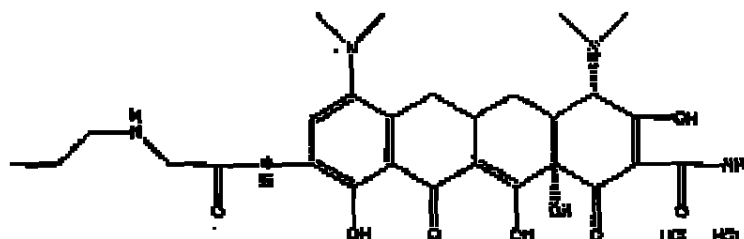
[4S-(4 α ,4a α ,5a α ,12a α)]-4,7-Bis(dimethylamino)-9-[(n-butylamino)acetylamino]-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
20 naphthacenecarboxamide.



MS (FAB) m/z 586 ((M+H)+;

Example 48

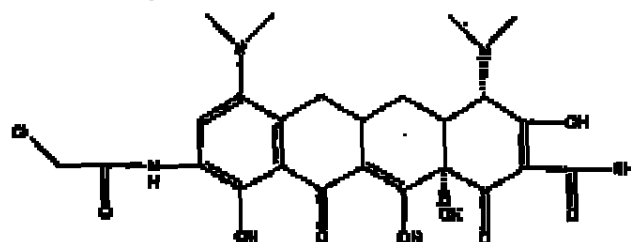
[4S-(4 α ,4a α ,5a α ,12a α)]-4,7-Bis(dimethylamino)-9-[[[(propylamino)acetyl]amino]-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide



MS (FAB) m/z 572 ($(M+H)^+$;

Example 49

[4S-(4 α ,4a α ,5a α ,12a α)]-4,7-Bis(dimethylamino)-9-[(chloroacetyl)amino]-
1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-
naphthacenecarboxamide



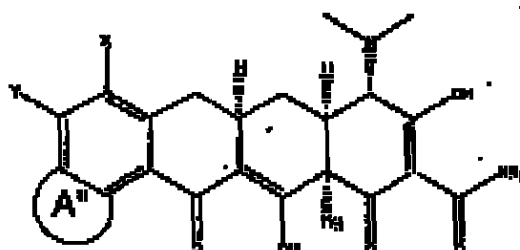
MS (FAB) m/z 549 ($(M+H)^+$;

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WHAT IS CLAIMED IS:

1. A compound of Formula (I);

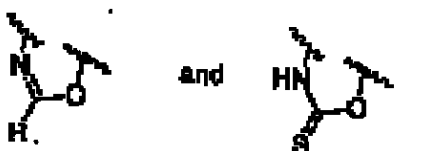


5

wherein:

- 10 X is selected from hydrogen, amino, $\text{NR}^{11}\text{R}^{12}$, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

A' is a moiety selected from the group:



15

R^{11} and R^{12} are each independently H or alkyl of 1 to 12 carbon atoms or R^{11} and R^{12} when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

20

Y is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, alkenyl of 2 to 12 carbon atoms optionally substituted, vinyl, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

25

R is selected from alkyl of 1 to 12 carbon atoms optionally substituted, alkenyl of 2 to 6 carbon atoms optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted, $-\text{CH}_2\text{NR}^1\text{R}^2$, aryl of 5, 10 or 14 carbon atoms optionally substituted, aralkyl of 7 to 16 carbon atoms optionally substituted, aryl of 7 to 13 carbon atoms optionally substituted, SR^3 , heteroaryl of 5 or 6 ring atoms optionally substituted, containing 1 to 4 heteroatoms which may be the same or different, independently selected from nitrogen, oxygen and sulfur, and heteroarylcarbonyl of 5 or 6 ring atoms optionally substituted containing 1 to 4 heteroatoms which may be the same or different, independently selected from nitrogen, oxygen and sulfur;

10

R^1 and R^2 are each independently H or alkyl of 1 to 12 carbon atoms or R^1 and R^2 when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

15

R^3 is alkyl of 1 to 12 carbon atoms optionally substituted, $-\text{CH}_2$ -aryl optionally substituted, aralkyl of 7 to 16 carbon atoms optionally substituted, aryl, $-\text{CH}_2(\text{CO})\text{OCH}_2$ -aryl optionally substituted, $-\text{CH}_2$ -alkenyl of 2 to 12 carbon atoms optionally substituted, and $-\text{CH}_2$ -alkynyl of 2 to 12 carbon atoms optionally substituted;

20

with the proviso that when X is NR^1R^2 and R^1 is hydrogen, then R^2 is methyl, ethyl, n-propyl, n-butyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl; and that when R^1 is methyl or ethyl then R^2 is methyl, ethyl, n-propyl, 1-methylethyl, n-propyl, 1-methylpropyl, or 2-methylpropyl;

25

or a tautomer or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R is phenyl optionally substituted with 1 to 3 substituents or a pharmaceutically acceptable salt thereof.

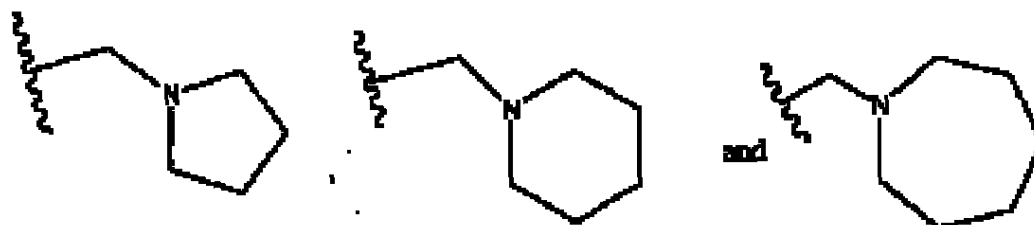
30

3. A compound according to claim 1 wherein R of Formula (I) is selected from the group alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, and alkyl-heterocyclyl or a pharmaceutically acceptable salt thereof.

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4. A compound according to claim 3 wherein alkyl-heterocyclyl is selected from moieties of the group

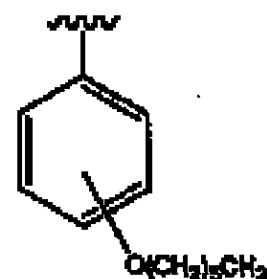
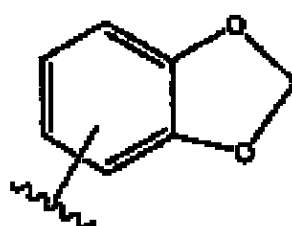
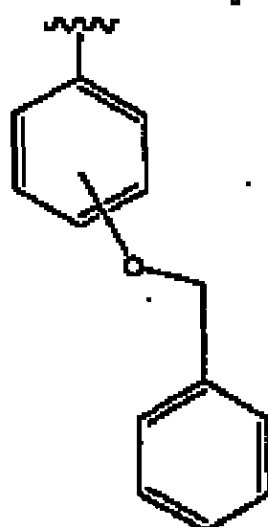
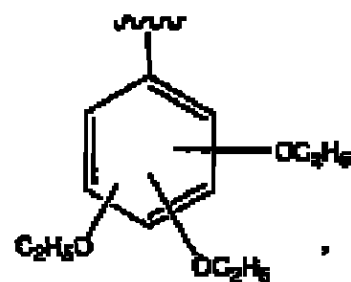
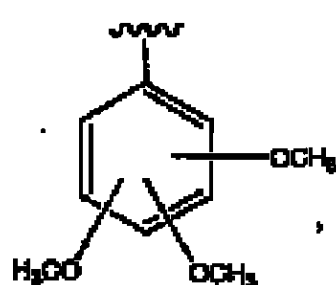
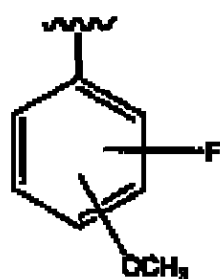
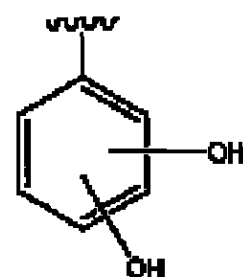
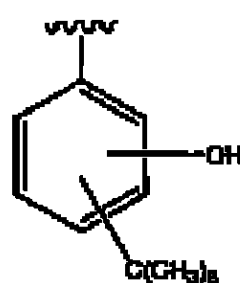
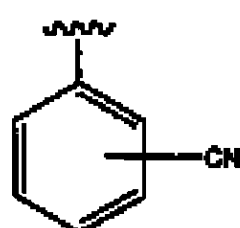
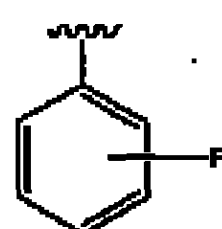
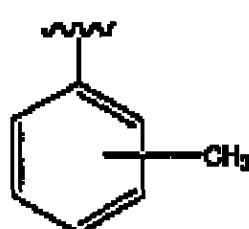
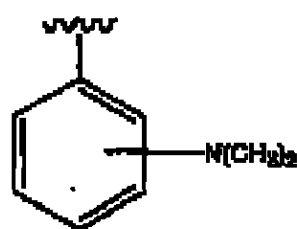


or a pharmaceutically acceptable salt thereof.

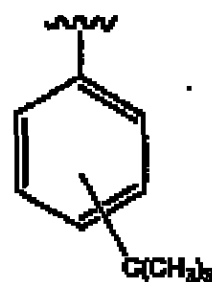
10

5. A compound according to claim 2 wherein R is selected from moieties of the group

15



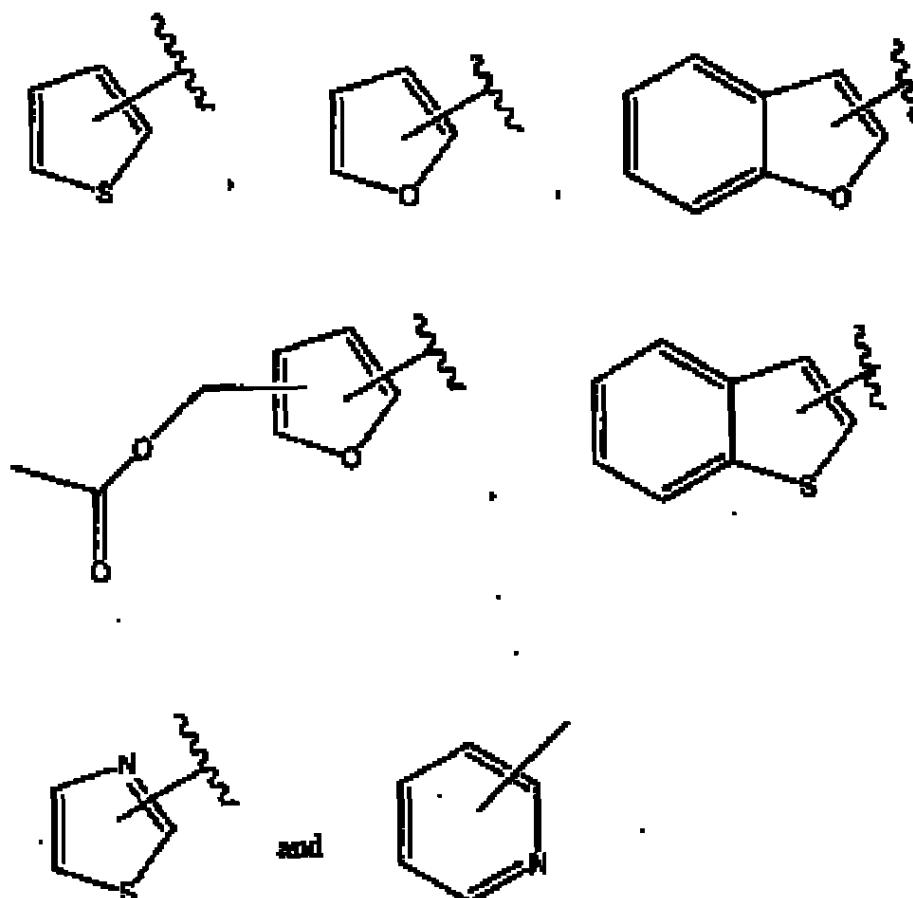
and



or a pharmaceutically acceptable salt thereof.

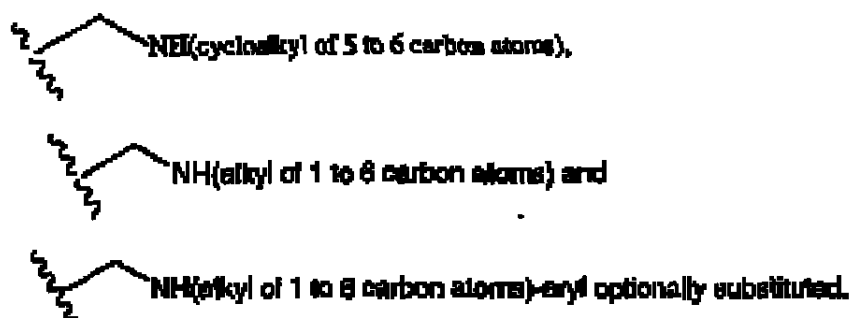
6. A compound according to claim 1 wherein R is heteroaryl or a
5 pharmaceutically acceptable salt thereof.

7. A compound according to claim 6 wherein R is selected from moieties
selected from the group
10



or a pharmaceutically acceptable salt thereof.

8. A compound according to claim 1 wherein R is alkyl of 1 to 5 carbon atoms
optionally substituted, alkenyl of 2 to 5 carbon atoms optionally substituted,



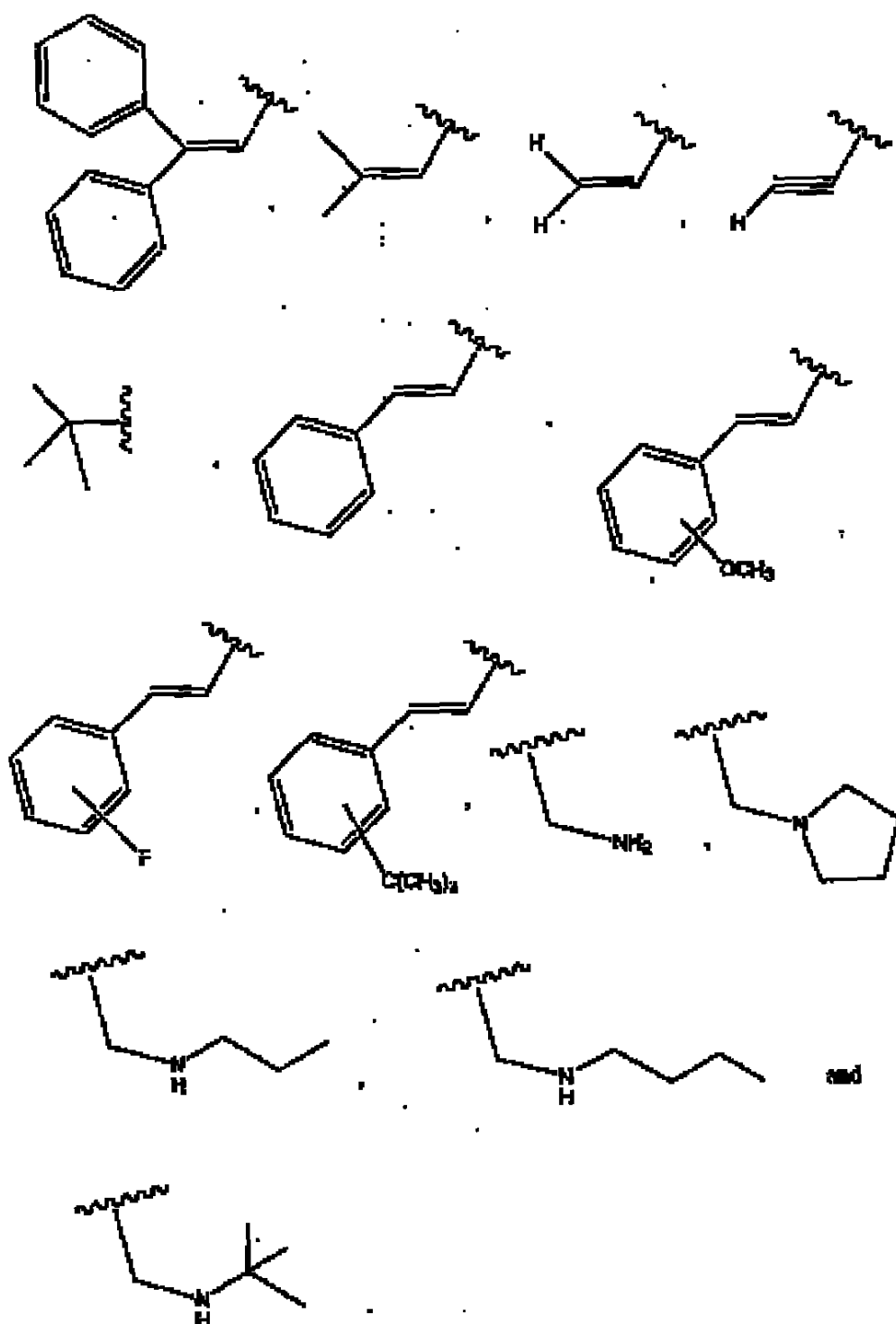
or a pharmaceutically acceptable salt thereof.

5

9. A compound according to claim 1 wherein R is selected from moieties

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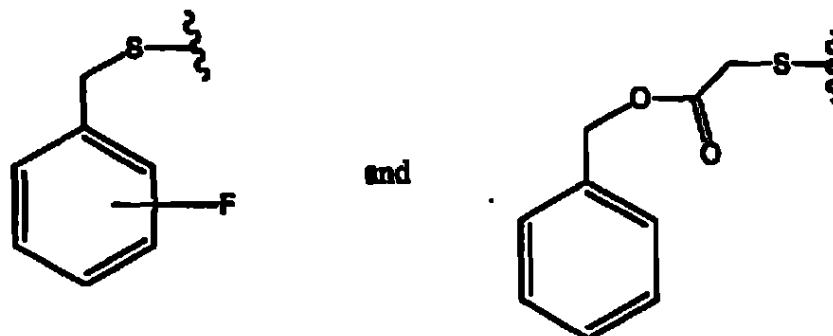


or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 1 wherein R is S-alkyl of 1 to 12 carbon atoms, S-CH₂-aryl optionally substituted and S-CH₂(CO)OCH₂-aryl optionally substituted or a pharmaceutically acceptable salt thereof.

11. A compound according to claim 10 wherein R is selected from moieties of the group

10



or a pharmaceutically acceptable salt thereof.

12. A compound according to any one of claims 1 to 11 wherein Y is H.

15

13. A compound according to any one of claims 1 to 12 wherein X is -NMe₂.

14. A compound according to claim 1 selected from the group:

20

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(2,2-diphenylvinyl)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- 25 (7aS,8S,11aS)-8-(dimethylamino)-9,11a,13-trihydroxy-2-(2-methyl-1-propenyl)-11,12-dioxo-7,7a,8,11,11a,12-hexahydronaphthaceno[2,1-d][1,3]oxazole-10-carboxamide,

- (6aR,7aS,8S,11aS)-2-*tert*-butyl-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 5 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(*E*)-2-(2-furyl)ethenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 10 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-[(*E*)-2-phenylethenyl]-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 15 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-[(*E*)-2-(4-methoxyphenyl)ethenyl]-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 20 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-[(*E*)-2-(3-methoxyphenyl)ethenyl]-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-[(*E*)-2-(2-methoxyphenyl)ethenyl]-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 25 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(*E*)-2-(4-fluorophenyl)ethenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,
- 30 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(*E*)-2-(2-fluorophenyl)ethenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

(6aR,7aS,8S,11aS)-2-(chloromethyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

5

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[(dimethylamino)methyl]-9,11a,12-trihydroxy-11,13-dioxo-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

10 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(pyrrolidin-1-ylmethyl)-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

15 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-[(propylamino)methyl]-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

20 (6aR,7aS,8S,11aS)-2-[(butylamino)methyl]-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-[(propylamino)methyl]-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide and

25

(6aR,7aS,8S,11aS)-2-[(*tert*-butylamino)methyl]-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,8a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide; or a pharmaceutically acceptable salt thereof.

30 15. A compound according to claim 1 selected from the group:

(7aS,8S,11aS)-8-(dimethylamino)-2-[4-(dimethylamino)phenyl]-9,11a,13-trihydroxy-11,12-dioxo-7,7a,8,11,11a,12-hexahydronaphthaceno[2,1-d][1,3]oxazole-10-carboxamide,

- 5 (6aR,7aS,8S,11aS)-2-tert-butyl-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- 10 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-(4-methylphenyl)-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- 15 (7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(3-fluorophenyl)-9,11a,13-trihydroxy-11,12-dioxo-7,7a,8,11,11a,12-hexahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

(6aR,7aS,8S,11aS)-2-(4-cyanophenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- 20 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-[4-(dimethylamino)phenyl]-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- 25 (6aR,7aS,8S,11aS)-2-(5-tert-butyl-2-hydroxyphenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- 30 (6aR,7aS,8S,11aS)-2-[4-(benzyloxy)phenyl]-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

(6aR,7aS,8S,11aS)-2-(2,4-dihydroxyphenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- 5 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(3-fluoro-4-methoxyphenyl)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- 10 (6aR,7aS,8S,11aS)-2-(1,3-benzodioxol-5-yl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- 15 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(2,4,6-trimethoxyphenyl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(2,4,5-triethoxyphenyl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- 20 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-2-(1-methyl-1H-indol-2-yl)-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

- 25 (6aR,7aS,8S,11aS)-2-(4-tert-butylphenyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide and

- 30 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(4-nonyloxyphenyl)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

or a pharmaceutically acceptable salt thereof.

16. A compound according to claim 1 selected from the group:

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-thien-3-yl-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

5

(6aR,7aS,8S,11aS)-2-(1-benzofuran-2-yl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

10 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-2-(2-furyl)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

{5-[(6aR,7aS,8S,11aS)-10-(aminocarbonyl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazol-2-yl]-2-furyl}methyl acetate,

15

(6aR,7aS,8S,11aS)-2-(1-benzothien-3-yl)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

20

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-(1,3-thiazol-2-yl)-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide,

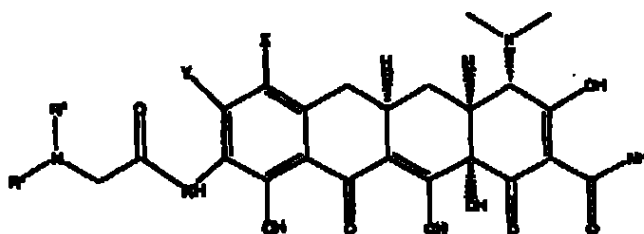
25 (6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-pyridin-4-yl-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide and

(6aR,7aS,8S,11aS)-5,8-bis(dimethylamino)-9,11a,12-trihydroxy-11,13-dioxo-2-pyridin-3-yl-6,6a,7,7a,8,11,11a,13-octahydrotetraceno[2,1-d][1,3]oxazole-10-carboxamide

30

or a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition comprising a compound according to any one of claims 1 to 16 or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier.
- 5 18. A method for the treatment or control of bacterial infections in warm-blooded animals which comprises administering to said animal a pharmacologically effective amount of a compound according to any one of claims 1 to 16 or a pharmaceutically acceptable salt thereof.
- 10 19. A process for the preparation of a compound of the formula



or a pharmaceutically acceptable salt thereof

- 15 wherein:

X is selected from hydrogen, amino, $\text{NR}^{11}\text{R}^{12}$, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl, optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

20

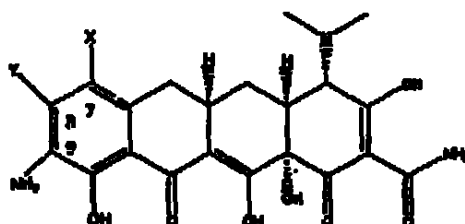
R^1 and R^2 are each independently H or alkyl of 1 to 12 carbon atoms or R^1 and R^2 when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

- 25 R^{11} and R^{12} are each independently H or alkyl of 1 to 12 carbon atoms or R^{11} and R^{12} when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

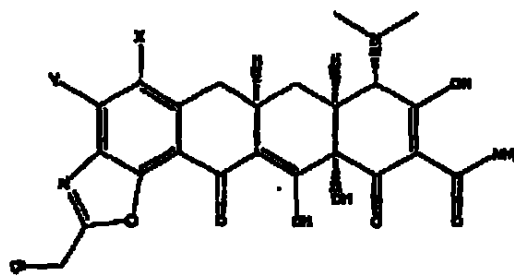
Y is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, alkanyl of 2 to 12 carbon atoms optionally substituted, vinyl, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

5 comprising the steps:

a. reacting 7-(substituted)-6-(substituted)-9-amino-6-demethyl-6-deoxytetracycline of the formula

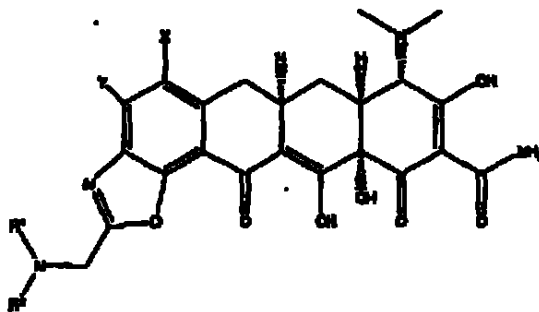


10 or a pharmaceutically acceptable salt thereof
with 2-chlorotrimethoxyethane in an aprotic solvent to afford a chloro compound of the formula

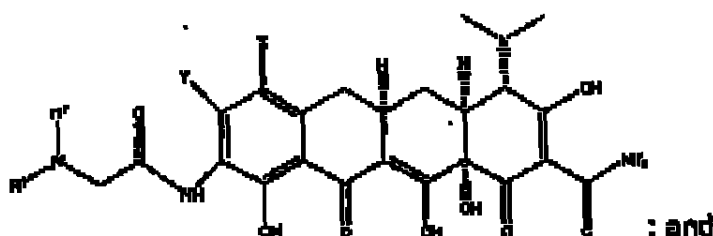


15

b. reacting the chloro compound with an amine R^1R^2NH to form a substituted amine of the formula



c. hydrolyzing the substituted amine with acid to give a compound of the formula



d. isolating the compound or a pharmaceutically acceptable salt thereof.

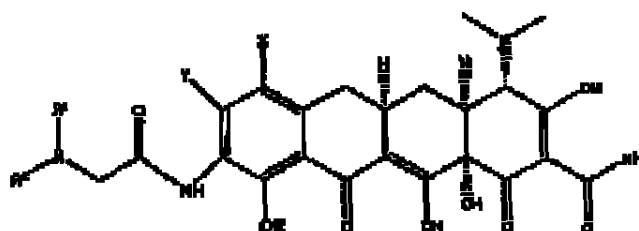
20. The process according to claim 19 wherein X is $N(CH_3)_2$.

21. The process according to claim 19 or claim 20 wherein the amine R^1R^2NH is *t*-butyl amine.

22. The process according to any one of claims 19 to 21 wherein the aprotic solvent is N,N-dimethylformamide.

23. The process according to any one of claims 19 to 22 wherein [4S-(4a,4a,5a,12a)]-4,7-Bis(dimethylamino)-9-[2-(1,1-dimethylethylamino)acetyl]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,1-dioxo-2-naphthacene-9-carboxamide or a pharmaceutically acceptable salt thereof is prepared.

24. A process for the preparation of a compound of the formula



wherein:

X is selected from hydrogen, amino, NR^1R^2 , alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl, optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

R^1 and R^2 are each independently H or alkyl of 1 to 12 carbon atoms or R^1 and R^2 when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

R^{11} and R^{12} are each independently H or alkyl of 1 to 12 carbon atoms or R^{11} and R^{12} when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

15

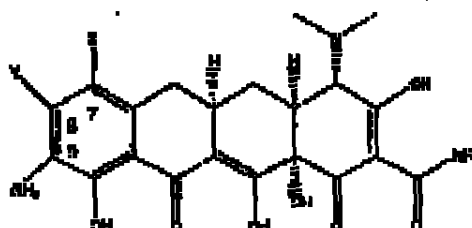
Y is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl, alkynyl of 2 to 12 carbon atoms optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

20

or a pharmaceutically acceptable salt thereof comprising the steps:

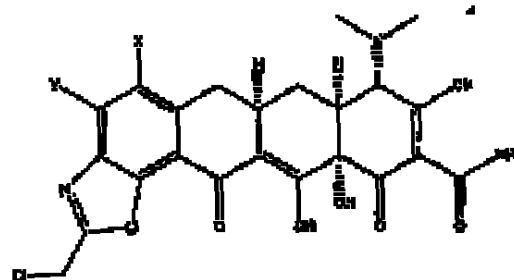
a. reacting 7-(substituted)-8-(substituted)-9-amino-8-demethyl-6-deoxytetracycline of the formula

25

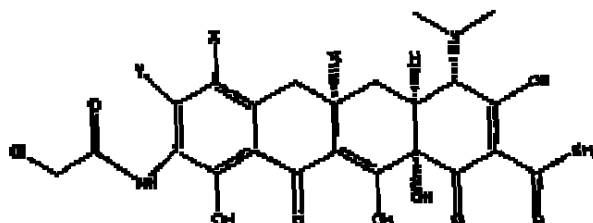


or a pharmaceutically acceptable salt thereof

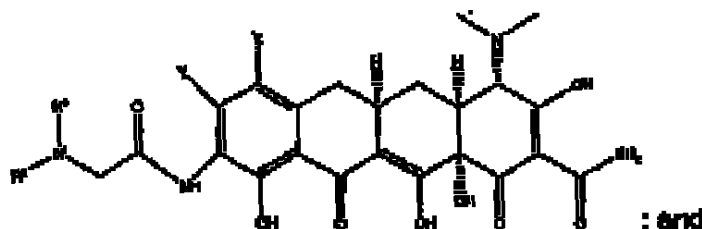
with 2-chlorotrimethoxyethane in an aprotic solvent to afford a chloro compound of the formula



- b. reacting the chloro compound with acid to give 9-(2-chloromethylcarbonylamino)substituted-6-demethyl-6-deoxytetracycline of the formula



- c. reacting the 9-(2-chloromethylcarbonylamino)substituted-6-demethyl-6-deoxytetracycline with amine R^1R^2NH to give a compound of the formula

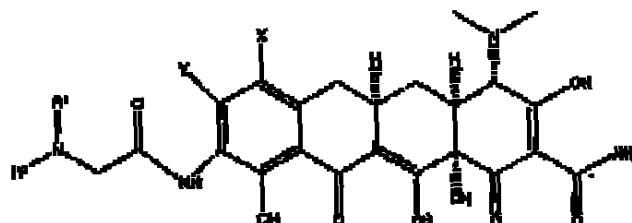


- e. isolating the compound or a pharmaceutically acceptable salt thereof.
25. The process according to claim 24 wherein X is $N(CH_3)_2$.
26. The process according to claim 24 or claim 25 wherein the amine R^1R^2NH is t-butyl amine.

27. The process according to any one of claims 24 to 26 wherein the aprotic solvent is N,N-dimethylformamide.

28. The process according to any one of claim 24 to 27 wherein [4S-(4 α ,4a α ,5a α ,12a α)]-4,7-Bis(dimethylamino)-9-[2-(1,1-dimethylethylamino)acetylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide or a pharmaceutically acceptable salt thereof is prepared.

29. A compound of the formula



or a pharmaceutically acceptable salt thereof

wherein:

X is selected from hydrogen, amino, NR¹¹R¹², alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl, optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

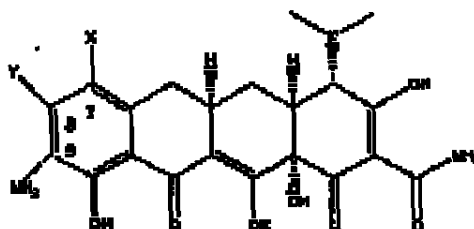
R¹ and R² are each independently H or alkyl of 1 to 12 carbon atoms or R¹ and R² when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

R¹¹ and R¹² are each independently H or alkyl of 1 to 12 carbon atoms or R¹¹ and R¹² when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

Y is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, alkenyl of 2 to 12 carbon atoms optionally substituted vinyl, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

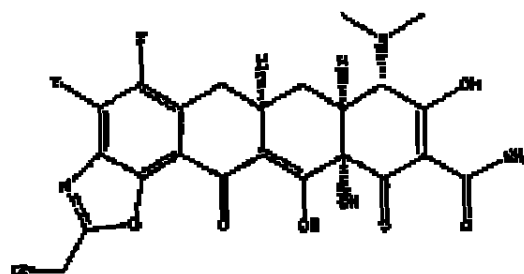
5 produced by the process comprising the steps:

a. reacting 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-deoxytetracycline of the formula



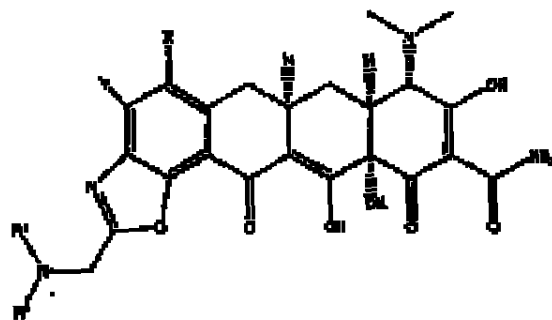
10 or a pharmaceutically acceptable salt thereof

with 2-chlorobromethoxyethane in an aprotic solvent to afford a chloro compound of the formula

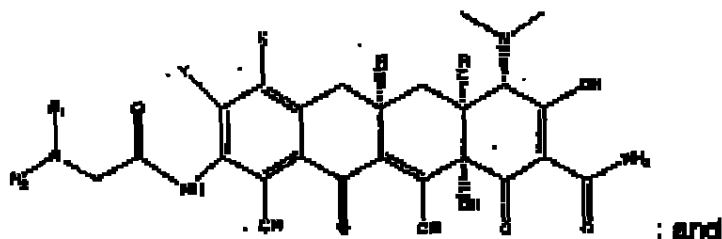


15

b. reacting the chloro compound with an amine R^1R^2NH to form a substituted amine of the formula



- c. hydrolyzing the substituted amine with acid to give a compound of the formula



5

- d. isolating the compound or a pharmaceutically acceptable salt thereof.

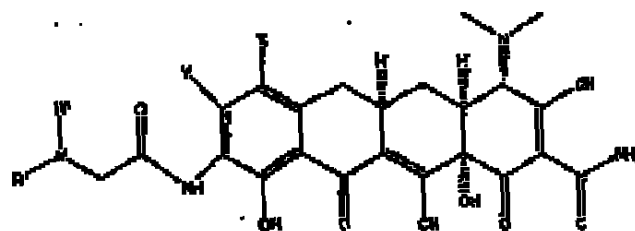
30. The product produced by the process according to claim 29 wherein X is
10 $N(CH_3)_2$.

31. The product produced by the process according to claim 29 or claim 30
wherein the amine R^1R^2NH is 1-butyl amine.

- 15 32. The product produced by the process according to any one of claims 29 to 31
wherein the aprotic solvent is N,N-dimethylformamide.

33. The product produced by the process according to any one of claims 29 to 31
which is [4S-(4 α ,4 α ,5 α ,12 α)]-4,7-Bis(dimethylamino)-9-[2-(1,1-
20 dimethylethylamino)acetylaminol-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-
tetrahydroxy-1,11-dioxo-2-naphthoquinonecarboxamide or a pharmaceutically
acceptable salt thereof.

- 25 34. A compound of the formula



what's:

- 5 X is selected from hydrogen, amino, NR^1R^2 , alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, vinyl optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted and halogen;

R¹ and R² are each independently H or alkyl of 1 to 12 carbon atoms or

- 10 R¹ and R² when optionally taken together with the nitrogen atom to which each is attached form a 3 to 7 membered saturated hydrocarbon ring;

R¹¹ and R¹² are each independently H or alkyl of 1 to 12 carbon atoms or

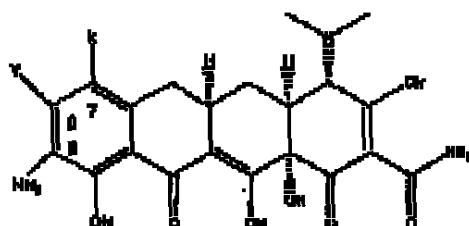
- R¹¹ and R¹² when optionally taken together with the nitrogen atom to which each is**
15 attached form a 3 to 7 membered saturated hydrocarbon ring;

Y is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, alkenyl of 2 to 12 carbon atoms optionally substituted, vinyl, alkynyl of 2 to 12 carbon atoms optionally substituted

- 20 and halogen:**

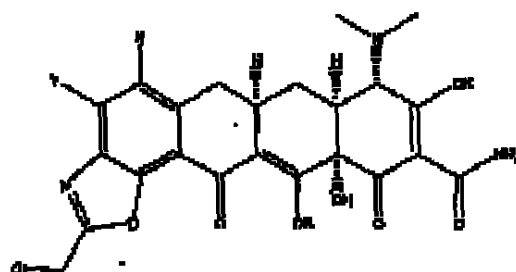
or a pharmaceutically acceptable salt thereof produced by the process comprising the steps:

- a. reading 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-deoxytetracycline of the formula

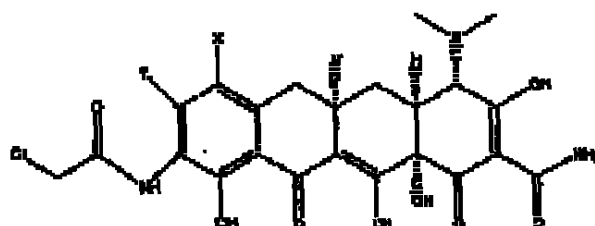


or a pharmaceutically acceptable salt thereof

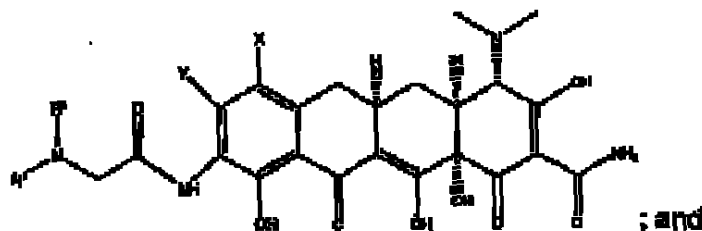
with 2-chlorotrimethoxyethane in an aprotic solvent to afford a chloro compound of the formula



b. reacting the chloro compound with acid to give 6-(2-chloromethyl(carbonylamino)substituted-6-demethyl-4-oxo-5-deoxytetracycline of the formula



d. reacting the 9-(2-chloromethylcarbonylamino)substituted-6-demethyl-6-deoxytetracycline with amine R^1R^2NH to give a compound of the formula



d. isolating the compound or a pharmaceutically acceptable salt thereof.

35. The product prepared by the process according to claim 34 wherein X is
5 $N(CH_3)_2$.

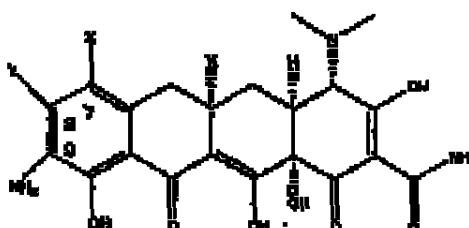
36. The product prepared by the process according to claim 34 or claim 35
wherein the amine R^1R^2NH is t-butyl amine.

10 37. The product prepared by the process according to any one of claims 32 to 36
wherein the aprotic solvent is N,N-dimethylformamide.

38. The product prepared by the process according to any one of claims 34 to 37
which is {4S-(4 α ,4 α ,5 α ,12 α)}-4,7-Bis(dimethylamino)-9-[2-(1,1-
15 dimethylethylamino)acetylamino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-
tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide or a pharmaceutically
acceptable salt thereof.

39. A process for preparing a compound of formula I according to claim 1 which
20 comprises

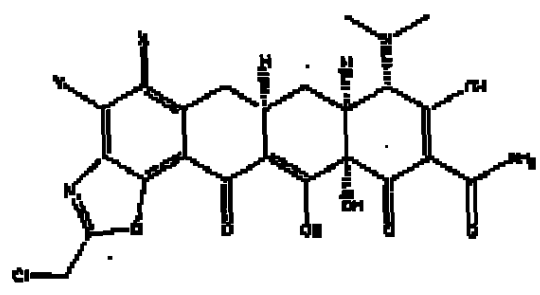
a). reacting 7-(substituted)-8-(substituted)-9-amino-6-demethyl-6-
deoxytetracycline of the formula



25 or a pharmaceutically acceptable salt thereof
with 2-chlorotrimethoxyethane in an aprotic solvent to afford a chloro compound of
the formula

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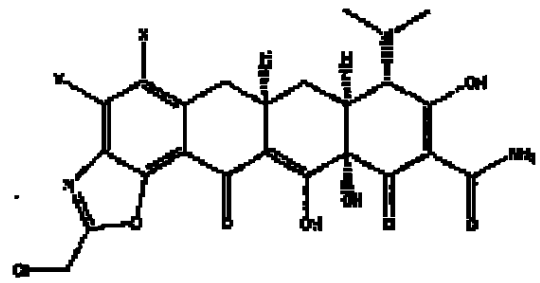
PCT/US2004/010850



wherein the variables are as defined in claim 1;

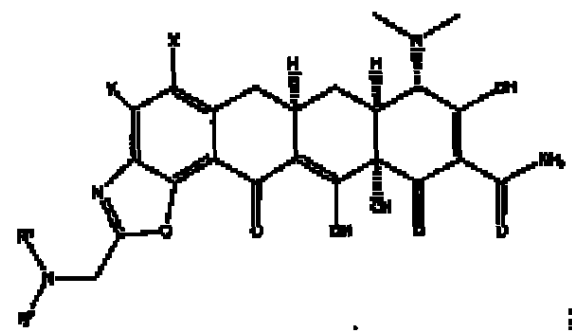
or

- 5 b. reacting a chloro compound of formula



wherein the variables are as defined in claim 1; with an amine R^1R^2NH to form a substituted amine of the formula

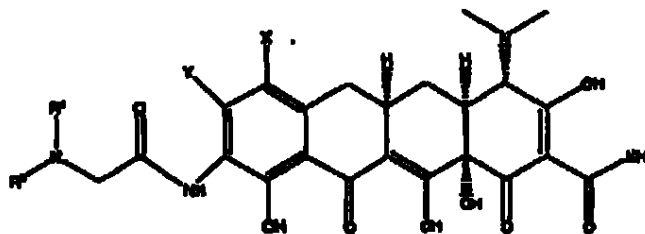
10



or

- 15 c) converting a basic compound of formula 1 as defined in claim 1 to a pharmaceutically acceptable salt thereof or vice versa.

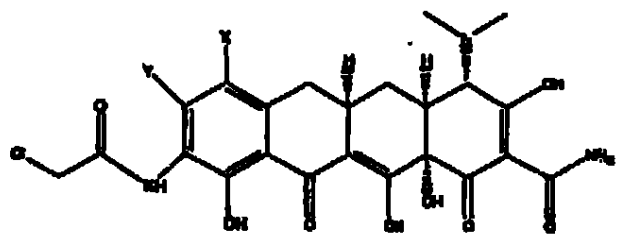
40. A process for preparing a compound of formula:



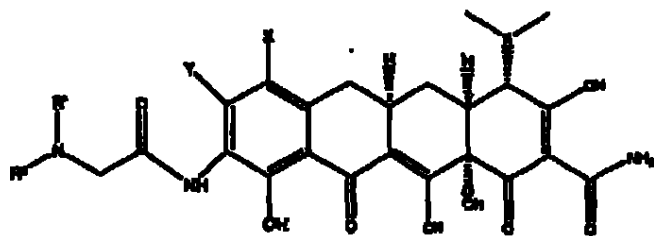
wherein the variables are as defined in claim 34 which comprises:

5

a) reacting a 9-(2-chloromethylcarbonylamino)substituted-6-demethyl-6-deoxytetracycline of the formula



10 with an amine R^1R^2NH to give a compound of the formula



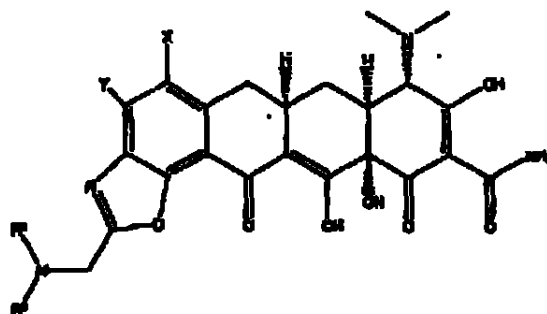
15

or

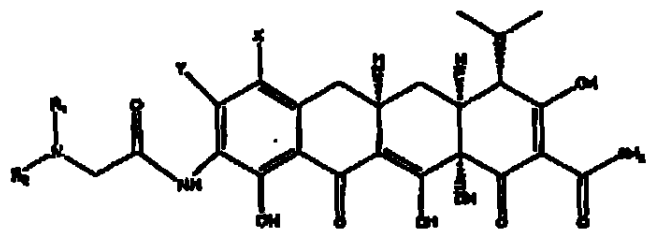
b) hydrolyzing a substituted amine of formula

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wherein the variables are as defined in claim 28,
with acid to give a compound of the formula



5

and if desired converting the product to a pharmaceutically acceptable salt thereof.

10

INTERNATIONAL SEARCH REPORT

 International Application No.
PCT/US2004/040850

87

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D263/52 C07C237/26 A61K31/423 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum description searched is classification system followed by classification symbols

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation is the extent that such documents are indicated in the fields searched

Declaration: data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 494 903 A (HLAVKA ET AL) 27 February 1996 (1996-02-27) cited in the application	1-28, 39, 40
X	examples	29-38
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X	page 15; claim 7; examples	40



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

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

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"O" Document referring to an oral disclosure, use, exhibition or other means

"P" Document published prior to the international filing date but later than the priority date claimed

"T" Document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" Document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

7 Apr 11 2005

Date of mailing of the international search report

14/04/2005

Name and mailing address of the ISA

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Fax: (+31-78) 340-3016

Authorized officer

Lauro, P

INTERNATIONAL SEARCH REPORT

Inventor: Application No.
PET/US2004/040850

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Int'l Application No
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DERIVADOS OXAZOL DE TETRACICLINA

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CAMPO DE LA INVENCION

La presente invención se relaciona con derivados oxazol de tetraciclinas novedosas que son útiles como agentes antibióticos y exhiben actividad antibacterial contra un amplio espectro de organismos que incluyen organismos que son resistentes a tetraciclinas y otros antibióticos. La invención también se relaciona con intermedios de tetraciclina novedosos útiles para la elaboración de compuestos novedosos y métodos novedosos para producir los compuestos novedosos y los compuestos intermedios.

ANTECEDENTES DE LA INVENCION

Desde 1947 han sido sintetizados una variedad de antibióticos de tetraciclina y se han descrito para el tratamiento de enfermedades infecciosas en el hombre y en animales. Las tetraciclinas inhiben la síntesis de proteína al unirse a la subunidad 30S del ribosoma bacterial evitando la unión del ARN aminoacilo (Chopra, Handbook of Experimental Pharmacology, Vol. 78, 317-392, Springer-Verlag, 1985). La resistencia a las tetraciclinas ha surgido entre muchos organismos clínicamente importantes que limitan la utilidad de estos antibióticos. Existen dos mecanismos principales de resistencia bacterial a las tetraciclinas: a) el flujo dependiente de energía del antibiótico mediado por proteínas localizadas en la membrana citoplasmática que evita la acumulación intracelular de la tetraciclina (S. B. Levy, et al.,

Antimicrob. Agents Chemotherapy 33, 1373-1374 (1989)) y b) protección ribosomal mediada por una proteína citoplasmática que interactúa con el ribosoma de tal forma que la tetraciclina ya no puede inhibir la síntesis de proteína (A. A. Salyers, B. S. Speers and N. B. Shoemaker, Mol. Microbiol, 4:151-156, 1990). El mecanismo de flujo de resistencia es codificado por los determinantes de resistencia designados tetA-tetL. Ellos son comunes en muchas bacterias Gram negativas (genes de resistencia Clase A-E), tales como Enterobacteriaceae, Pseudomonas, Haemophilus y Aeromonas, y en bacterias Gram positivas (resistencia a genes Clase K y L), tales como Staphylococcus, Bacillus y Streptococcus. El mecanismo de protección ribosomal de resistencia se codifica mediante los determinantes de resistencia asignados TetM, N y O, y es común en Staphylococcus, Streptococcus, Campylobacter, Gardnerella, Haemophilus y Mycoplasma (A. A. Salyers, B. S. Speers and N. B. Shoemaker, Mol. Microbiol, 4:151-156 1990).

Un compuesto de tetraciclina particularmente útil es el 7-(dimetilamino)-5-dimetil-6-desoxitetraciclina, conocido como minociclina (ver Patente U.S. No. 3,148,212, Patente U.S. No. RE 26,253 y Patente U.S. No. 3,226,436 que se discuten adelante). Sin embargo, las cepas que resguardan el mecanismo tetB (eflujo en bacterias gram negativas) pero no el tetK (eflujo en Staphylococcus) son resistentes a aminociclina. También, las cepas que llevan tetM (protección ribosomal) son resistentes a minociclina. Esta invención describe la síntesis de compuestos de tetraciclina novedosos que demuestran actividad significativa in vitro e in vivo versus las cepas susceptibles a tetraciclina y

minociclina y a algunas cepas resistentes a tetraciclina y minociclina, esto es, aquellas que resguardan los determinantes de resistencia tetM (protección ribosomal).

Duggar, Patente U.S. No. 2,482,055, describe la preparación de Aureomicina.RTM, mediante la fermentación que tiene actividad antibacterial. Growich et al., Patente U.S. No. 3,007,965, describe las mejoras a la preparación de fermentación. Beereboom et al., Patente U.S. No. 3,043,875 describe los derivados de tetraciclina Boothe et al., Patente U.S. No. 3,148,212, republicada como la Patente U.S. No. RE 26,253, y Petisi et al., Patente U.S. No. 3,228,436, describe los derivados de tetraciclina que son útiles para tratar infecciones bacterianas. Blackwood et al., Patente U.S. No. 3,200,149 describe derivados de tetraciclina que poseen actividad microbiológica. Petisi et al., Patente U.S. No. 3,335,963 describe compuestos de tetraciclina que tiene actividad antibacterial de amplio espectro. Sitha et al., Patente U.S. No. 3,341,585 describe compuestos de tetraciclina que tienen actividad antibacterial de amplio espectro. Shu, Patente U.S. No. 3,360,557 describe 9-hidroxitetraciclinas que se ha encontrado que poseen actividad antibacterial. Zambrano, Patente U.S. No. 3,360,561 describe un proceso para preparar 9-nitrotetraciclinas. Marcelli et al., Patente U.S. No. 3,518,306 describe tetraciclinas que poseen actividad antibacterial in vivo.

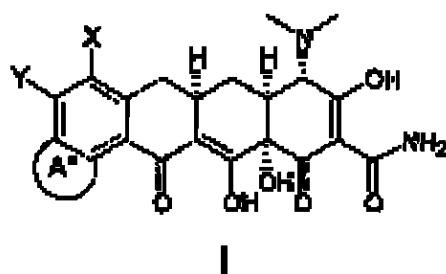
En la Patente U.S. No. 5,021,407 se describe un método para contrarrestar la resistencia de bacterias resistentes a la tetraciclina. El método involucra utilizar un compuesto agente de

bloqueo en conjunto con un antibiótico tipo tetraciclina. Esta patente no describe compuestos de tetraciclina novedosos que tengan ellos mismos actividad contra organismos resistentes. Se describe en la Patente No. 5,494,903 los amino-6-desetil-6-desoxitetraciclinas 7-substituido-9-substituido que tienen actividad antibacterial de amplio espectro.

En resumen, ninguna de las patentes anteriores enseña o sugiere los compuestos novedosos de esta solicitud. Además, ninguna de las patentes anteriores enseña o sugiere compuestos de tetraciclina novedosos de la invención que tengan actividad contra las cepas resistentes a tetraciclina y minociclina así como también las cepas que son normalmente susceptibles a tetraciclinas.

RESUMEN DE LA INVENCIÓN

De acuerdo con la presente invención, se suministran compuestos representados por la Fórmula (I);

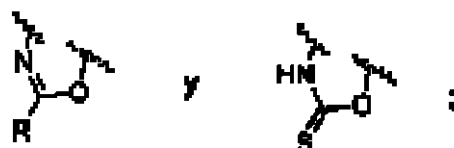


en donde:

X se selecciona del grupo hidrógeno, amino, $NR^{11}R^{12}$, alquilo de 1 a 12 átomos de carbono opcionalmente sustituido, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituido, vinilo

opcionalmente sustituido, alquínilo de 2 a 12 átomos de carbono opcionalmente sustituido y halógeno;

A" es una porción seleccionada del grupo:



R¹¹ y R¹² son cada uno independientemente H o alquilo de 1 a 12 átomos de carbono o R¹¹ y R¹² cuando se toman opcionalmente juntos con el átomo de nitrógeno al cual cada uno está unido forman un anillo de hidrocarburo saturado de 3 a 7 miembros;

Y se selecciona de hidrógeno, alquilo de 1 a 12 átomos de carbono opcionalmente sustituido, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituido, alquénilo de 2 a 12 átomos de carbono opcionalmente sustituido, vinilo, alquínilo de 2 a 12 átomos de carbono opcionalmente sustituido y halógeno;

R se selecciona de alquilo de 1 a 12 átomos de carbono opcionalmente sustituido, alquénilo de 2 a 12 átomos de carbono opcionalmente sustituido, alquínilo de 2 a 12 átomos de carbono opcionalmente sustituido, -CH₂NR¹R², arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituido, aralquilo de 7 a 16 átomos de carbono opcionalmente sustituido, arilo de 7 a 13 átomos de carbono opcionalmente sustituido, SR¹, heteroarilo de 5 o 6 átomos por anillo opcionalmente sustituido, que contiene 1 a 4 heteroátomos que pueden ser iguales o diferentes,

independientemente seleccionados de nitrógeno, oxígeno y azufre, y heterocárilcarbónilo de 5 o 6 átomos por anillo opcionalmente sustituido que contiene 1 a 4 heteroátomos que pueden ser iguales o diferentes, independientemente seleccionados de nitrógeno, oxígeno y azufre;

R^1 y R^2 son cada uno independientemente H o alquilo de 1 a 12 átomos de carbono o R^1 y R^2 cuando opcionalmente se toman juntos con el átomo de nitrógeno al cual cada uno está unido forman un anillo de hidrocarburo saturado de 3 a 7 miembros;

R^3 es alquilo de 1 a 12 átomos de carbono opcionalmente sustituido, $-CH_2$ -arilo opcionalmente sustituido, aralquilo de 7 a 16 átomos de carbono opcionalmente sustituido, aroilo, $-CH_2(CO)OCH_2$ arilo opcionalmente sustituido, $-CH_2$ -alquenilo de 2 a 12 átomos de carbono opcionalmente sustituido, y $-CH_2$ -alquinilo de 2 a 12 átomos de carbono opcionalmente sustituido;

con la condición de que cuando X es NR^1R^2 y R^1 es hidrógeno, entonces R^2 es metilo, etilo, n-propilo, n-butilo, i-metiletilo, 1-metilpropilo, 2-metilpropilo o 1,1-dimetiletilo; y que cuando R^1 es metilo o etilo entonces R^2 es metilo, etilo, n-propilo, 1-metiletilo, n-propilo, 1-metilpropilo, o 2-metilpropilo;

o un tautómero o sales farmacéuticamente aceptables de estos.

DEFINICIONES

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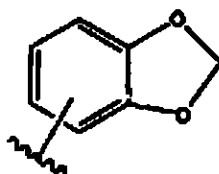
El término alquilo como un grupo o una porción de un grupo significa una porción alquilo recta o ramificada de 1 a 12 átomos de carbono que puede ser opcionalmente independientemente sustituido con 1 a 3 sustituyentes seleccionado del grupo halógeno, amino, ciano, cicloalquilo de 3 a 6 átomos de carbono, alquilo de 1 a 12 átomos de carbono, arilo opcionalmente sustituido, fenilo, hidroxilo, alcoxi de 1 a 12 átomos de carbono, NH-alquilo de 1 a 12 átomos de carbono, N-cicloalquilo de 3 a 6 átomos de carbono, NH-(alquilo de 1 a 12 átomos de carbono)-arilo opcionalmente sustituido y heterociclilo de anillo de 3 a 6 miembros. En algunas modalidades de la invención el alquilo es una porción de 1 a 6 átomos de carbono. En otras modalidades de la invención alquilo es una porción de 1 a 3 átomos de carbono. En otras modalidades alquilo es sustituido por heterociclilo de 4 a 7 miembros por anillo (por ejemplo pirrolidinilo)

El término alquénilo significa una cadena de carbono recta o ramificada de 2 a 12 átomos de carbono que tiene al menos un sitio de insaturación opcionalmente independientemente sustituido con 1 a 3 sustituyentes seleccionados del grupo arilo, fenilo, heteroarilo, halógeno, amino, ciano, alquilo opcionalmente sustituido de 1 a 12 átomos de carbono, hidroxilo, y alcoxi de 1 a 12 átomos de carbono.

El término vinilo significa una porción $\text{CH}_2=\text{CH}-$.

Como se utiliza aquí el término alcoxi como un grupo o porción de un grupo se refiere a alquil-O- en donde alquilo se define adelante.

Como se utiliza aquí el término arilo como un grupo o porción de un grupo, por ejemplo, aralquilo, aroilo, significa una porción aromática que tiene 6, 10 o 14 átomos de carbono preferiblemente 6 a 10 átomos de carbono, que pueden ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alquenoilo, hidroxilo, alquilo, haloalquilo, alcoxi, benciloxi, amino, alquiloamino, dialquiloamino, carboxilo, alcóxicarbonilo, metilenoedioxi y fenilo. En particular, arilo es fenilo o naftilo opcionalmente sustituido con 1 a 3 sustituyentes. Fenilo sustituido puede opcionalmente ser la porción.



El término aralquilo como se utiliza aquí de 7 a 16 átomos de carbono significa un alquilo sustituido con un grupo arilo en el cual el grupo arilo y alquilo están definidos previamente. Ejemplos no limitantes de grupos aralquilo incluyen bencilo y fenetilo y similares.

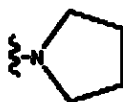
El fenilo como se utiliza aquí se refiere a un anillo aromático con 6 carbonos miembro.

Como se utiliza aquí el término alquínilo incluye tanto porciones de cadena recta como ramificada que contienen 2 a 12 átomos de carbono que tienen al menos un enlace triple carbono a carbono opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados del grupo halógeno, amino, ciano, alquilo de 1 a 12 átomos de carbono, hidroxilo, y alcoxi de 1 a 12 átomos de carbono.

Como se utiliza aquí el término halógeno o halo significa F, Cl, Br o I.

Como se utiliza aquí el término cicloalquilo significa un anillo monocíclico saturado de 3 a 6 átomos de carbono. Anillos cicloalquilo de ejemplo incluyen pero no están limitados a ciclopropilo, ciclobutilo, ciclopentilo, y ciclohexilo. En una modalidad de la invención el cicloalquilo es una porción de 5 o 6 átomos de carbono.

Como se utiliza aquí, R^1 y R^2 y R^{11} y R^{12} cuando se toman opcionalmente junto con el átomo de nitrógeno al cual cada uno está unido forman un anillo de hidrocarburo saturado de 3 a 7 miembros, donde un ejemplo no limitante es pirrolidinilo,



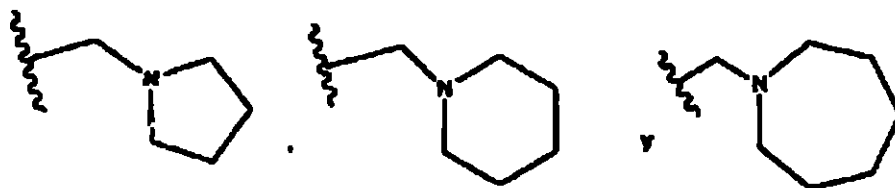
El término aroilo significa un grupo aril-C(O)- en el cual el grupo arilo es como se definió previamente. Ejemplos no limitantes incluyen benzoil y naftoil.

El término heteroarilo significa un anillo heterocíclico, monocíclico aromático de 5 o 6 átomos por anillo que contiene 1 a 4 heteroátomos independientemente seleccionados de O, N y S. Los anillo heteroarilo pueden opcionalmente ser sustituidos con 1 a 3 sustituyentes seleccionados del grupo halógeno, ciano, nitro, hidroxilo, amino, alquilamino, dialquilamino, alcoxi, ariloxi, $-\text{CH}_2\text{OCOCH}_3$ y carboxi. Porciones heteroarilo no limitantes opcionalmente sustituidas incluyen: furanilo, tienilo, piridilo, tetrazolilo, imidazo, tiazolilo y similares. Adicionalmente incluido está el benzofuranilo, benzotienilo y quinolinilo.

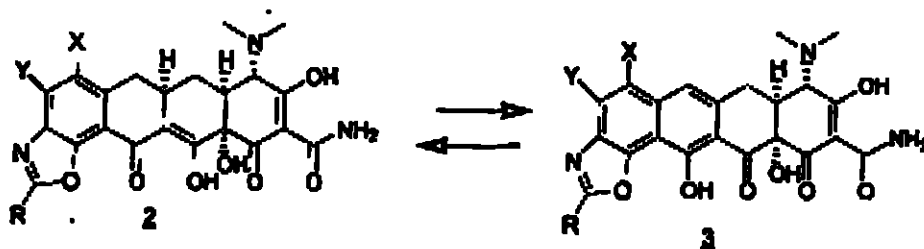
El término heteroarilcarbonilo significa un grupo heteroaril-C(O)- en el cual el grupo heteroarilo es como se definió previamente.

El término heterociclilo como se utiliza aquí representa un anillo saturado de 3 a 8 miembros que contiene uno a tres heteroátomos seleccionados de nitrógeno, oxígeno y azufre. Los ejemplos representativos son pirrolidilo, piperidil, piperazinilo, morfolinilo, tiomorfolinilo, aziridinilo, tetrahydrofuranilo y similares.

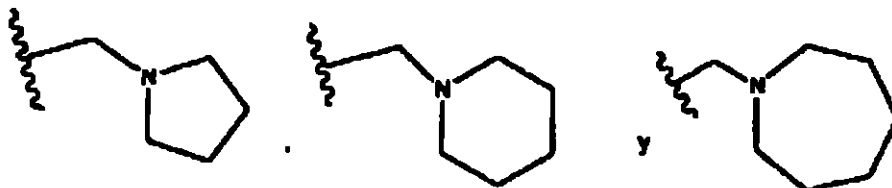
El término alquiheterociclilo significa un grupo alquiheterociclilo en el cual el grupo alquilo y heterociclilo están definidos previamente. Ejemplos no limitantes de los grupos alquiheterociclilo incluyen porciones de las fórmulas:



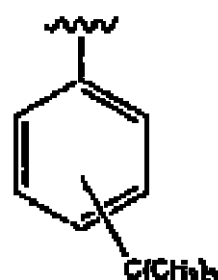
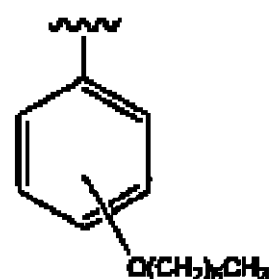
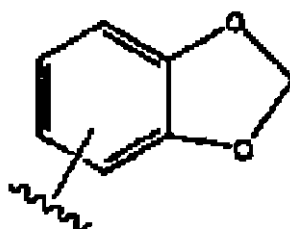
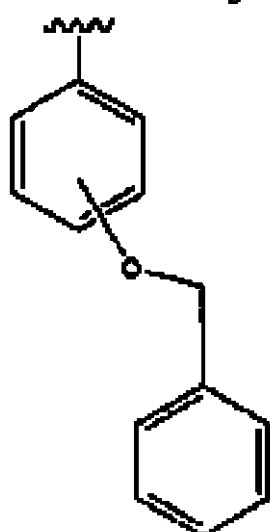
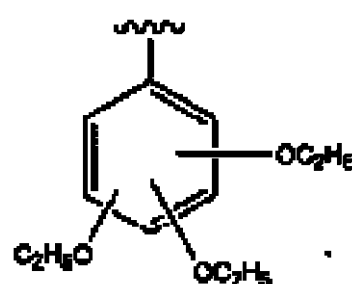
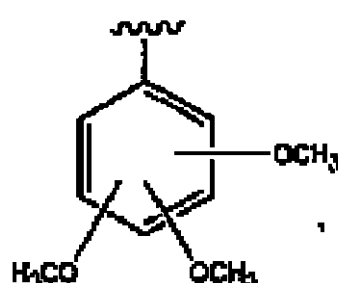
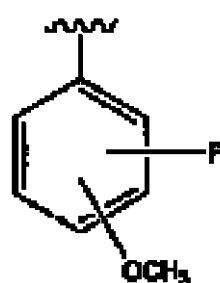
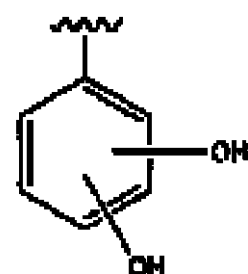
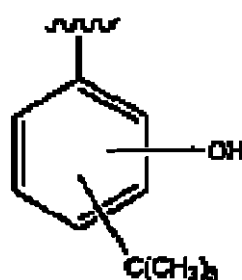
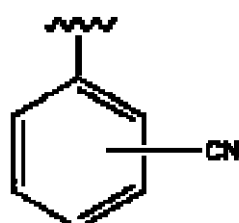
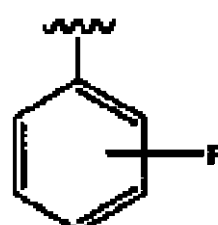
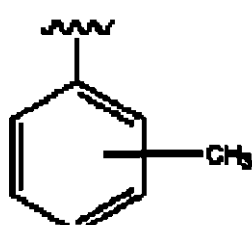
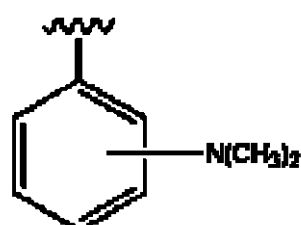
Algunos de los compuestos de fórmula (I) también pueden existir en sus formas tautoméricas. Tales formas aunque no explícitamente indicadas en la fórmula anterior pretenden estar incluidas dentro del alcance de la presente invención. Por ejemplo, los compuestos de la fórmula (I) que existen como tautómeros son descritos adelante:



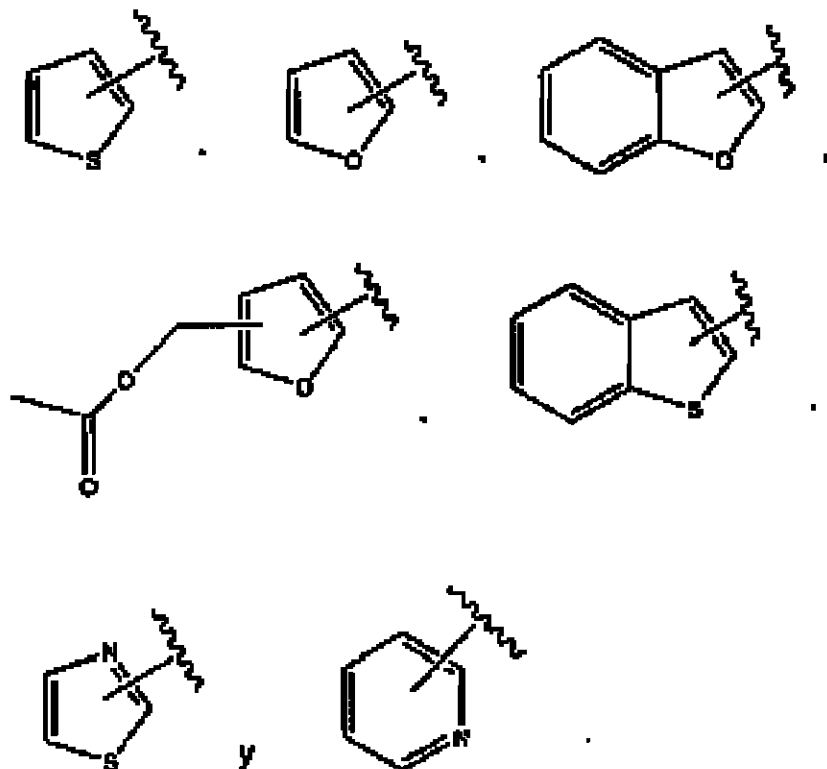
Una modalidad de esta invención es donde R de Fórmula (I) se selecciona del grupo alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, y alquil-(heterociclilo) seleccionado de las porciones del grupo



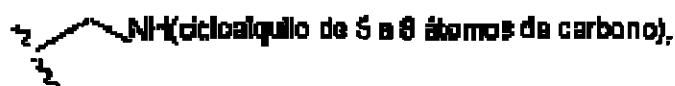
Otra modalidad de la invención es donde R de la Fórmula (I) es fenilo opcionalmente sustituido con 1 a 3 sustituyentes. En una modalidad preferida R se selecciona de porciones del grupo



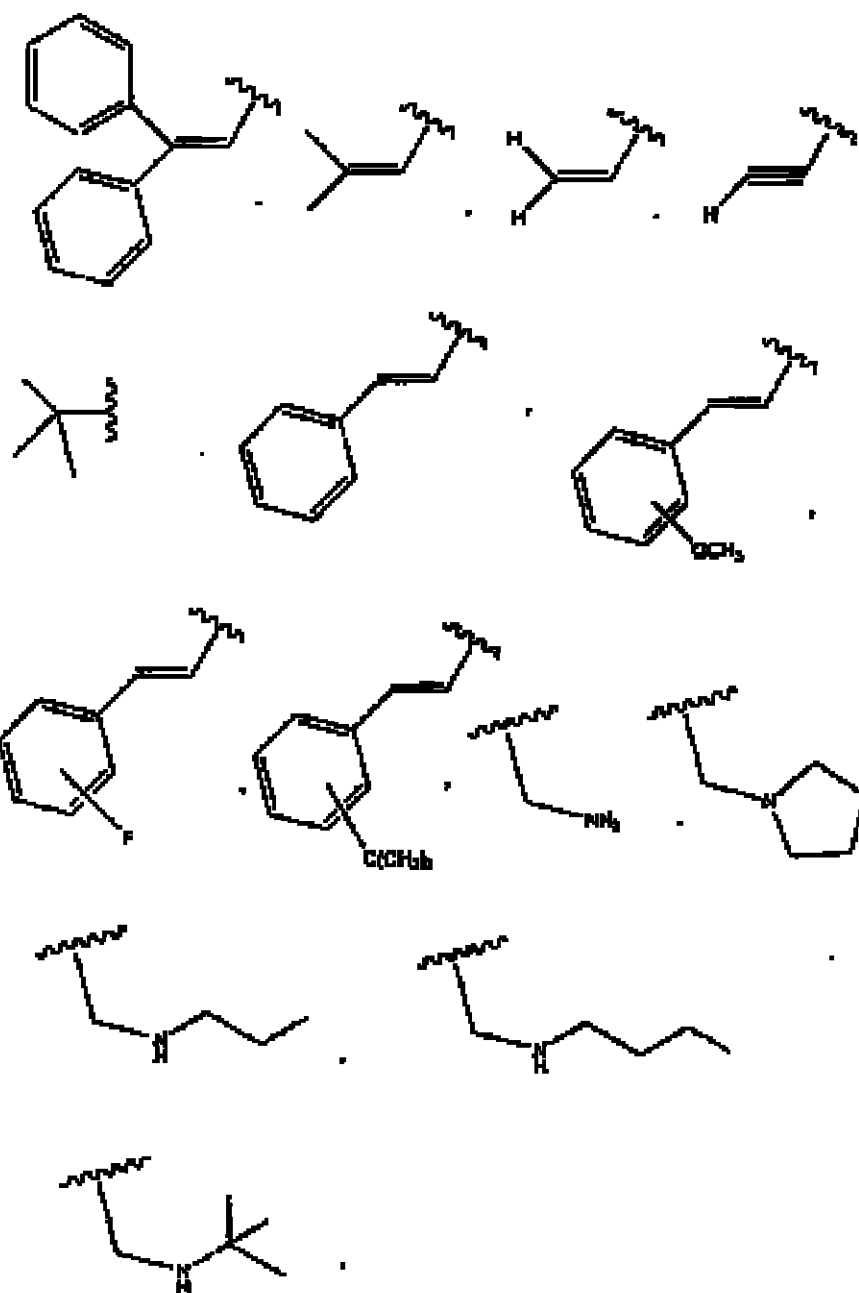
Una modalidad preferida de la invención es donde R es heteroarilo. En una modalidad preferida R se selecciona de las porciones del grupo



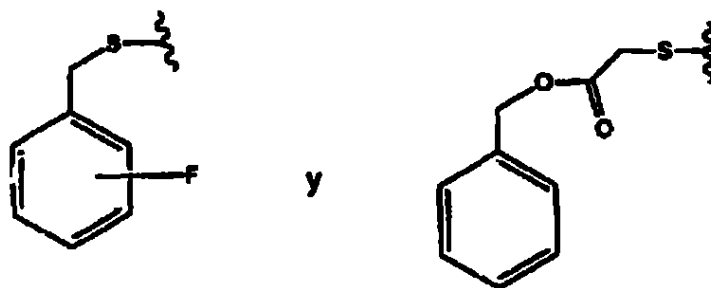
Una modalidad adicional de la invención es donde R es alquilo de 1 a 6 átomos de carbono opcionalmente sustituido, alquénilo de 2 a 6 átomos de carbono opcionalmente sustituido,



En una modalidad preferida se selecciona de las porciones del grupo

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Una modalidad adicional de la invención es donde R de la Fórmula (I) es S-alquilo de 1 a 12 átomos de carbono, S-CH₂-arilo opcionalmente sustituido y S-CH₂(CO)OCH₂arilo opcionalmente sustituido. En una modalidad preferida R se selecciona de las porciones del grupo



Los compuestos preferidos de la invención incluyen aquellos seleccionados del grupo:

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -2- (2, 2-difenilvinil) -9, 11a, 12-trihidroxi-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3]oxazol-10-carboxamida,

(7aS, 8S, 11aS) -5- (dimetilamino) -9, 11a, 13-trihidroxi-2- (2-metil-1-propenil) -11, 12-dioxo-7, 7a, 8, 11, 11a, 12-hexahidronaftaceno[2, 1-d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -2-tert-butil-5, 8-bis(dimetilamino) -9, 11a, 12-trihidroxi-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -2- [(S) -2- (2-furil)etenil] -9, 11a, 12-trihidroxi-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -9, 11a, 12-trihidroxi-11, 13-dioxo-2- [(E) -2-feniletetil] -6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3]oxazol-10-carboxamida,

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(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -9, 11a, 12-trihidroxi-
2-[(E)-2-(4-metoxifenil)etenil]-11, 13-dioxo-
6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d][1, 3]oxazol-10-
carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -9, 11a, 12-trihidroxi-
2-[(E)-2-(3-metoxifenil)etenil]-11, 13-dioxo-
6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d][1, 3]oxazol-10-
carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -9, 11a, 12-trihidroxi-
2-[(E)-2-(2-metoxifenil)etenil]-11, 13-dioxo-
6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d][1, 3]oxazol-10-
carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -2-[(E)-2-(4-
fluorofenil)etenil]-9, 11a, 12-trihidroxi-11, 13-dioxo-
6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d][1, 3]oxazol-10-
carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -2-[(E)-2-(2-
fluorofenil)etenil]-9, 11a, 12-trihidroxi-11, 13-dioxo-
6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d][1, 3]oxazol-10-
carboxamida,

(6aR, 7aS, 8S, 11aS) -2-(clorometil) -5, 8-bis(dimetilamino) -
9, 11a, 12-trihidroxi-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-
octahidrotetraceno[2, 1-d][1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis (dimetilamino) -2-
[(dimetilamino)metil] -9, 11a, 12-trihidroxi-11, 13-dioxo-
6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno [2, 1-d] [1, 3]oxazol-10-
carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis (dimetilamino) -9, 11a, 12-trihidroxi-
11, 13-dioxo-2- (pirrolidin-1-ilmetil) -6, 6a, 7, 7a, 8, 11, 11a, 13-
octahidrotetraceno [2, 1-d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis (dimetilamino) -9, 11a, 12-trihidroxi-
11, 13-dioxo-2- [(propilamino)metil] -6, 6a, 7, 7a, 8, 11, 11a, 13-
octahidrotetraceno [2, 1-d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -2- [(butilamino)metil] -5, 8-
bis (dimetilamino) -9, 11a, 12-trihidroxi-11, 13-dioxo-
6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno [2, 1-d] [1, 3]oxazol-10-
carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis (dimetilamino) -9, 11a, 12-trihidroxi-
11, 13-dioxo-2- [(propilamino)metil] -6, 6a, 7, 7a, 8, 11, 11a, 13-
octahidrotetraceno [2, 1-d] [1, 3]oxazol-10-carboxamida y

(6aR, 7aS, 8S, 11aS) -2- [(tert-butilamino)metil] -5, 8-
bis (dimetilamino) -9, 11a, 12-trihidroxi-11, 13-dioxo-
6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno [2, 1-d] [1, 3]oxazol-10-
carboxamida.

Los compuestos preferidos de la invención incluyen aquellos seleccionados del grupo:

(7aS, 8S, 11aS) - 8 - (dimetilamino) - 2 - [4 - (dimetilamino) fenil] -
9, 11a, 13-trihidroxi-11, 12-dioxo-7, 7a, 8, 11, 11a, 12-
hexahidronaftaceno [2, 1-d] [1, 3] oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) - 2 - tert-butil-5, 8-bis(dimetilamino) -
9, 11a, 12-trihidroxi-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-
octahidrotetraceno [2, 1-d] [1, 3] oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) - 5, 8-bis(dimetilamino) - 9, 11a, 12-trihidroxi-
2 - (4-metilfenil) - 11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-
octahidrotetraceno [2, 1-d] [1, 3] oxazol-10-carboxamida,

(7aS, 8S, 11aS) - 5, 8-bis(dimetilamino) - 2 - (3-fluorofenil) -
9, 11a, 13-trihidroxi-11, 12-dioxo-7, 7a, 8, 11, 11a, 12-
hexahidrotetraceno [2, 1-d] [1, 3] oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) - 2 - (4-cianofenil) - 5, 8-bis(dimetilamino) -
9, 11a, 12-trihidroxi-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-
octahidrotetraceno [2, 1-d] [1, 3] oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) - 5, 8-bis(dimetilamino) - 2 - [4 -
(dimetilamino) fenil] - 9, 11a, 12-trihidroxi-11, 13-dioxo-
6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno [2, 1-d] [1, 3] oxazol-10-
carboxamida,

(6aR,7aS,8S,11aS)-2-(5-tert-butyl-2-hidroxiifenil)-5,8-bis(dimetilamino)-9,11a,12-trihidroxi-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida,

(6aR,7aS,8S,11aS)-2-[4-(benciloxi)fenil]-5,8-bis(dimetilamino)-9,11a,12-trihidroxi-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida,

(6aR,7aS,8S,11aS)-2-(2,4-dihidroxiifenil)-5,8-bis(dimetilamino)-9,11a,12-trihidroxi-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida,

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-2-(3-fluoro-4-metoxifenil)-9,11a,12-trihidroxi-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida,

(6aR,7aS,8S,11aS)-2-(1,3-benzodioxol-5-il)-5,8-bis(dimetilamino)-9,11a,12-trihidroxi-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida,

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-9,11a,12-trihidroxi-11,13-dioxo-2-(2,4,6-trimetoxifenil)-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -9, 11a, 12-trihidroxi-11, 13-dioxo-2-(2, 4, 5-trietoxifenil) -6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -9, 11a, 12-trihidroxi-2-(1-metil-1H-indol-2-il) -11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -2-(4-tert-butilfenil) -5, 8-bis(dimetilamino) -9, 11a, 12-trihidroxi-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3]oxazol-10-carboxamida y

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -2-(4-(hexiloxil) fenil) -9, 11a, 12-trihidroxi-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3]oxazol-10-carboxamida.

Los compuestos preferidos incluyen aquellos seleccionados del grupo:

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -9, 11a, 12-trihidroxi-11, 13-dioxo-2-tien-3-il-6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -2-(1-benzofuran-2-il) -5, 8-bis(dimetilamino) -9, 11a, 12-trihidroxi-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3]oxazol-10-carboxamida,

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(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -2-(2-furil) -
9, 11a, 12-trihidroxi-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-
octahidrotetraceno [2, 1-d] [1, 3] oxazol-10-carboxamida,

{5-[(6aR, 7aS, 8S, 11aS) -10-(aminocarbonil) -5, 8-
bis(dimetilamino) -9, 11a, 12-trihidroxi-11, 13-dioxo-
6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno [2, 1-d] [1, 3] oxazol-2-il] -
2-furil}metil acetato,

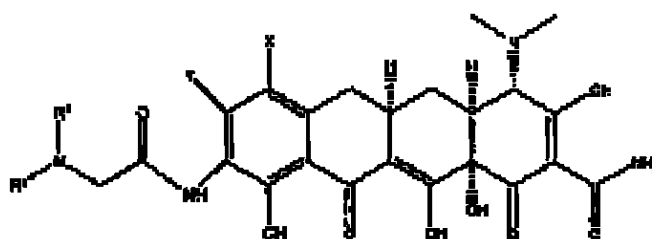
(6aR, 7aS, 8S, 11aS) -2-(1-benzotien-3-il) -5, 8-
bis(dimetilamino) -9, 11a, 12-trihidroxi-11, 13-dioxo-
6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno [2, 1-d] [1, 3] oxazol-10-
carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -9, 11a, 12-trihidroxi-
11, 13-dioxo-2-(1, 3-diazol-2-il) -6, 6a, 7, 7a, 8, 11, 11a, 13-
octahidrotetraceno [2, 1-d] [1, 3] oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -9, 11a, 12-trihidroxi-
11, 13-dioxo-2-piridin-4-il-6, 6a, 7, 7a, 8, 11, 11a, 13-
octahidrotetraceno [2, 1-d] [1, 3] oxazol-10-carboxamida y

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -9, 11a, 12-trihidroxi-
11, 13-dioxo-2-piridin-3-il-6, 6a, 7, 7a, 8, 11, 11a, 13-
octahidrotetraceno [2, 1-d] [1, 3] oxazol-10-carboxamida.

Una modalidad adicional de la invención es el proceso para
la preparación del compuesto de fórmula



o una sal farmacéuticamente aceptable de este

en donde:

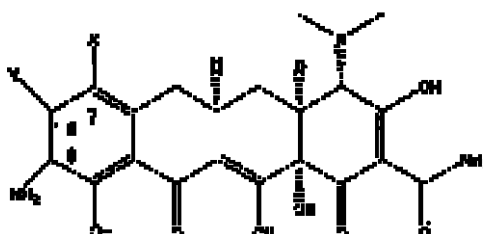
X se selecciona de hidrógeno, amino, NR^1R^2 , alquilo de 1 a 12 átomos de carbono opcionalmente sustituido, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituido, vinilo opcionalmente sustituido, alquínilo de 2 a 12 átomos de carbono opcionalmente sustituido y halógeno;

R^1 y R^2 son cada uno independientemente H o alquilo de 1 a 12 átomos de carbono o R^1 y R^2 cuando se toman opcionalmente juntas con el átomo de nitrógeno al cual cada uno está unido forman un anillo de hidrocarburo saturado de 3 a 7 miembros;

Y se selecciona de hidrógeno, alquilo de 1 a 12 átomos de carbono opcionalmente sustituido, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituido, alquénilo de 2 a 12 átomos de carbono opcionalmente sustituido, vinilo, alquínilo de 2 a 12 átomos de carbono opcionalmente sustituido y halógeno;

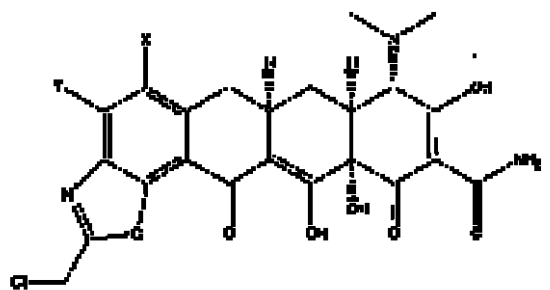
que comprenden las etapas:

a. hacer reaccionar 9-amino-6-desmetil-6-desoxitetraciclina
7-(sustituido)-8-(sustituido) de la fórmula

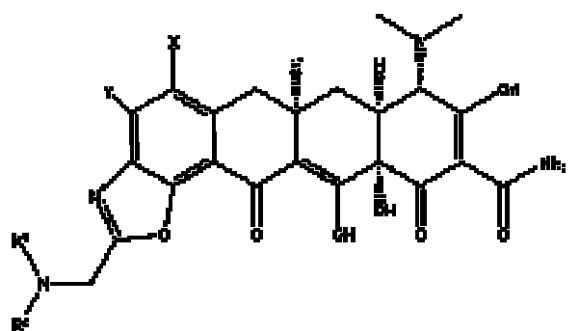


o una sal farmacéuticamente aceptable de este

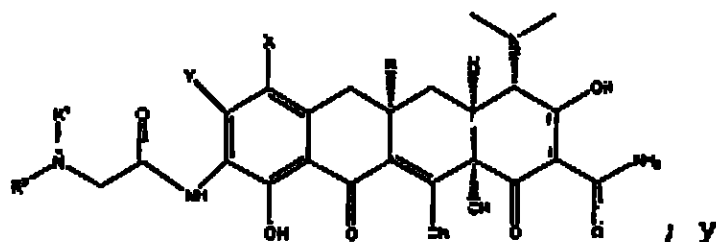
con 2-clorotrimetoxietano en un solvente aprótico para
lograr un compuesto cloro de la fórmula



b. hacer reaccionar el compuesto cloro con una amina R^1R^2NH
para formar una amina sustituida de la fórmula



c. hidrólizar la amina sustituida con ácido para dar un
compuesto de la fórmula

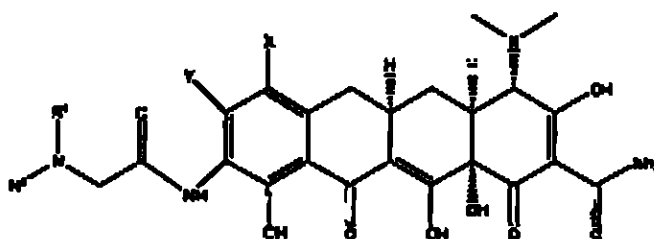


d. aislar el compuesto o una sal farmacéuticamente aceptable de este

En una modalidad preferida del proceso X es $N(CH_3)_2$ y la amina R^1R^2NH es t-butila amina.

En una modalidad preferida del proceso se prepara el compuesto [4S-(4a,4aa,5aa,12aa)]-4,7-Bis(dimetilamino)-9-[2-(1,1-dimetiletilamino)acetilamino]-1,4,4a,5,5a,6,11,12a-octahidro-3,10,12,12a-tetrahidroxí-1,11-dioxo-2-naftacenocarboxamida o una sal farmacéuticamente aceptable de este.

Una modalidad adicional de la invención es un proceso para la preparación de un compuesto de la fórmula



en donde:

X se selecciona de hidrógeno, amino, NR^1R^2 , alquilo de 1 a 12 átomos de carbono opcionalmente sustituid, arilo de 6, 10

14 átomos de carbono opcionalmente sustituido, vinilo, opcionalmente sustituido, alquínilo de 2 a 12 átomos de carbono opcionalmente sustituido y halógeno;

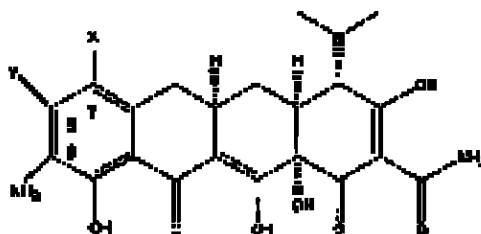
R^1 y R^2 son cada uno independientemente H o alquilo de 1 a 12 átomos de carbono o R^1 y R^2 cuando se toman opcionalmente juntos con el átomo de nitrógeno al cual cada uno esté unido forman un anillo de hidrocarburo saturado de 3 a 7 miembros;

Y se selecciona de hidrógeno, alquilo de 1 a 12 átomos de carbono opcionalmente sustituido, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituido, alquenilo de 2 a 12 átomos de carbono opcionalmente sustituido, vinilo, alquinilo de 2 a 12 átomos de carbono opcionalmente sustituido y halógeno;

o una sal farmacéuticamente aceptable de este

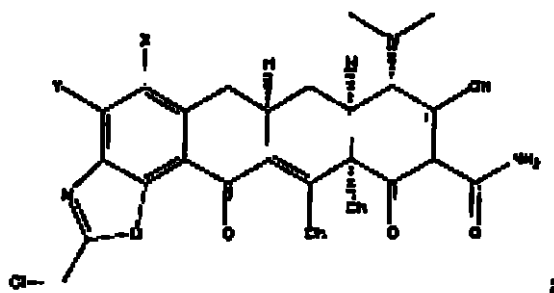
que comprenden las etapas de:

a. hacer reaccionar 9-amino-6-ácetil-6-desoxitetraciclina
7-(sustituido)-8-(sustituido) de la fórmula

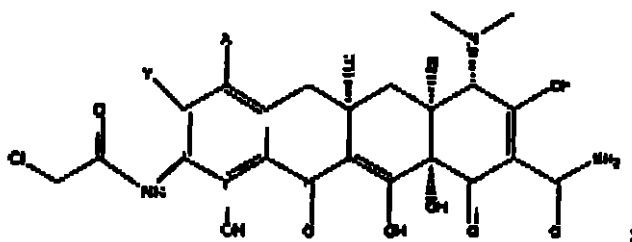


c una sal farmacéuticamente aceptable de este

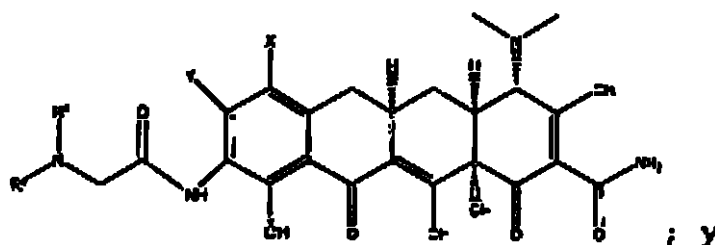
con 2-clor trimetoxietano en un solvente aprótico para lograr un compuesto de cloro de la fórmula

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b. hacer reaccionar el compuesto cloro con ácido para dar 9-(2-clorometilcarbonilamino)sustituido-6-demetil-6-desoxitetraciclina de la fórmula



c. hacer reaccionar el 9-(2-clorometilcarbonilamino)sustituido-6-demetil-6-desoxitetraciclina con amina R^1R^2NH para dar un compuesto de la fórmula

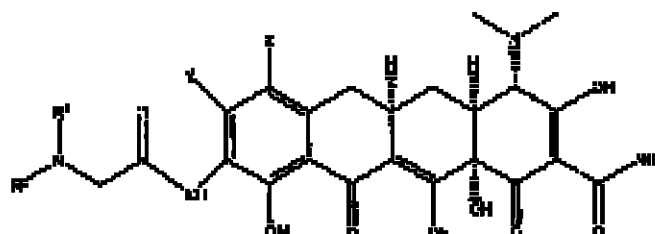


d. aislar el compuesto o una sal farmacéuticamente aceptable de este.

En una modalidad preferida del proceso X es $N(CH_3)_2$ y la amina R^1R^2NH es t-butil amina.

En una modalidad preferida del proceso se prepara el compuesto [4S-(4 α ,4 $\alpha\alpha$,5 $\alpha\alpha$,12 $\alpha\alpha$)]-4,7-Bis(dimetilamina)-9-[2-(1,1-dimetiletilamina)acrilamino]-1,4,4a,5,5a,6,11,12a-octahidro-3,10,12,12a-tetrahidroxi-1,11-dioxo-2-naftaceno-carboxamida o una sal farmacéuticamente aceptable de este.

Una modalidad adicional de la invención es un compuesto de la fórmula



o una sal farmacéuticamente aceptable de este

en donde:

X se selecciona de hidrógeno, amino, NR^1R^2 , alquilo de 1 a 12 átomos de carbono opcionalmente sustituido, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituido, vinilo opcionalmente sustituido, alquínilo de 2 a 12 átomos de carbono opcionalmente sustituido y halógeno;

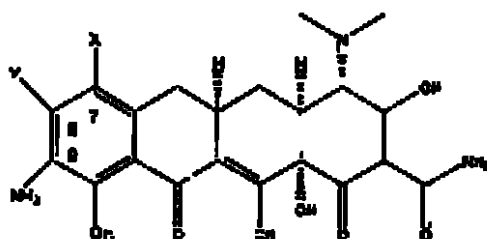
R^1 y R^2 son cada uno independientemente H o alquilo de 1 a 12 átomos de carbono o R^1 y R^2 cuando se toman con el átomo de

nitrógeno al cual cada uno está unido forman un anillo de hidrocarburo saturado de 3 a 7 miembros;

y se selecciona de hidrógeno, alquilo de 1 a 12 átomos de carbono opcionalmente sustituido, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituido, alqueno de 2 a 12 átomos de carbono opcionalmente sustituido, vinilo, alquino de 2 a 12 átomos de carbono opcionalmente sustituido y halógeno;

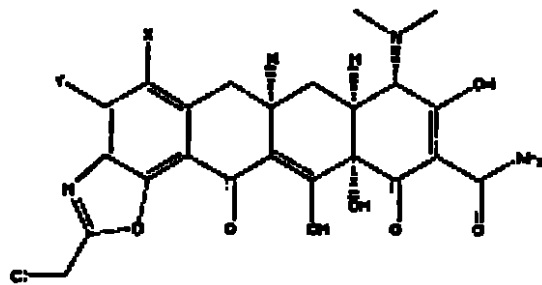
Producido por el proceso que comprenden las etapas:

a. hacer reaccionar 9-amino-6-dimetil-6-desoxitetraciclina 7-(sustituido)-8-(sustituido) de la fórmula

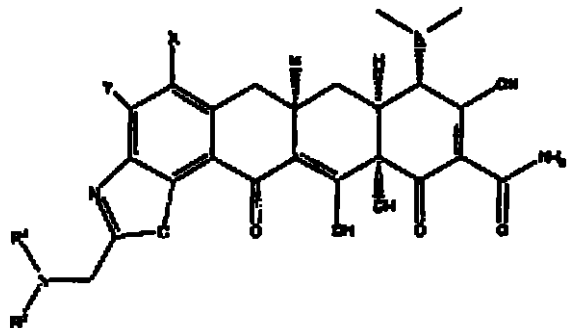


o una sal farmacéuticamente aceptable de este

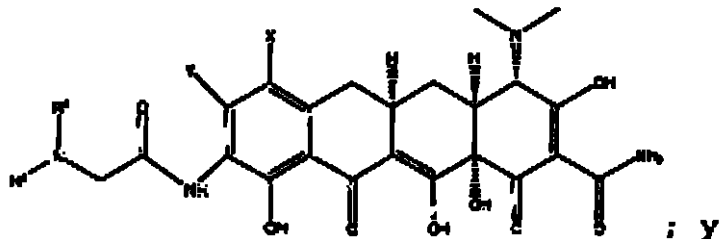
con 2-clorotrimetoxietano en un solvente aprótico para lograr un compuesto de cloro de la fórmula



b. hacer reaccionar el compuesto cloro con una amina R^1R^2NH para formar una amina sustituida de la fórmula



c. hidrolizar la amina sustituida con ácido para dar un compuesto de la fórmula

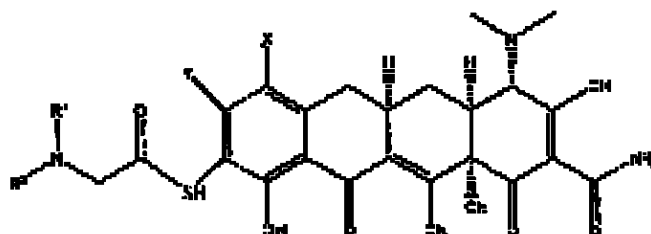


d. aislar el compuesto o una sal farmacéuticamente aceptable de este.

En una modalidad preferida del proceso X es $N(CH_3)_2$ y la amina R^1R^2NH es t-butil amina.

En una modalidad preferida del proceso el compuesto [4S-(4 α , 4a α , 5a α , 12a α)]-4,7-Bis(dimetilamino)-9-[2-(1,1-dimetiletilamino)acetilamino]-1,4,4a,5,5a,6,11,12a-octahidro-3,10,12,12a-tetrahidroxi-1,11-dioxo-2-naftacenocarboxamida o una sal farmacéuticamente aceptable de este se prepara.

En una modalidad adicional de la invención un compuesto de la fórmula



en donde:

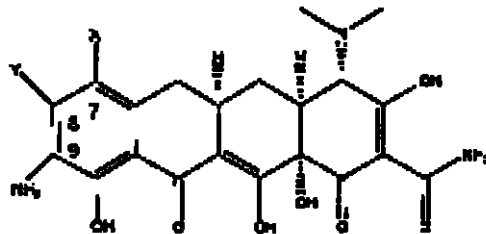
X se selecciona de hidrógeno, amino, NR^1R^2 , alquilo de 1 a 12 átomos de carbono opcionalmente sustituido, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituidos, vinilo opcionalmente sustituido, alquínilo de 2 a 12 átomos de carbono opcionalmente sustituido y halógeno;

R^1 y R^2 son cada uno independientemente H o alquilo de 1 a 12 átomos de carbono o cuando opcionalmente se toman juntos con el átomo de nitrógeno al cual cada uno está unido forman un anillo de hidrocarburo saturado de 3 a 7 miembros;

Y se selecciona de hidrógeno, alquilo de 1 a 12 átomos de carbono opcionalmente sustituido, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituido, alquénilo de 2 a 12 átomos de carbono opcionalmente sustituido, vinilo, alquínilo de 2 a 12 átomos de carbono opcionalmente sustituido y halógeno;

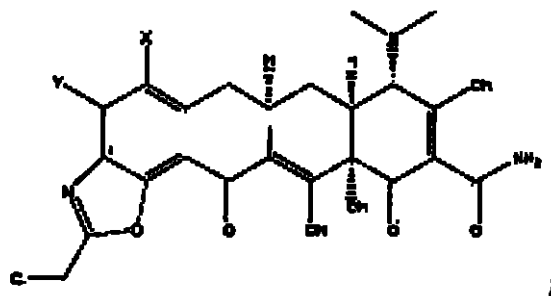
o una sal farmacéuticamente aceptable de este
producido por el proceso que comprenden las etapas:

a. hacer reaccionar 9-amino-6-demetil-6-desoxitetraciclina
7-(sustituido)-8-(sustituido) de la fórmula

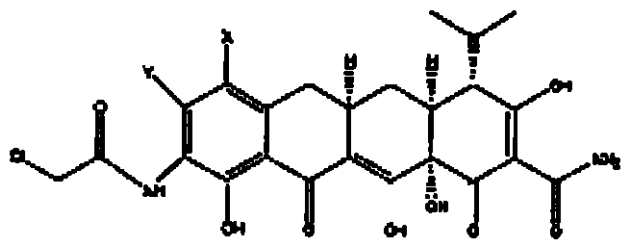


o una sal farmacéuticamente aceptable de este

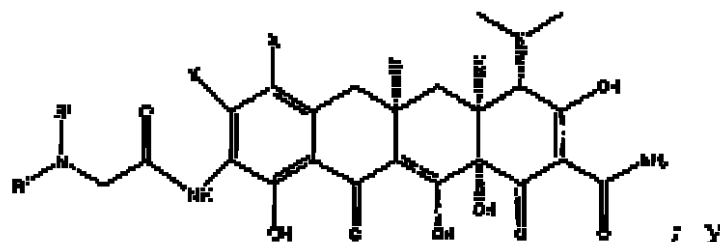
con 2-clorotrimetoxietano en un solvente aprótico para
lograr un compuesto cloro de la fórmula



b. hacer reaccionar el compuesto cloro con ácido para dar
9-(2-clorometilcarbonilamino)sustituido-6-demetil-6-
desoxitetraciclina de la fórmula



c. hacer reaccionar el 9-(2-clorometilcarboxilamino)sustituido-6-desmetil-6-desoxitetraciclina con amina R^1R^2NH para dar un compuesto de la fórmula



d. aislar el compuesto o una sal farmacéuticamente aceptable de este.

En una modalidad preferida del proceso X es $N(CH_3)_2$, y la amina R^1R^2NH es t-butil amina.

En una modalidad preferida el compuesto [4S-(4a,4a,5a,12a)]-4,7-Bis(dimetilamino)-9-[2-(1,1-dimetiletanolamino)acetilamino]-1,4,4a,5,5a,6,11,12a-octahidro-3,10,12,12a-tetrahidroxi-1,11-dioxo-2-naftacenocarboxamida o una sal farmacéuticamente aceptable de este se prepara mediante el proceso.

DESCRIPCIÓN DE LAS MODALIDADES PREFERIDAS

Los compuestos novedosos de la presente invención se pueden preparar fácilmente de acuerdo con el siguiente Esquema I.

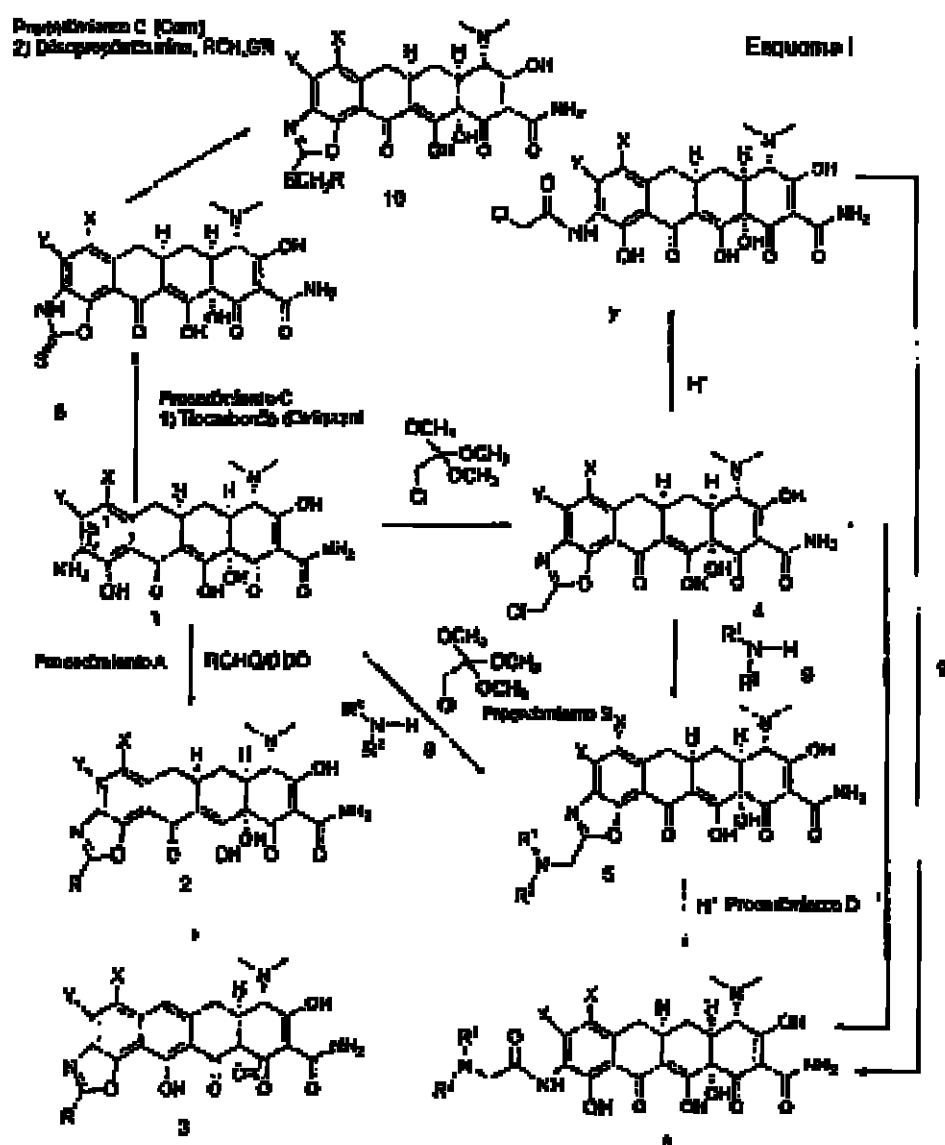
El 9-amino-6-desmetil-6-desoxitetraciclina 7-(sustituido)-8-(sustituido) de partida 1 o sales farmacéuticamente aceptables de

esta en donde X y Y son como se definió anteriormente se hacen reaccionar con aldehído RCHO en la presencia de 2,3-dicloro-5,6-diciano-1,4-benzoquinona (DDQ) para lograr benzoxazol 2 y 3 (Procedimiento A). Como se describe adicionalmente, la reacción de 9-amino-6-dimetil-6-desoxitetraciclinas 7-(sustituido)-8-(sustituido) 1 o sales farmacéuticamente aceptables de esta en donde X y Y son como se definió anteriormente y se hacen reaccionar con 2-cloro-1,1,1-trimetoxi-etano en un solvente aprótico tal como N,N-dimetilformamida (DMF) para dar clorometilbenzoxazol 4, opcionalmente aislado, entonces convertido a amina sustituida 5, mediante reacción adicional con una amina 9 (Procedimiento B). La hidrólisis de la amina 5 logra 9-(2-aminometil carbonilamino sustituido)-6-dimetil-6-desoxitetraciclina sustituido 6 (Procedimiento D). La hidrólisis clorometilbenzoxazol 4 da 9-(2-clorometilcarbonil-amino)-6-dimetil-6-desoxitetraciclina sustituido 7 que puede ser adicionalmente ser reaccionado con amina 9 para dar 9-(2-aminometil carbonilamino sustituido)-6-dimetil-6-desoxitetraciclina sustituido 6.

Adicionalmente, la reacción de 9-amino-6-dimetil-6-desoxitetraciclinas 7-(sustituido)-8-(sustituido) 1 o las sales farmacéuticamente aceptables de estas con tiocarbonildiimidazol suministra tio 8 seguido por la alquilación con RCH_2Br en la presencia de una amina de N,N-diisopropiletilamina logra oxazol 10 (Procedimiento C).

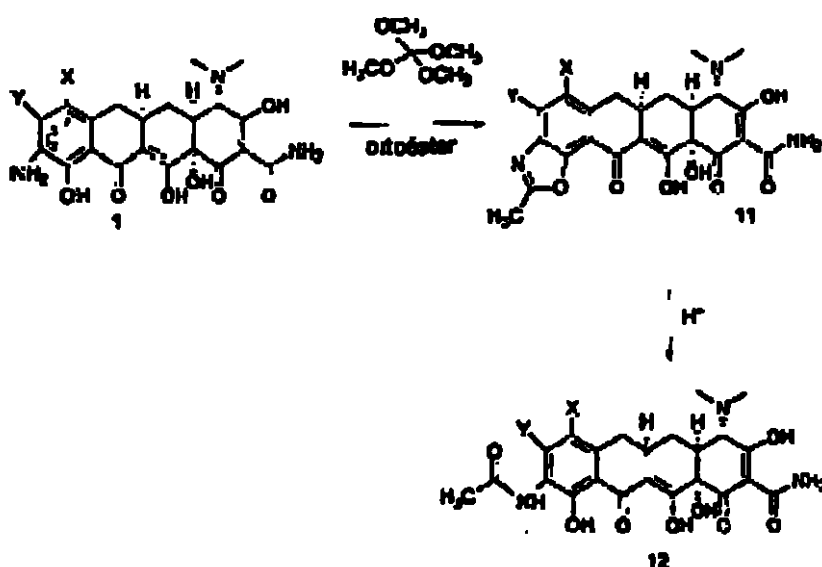
Preferiblemente, la amina 9 en la preparación 9-(2-aminometil carbonilamino sustituido)-6-dimetil-6-

desoxitetraciclina sustituido 6, en el Esquema I es t-butil amina.



como se muestra en el Esquema II, el 9-amino-6-demetil-6-desoxitetraciclinas 7-(sustituido)-8-(sustituido) 1 de partida o unas sales farmacéuticamente aceptables de esta en donde X y Y son como se definió anteriormente, se hacen reaccionar con un metil ortoéster para lograr el derivado metil benzoxazol 11. La hidrólisis ácida del derivado de metil benzoxazol 11 logra el derivado de N-acetil 12.

Esquema II



Las reacciones son desarrolladas en un solvente apropiado a los reactivos y materiales empleados y adecuados para la transformación que está siendo efectuada. Se entiende por aquellos expertos en la técnica de síntesis orgánica que varias funcionalidades presentes en la molécula deben ser consistentes con las transformaciones químicas propuestas. Esto puede necesitar juicio con el fin de ordenar las etapas sintéticas, proteger los grupos, si se requiere y la desprotección de las condiciones. Los sustituyentes en los compuestos de partida *m* pueden ser incompatibles con algunas de las condiciones de reacción. Tales restricciones a los sustituyentes que son compatibles con las condiciones de reacción serán evidentes para un experto en la técnica.

Algunos de los compuestos de los esquemas descritos anteriormente tienen un centro de asimetría. Los compuestos pueden, por lo tanto existir en al menos dos y a menudo más formas estereoisoméricas. La presente invención comprende todos

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los estereoisómeros de los compuestos sean libres de otros estereoisómeros o mezclados con otros estereoisómeros en cualquier proporción y así incluye, por ejemplo, mezcla racémica de enantiómeros así como también mezcla diastereomérica de isómeros. La configuración absoluta de cualquier compuesto se puede determinar mediante cristalografía de rayos X convencional.

Las sales farmacéuticamente aceptables de los compuestos de la invención se pueden obtener como complejos metálicos tales como aluminio, calcio, hierro, magnesio, manganeso y sales de complejo; sales inorgánicas y orgánicas y los correspondientes aductos de base Mannich utilizando métodos conocidos por aquellos expertos en la técnica (Richard C. Larock, Comprehensive Organic Transformations, VCH Publishers, 411-415, 1989). Preferiblemente, los compuestos de la invención se obtiene como sales inorgánicas tales como clorhídrica, bromhídrica, yodhídrica, fosfórica, nítrica o fosfato; o sales orgánicas tales como acetato, benzoato, citrato, cisteína u otros aminoácidos, fumarato, glicolato, maleato, succinato, tartrato alquilsulfonato o arilsulfonato. La formación de sal preferencialmente ocurre con el grupo C(4)-dimetilamino cuando forma sales inorgánicas. Las sales son preferidas para administración oral y parenteral.

Procedimientos de Ensayo Farmacológico Estándar.

Los Métodos para Evaluación Antibacterial in Vitro.

La Concentración Inhibitoria mínima (MIC).

Ensayo de susceptibilidad antimicrobiana. Las actividades in vitro de los anticuerpos se determinan mediante el método de microdilución de caldo como lo recomienda el National Committee for Clinical Laboratory Standards (NCCLS) (1). El caldo Mueller-Hinton II (MHBII) (BBL Cockeysville, MD) es el medio empleado en los procedimientos de ensayo. Las placas de microtítulo que contienen diluciones en serie de cada agente antimicrobiano son inoculadas con cada organismo para producir la densidad apropiada (10^5 CFU/ml) en 100 μ l de volumen final. Las placas son incubadas durante 18-22 horas a 35° C en aire ambiente. La concentración inhibitoria mínima para todos los aislados se define como la concentración más baja del agente antimicrobiano que inhibe completamente el crecimiento del organismo según se detecta mediante inspección a ojo sin ayuda.

1. NCCLS. 2000. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards: M7-A5, vol. 20. National Committee for Clinical Laboratory Standards, Wayne, PA.

TABLA J

ACTIVIDAD ANTIBACTERIAL DE (7-SUSTITUIDO)-8-(SUSTITUIDO)-9-(SUSTITUIDO)-TETRACICLINAS

MIC ($\mu\text{g/ml}$) COMPUSSION

		Ejemplo 1	Ejemplo 2	Ejemplo 3	Ejemplo 4	Ejemplo 5	Ejemplo 6
1	E coli GC2270 (tet(M))	>64	>64	>64	>64	>64	>64
2	E coli GC4559 (GC4560 padre)	>64	>64	>64	>64	>64	>64
3	E coli GC4560 (IMP mutante)	32	8	16	16	4	8
4	E coli GC2203 (Control ATCC)	>64	>64	>64	>64	>64	>64
5	E coli GC1073 (tet(S))	>64	>64	>64	>64	>64	>64
6	S aureus GC1131 (Clínico)	16	8	2	16	4	4
7	S aureus GC6466 (tet(M))	32	8	2	32	4	4
8	S aureus GC6467 (tet(M)+(K))	32	8	2	32	4	4
9	S aureus GC1079 (tet(K))	16	8	1	16	4	4
10	S aureus GC4536 (Smith MP -In Vivo)	16	8	2	32	4	4
11	S aureus GC2216 (Control ATCC)	16	8	2	32	4	4
12	E faecalis GC4555 (Control ATCC)	32	8	2	32	4	8
13	E faecalis GC2267 (tet(L)+(M)+(S))	32	8	2	32	4	4
14	E faecalis GC2242 (Resistencia a van)	16	8	2	32	4	4
15	S pneumoniae* GC4465 (Clínico)	16	8	2	16	16	16
16	S pneumoniae* GC1894 (Clínico)	8			32	8	16
17	S pyogenes* GC4563 (Clínico)	8	8	8	16	16	16
18	M catarrhalis* GC6907 (Clínico)	>64			16	16	32
19	H influenzae<> GC6896 (Control ATCC)	>64			>64	>64	>64
20	C albicans GC3066 ATCC (Control)	>64	>64	>64	>64	>64	>64

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TABLA II

ACTIVIDAD ANTIBACTERIAL DE (7-SUSTITUIDO)-8-(SUSTITUIDO)-9-(SUSTITUIDO)-TETRACICLINAS

MIC (μ g/ml) COMPUESTO

		Ejemplo 7	Ejemplo 8	Ejemplo 10	Ejemplo 11
1	E coli GC2270 (tet(M))	>64	>64	>64	>64
2	E coli GC4559 (GC4560 padre)	>64	>64	>64	>64
3	E coli GC4560 (IMP mutante)	8	16	32	>64
4	E coli GC2203 (Control ATCC)	>64	>64	>64	>64
5	E coli GC1073 (tet(B))	>64	>64	>64	>64
6	S aureus GC1131 (Clínico)	8	8	8	32
7	S aureus GC6466 (tet(M))	8	16	16	64
8	S aureus GC6467 (tet(M)+(K))	8	8	16	32
9	S aureus GC1079 (tet(K))	8	16	16	64
10	S aureus GC4536 (Smith MP -In Vivo)	8	16	16	64
11	S aureus GC2216 (Control ATCC)	8	8	16	64
12	E faecalis GC4555 (Control ATCC)	8	32	16	64
13	E faecalis GC2267 (tet(L)+(M)+(S))	8	16	16	>64
14	E faecalis GC2242 (Resistente a Van)	8	8	8	64
15	S pneumoniae* GC4465 (Clínico)	8	32	16	32
16	S pneumoniae* GC1894 (Clínico)	16	16	8	32
17	S pyogenes* GC4563 (Clínico)	8	16	16	32
18	M catarrhalis* GC6907 (Clínico)	4	64	>64	32
19	H influenzae<> GC6896 (Control ATCC)	64	>64	>64	>64
20	C albicans GC3066 ATCC (Control)	>64	>64	>64	>64

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TABLA III

ACTIVIDAD ANTIBACTERIAL DE (7-SUSTITUIDO)-6-(SUSTITUIDO)-9-(SUSTITUIDO)-TETRACICLINAS

MIC ($\mu\text{g/ml}$) COMPUESTO

		Ejemplo 12	Ejemplo 13	Ejemplo 14	Ejemplo 15	Ejemplo 16
1	E coli GC2270 (tet(M))	>64	>64	>64	>64	>64
2	E coli GC4559 (GC4560 padre)	>64	>64	>64	>64	>64
3	E coli GC4560 (TKP mutante)	4	4	16	32	16
4	E coli GC2203 (Control AICL)	32	>64	>64	>64	>64
5	E coli GC1073 (tet(B))	>64	>64	>64	>64	>64
6	S aureus GC1431 (Clínico)	4	4	4	64	16
7	S aureus GC6466 (tet(M))	8	4	4	64	16
8	S aureus GC5467 (tet(M)+(K))	8	8	8	64	16
9	S aureus GC1079 (tet(K))	8	4	4	64	16
10	S aureus GC4536 (Smith MF -In Vivo)	8	8	4	64	16
11	S aureus GC2216 (Control ATCC)	4	4	4	64	16
12	E faecalis GC4555 (Control ATCC)	8	8	8	64	16
13	E faecalis GC2267 (tet(L)+(M)+(S))	8	8	8	64	16
14	E faecalis GC2242 (Resistente a Van)	8	8	4	64	16
15	S pneumoniae* GC1465 (Clínico)	8	32	16	>64	>64
16	S pneumoniae* GC1894 (Clínico)	8	16	16	>64	>64
17	S pyogenes* GC4567 (Clínico)	4	16	16	>64	64
18	K catarrhalis* GC6907 (Clínico)	4	16	4	64	>64
19	H influenzae<> GC6896 (Control ATCC)	16	>64	>64	>64	>64
20	C albicans GC1066 ATCC (Control)	>64	>64	>64	>64	>64

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TABLA IV

ACTIVIDAD ANTIBACTERIAL DE (7-SUSTITUIDO) 8-(SUSTITUIDO)-9-(SUSTITUIDO)-TETRACICLINAS

MIC ($\mu\text{g/ml}$) COMPUESTO

	Ejemplo 17	Ejemplo 18	Ejemplo 19	Ejemplo 20	Ejemplo 21
1 E coli GC2270 (tet(M))	>64	>64	>64	>64	>64
2 E coli GC4559 (GC4560 padre)	>64	>64	>64	>64	>64
3 E coli GC4560 (IMP mutante)	4	4	4	32	>64
4 E coli GC2203 (Control ATCC)	>64	>64	>64	>64	>64
5 E coli GC1073 (tet(B))	>64	>64	>64	>64	>64
6 S aureus GC1131 (Clínico)	8	4	4	32	64
7 S aureus GC6466 (tet(M))	8	4	4	32	32
8 S aureus GC6467 (tet(M)+(K))	8	4	4	32	32
9 S aureus GC1079 (tet(K))	8	4	4	32	32
10 S aureus GC4536 (Smith MP -In Vivo)	8	4	8	64	64
11 S aureus GC2216 (Control ATCC)	8	4	4	32	32
12 E faecalis GC4555 (Control ATCC)	8	4	8	64	>64
13 E faecalis GC2767 (tet(L)+(M)+(S))	16	4	8	64	64
14 E faecalis GC2242 (Resistente a Van)	8	4	4	32	32
15 S pneumoniae* GC4465 (Clínico)	32	16	4	>64	>64
16 S pneumoniae* GC1894 (Clínico)	32	16	4	64	>64
17 S pyogenes* GC4563 (Clínico)	16	16	8	32	>64
18 M catarrhalis* GC6907 (Clínico)	16	8	16	32	>64
19 H influenzae<> GC6896 (Control ATCC)	>64	>64	>64	>64	>64
20 C albicans GC3066 ATCC (Control)	>64	>64	>64	>64	>64

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961000

TABLA V

ACTIVIDAD ANTIBACTERIAL DE (7-SUSTITUIDO)-8-(SUSTITUIDO)-9-(SUSTITUIDO) TETRACICLINAS

MIC ($\mu\text{g/ml}$) COMPUESTO

		Ejemplo 22	Ejemplo 24	Ejemplo 25	Ejemplo 26
1	E coli GC2270 (tet(M))	>64	>64	>64	>64
2	E coli GC4559 (GC4560 padre)	>64	>64	>64	>64
3	E coli GC4560 (IMP mutante)	8	32	8	32
4	R coli GC2203 (Control ATCC)	>64	>64	>64	>64
5	E coli GC1073 (tet(B))	>64	>64	>64	>64
6	S aureus GC1131 (Clínico)	8	32	8	16
7	S aureus GC6466 (tet(M))	8	32	4	16
8	S aureus GC6467 (tet(M)+(K))	8	32	8	16
9	S aureus GC1079 (tet(K))	8	32	4	32
10	S aureus GC4536 (Smith MP -In Vivo)	8	32	8	32
11	S aureus GC2216 (Control ATCC)	8	64	4	16
12	E faecalis GC4555 (Control ATCC)	8	32	8	32
13	E faecalis GC2267 (tet(L)+(M)+(S))	8	32	4	16
14	E faecalis GC2242 (Resistente a Van)	8	32	4	16
15	S pneumoniae* GC4465 (Clínico)	32	64	32	>64
16	S pneumoniae* GC1894 (Clínico)	32	64	32	>64
17	S pyogenes* GC4563 (Clínico)	16	32	16	64
18	M catarrhalis* GC6907 (Clínico)	16	>64	16	>64
19	H influenzae<-> GC6896 (Control ATCC)	>64	>64	>64	>64
20	C albicans GC3066 ATCC (Control)	>64	>64	>64	>64

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TABLA VI

ACTIVIDAD ANTIBACTERIAL DE (1-SUSTITUIDO)-8-(SUSTITUIDO)-9-(SUSTITUIDO)-TETRACICLINAS

MIC ($\mu\text{g/ml}$) COMPUESTO

	Ejemplo 27	Ejemplo 28	Ejemplo 29	Ejemplo 30	Ejemplo 31
1 E coli GC2270 (LeL(M))	>64	>64	>64	>64	>64
2 E coli GC4559 (GC4560 padre)	>64	>64	>64	>64	>64
3 E coli GC4560 (IMP mutante)	32	16	8	8	4
4 E coli GC2287 (Control ATCC)	>64	>64	>64	>64	>64
5 E coli GC1073 (tet(R))	>64	>64	>64	>64	>64
6 S aureus C1111 (Clínico)	8	8	8	4	8
7 S aureus GC6466 (tet(M))	16	8	8	8	4
8 S aureus GC6467 (tet(M)+(K))	8	8	8	8	8
9 S aureus C11879 (tet(K))	8	16	8	8	8
10 S aureus GC4536 (Smith MP -In Vivo)	16	16	8	8	8
11 S aureus GC2216 (Control ATCC)	8	8	8	4	8
12 E faecalis GC4555 (Control ATCC)	16	16	8	8	8
13 E faecalis GC2267 (tet(L)+(M)+(S))	8	8	8	4	8
14 E faecalis GC2242 (Resistente a van)	8	8	8	4	8
15 S pneumoniae* GC4465 (Clínico)	64	32	32	16	8
16 S pneumoniae* GC1894 (Clínico)	64	64	32	16	8
17 S pyogenes* GC4563 (Clínico)	64	16	16	16	8
18 M catarrhalis* GC6907 (Clínico)	>64	64	16	32	16
19 H influenzae* GC6896 (Control ATCC)	>64	>64	>64	>64	>64
20 C albicans GC3066 ATCC (Control)	>64	>64	>64	>64	>64

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TABLA VII

ACTIVIDAD ANTIBACTERIAL DE (7-SUSTITUIDO) -8- (SUSTITUIDO) -9- (SUSTITUIDO) -TETRACICLINAS

MIC (μ g/ml) COMPUESTO

	Ejemplo 32	Ejemplo 33	Ejemplo 34	Ejemplo 35	Ejemplo 36
1 E coli GC2270 (tet(M))	>64	>64	>64	16	4
2 E coli GC4559 (GC4560 padre)	>64	>64	>64	8	4
3 E coli GC4560 (IMP mutante)	>64	16	32	0 50	1
4 E coli GC2203 (Control ATCC)	>64	64	>64	4	2
5 E coli GC1073 (tet(B))	>64	>64	>64	32	4
6 S aureus GC1131 (Clínico)	>64	16	32	0 50	4
7 S aureus GC6466 (tet(M))	>64	32	64	1	4
8 S aureus GC6467 (tet(M)+(K))	>64	32	64	8	16
9 S aureus GC1079 (tet(K))	>64	16	32	4	4
10 S aureus GC4536 (Smith MP -In Vivo)	>64	16	64	1	4
11 S aureus GC2216 (Control ATCC)	>64	16	32	0 50	2
12 E faecalis GC4555 (Control ATCC)	64	16	32	1	4
13 E faecalis GC2267 (tet(L)+(M)+(S))	>64	16	32	4	4
14 E faecalis GC2242 (Resistente a Van)	64	16	32	1	4
15 S pneumoniae* GC4465 (Clínico)	16	16	32	0 50	1
16 S pneumoniae* GC1894 (Clínico)	8	32	64	0 25	1
17 S pyogenes* GC4563 (Clínico)	16	8	32	0 25	1
18 M catarrhalis* GC6907 (Clínico)	32	8	16	0 50	1
19 H influenzae<-> GC6896 (Control ATCC)	>64	32	>64	2	4
20 C albicans GC3066 ATCC (Control)	>64	>64	>64	>64	>64

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TABLA VIII

ACTIVIDAD ANTIBACTERIAL DE (7-SUSTITUIDO)-8- (SUSTITUIDO)-9 (SUSTITUIDO)-TETRACICLINAS

MIC (μ g/ml) COMPUESTO

		Ejemplo 37	Ejemplo 38	Ejemplo 39
1	E coli GC2270 (tet(M))	4	32	32
2	E coli GC4559 (GC4560 padre)	2	32	32
3	E coli GC4560 (IMP mutante)	1	8	8
4	E coli GC2203 (Control ATCC)	2	32	32
5	E coli GC1073 (tet(B))	2	32	32
6	S aureus GC1131 (Clínico)	4	32	32
7	S aureus GC6466 (tet(M))	4	32	32
8	S aureus GC6467 (tet(M)+(K))	8	>64	>64
9	S aureus GC1079 (tet(K))	4	64	64
10	S aureus GC4536 (Smith MP -In Vivo)	4	16	32
11	S aureus GC2216 (Control ATCC)	4	32	32
12	E faecalis GC4555 (Control ATCC)	2	16	32
13	E faecalis GC2267 (tet(L)+(M)+(S))	4	64	64
14	E faecalis GC2242 (Resistente a Van)	2	16	32
15	S pneumoniae* GC4465 (Clínico)	1	4	8
16	S pneumoniae* GC1894 (Clínico)	1	4	8
17	S pyogenes* GC4563 (Clínico)	1	4	8
18	M catarrhalis* GC6907 (Clínico)	1	4	8
19	H influenzae <> GC6896 (Control ATCC)	4	64	64
20	C albicans GC3066 ATCC (Control)	>64	>64	>64

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Quando los compuestos de la invención son empleados como antibacteriales, ellos se pueden combinar con uno o más portadores farmacéuticamente aceptables, por ejemplo, solventes, diluyentes y similares, y se pueden administrar oralmente en tales formas como tabletas, cápsulas, polvos dispersables, gránulos o suspensiones que contienen, por ejemplo, desde aproximadamente 0.05 a 5% de agentes de suspensión, melazas que contienen, por ejemplo, desde aproximadamente 10 a 50% de azúcar, y elixires que contienen por ejemplo, desde aproximadamente 20 a 50% de etanol, y similares, o parenteralmente en la forma de soluciones o suspensiones estériles inyectables que contienen desde aproximadamente 0.05 a 5% de agente de suspensión en un medio isotónico. Tales preparaciones farmacéuticas pueden contener, por ejemplo, desde aproximadamente 25 a aproximadamente 90% del ingrediente activo en combinación con el portador más usualmente entre aproximadamente 5% y 60% en peso.

Una cantidad efectiva del compuesto es de aproximadamente 2.0 mg/kg de peso de cuerpo a aproximadamente 100.0 mg/kg se puede administrar una a cinco veces por día por vía de cualquier ruta típica de administración que incluye pero no está limitada a oral, parenteral (que incluye inyección o técnicas de infusión subcutánea, intravenosa, intramuscular, intrasternal), tópica o rectal, en formulaciones unitarias de dosis que contiene portadores farmacéuticamente aceptables no tóxicos convencionales, adyuvantes y vehículos. Se entenderá, sin embargo, que el nivel de dosis específico y la frecuencia de la dosis para cualquier paciente particular puede variar y dependerá

de una variedad de factores que incluyen la actividad del compuesto específico emplead , la estabilidad metabólica y la longitud de acción de ese compuesto, la edad, el peso del cuerpo, la salud general, el sexo, la dieta, el modo y tiempo de administración, la proporción de excreción, la combinación de la droga, la severidad de la condición particular, y la terapia que lleve el huésped.

Estos compuestos activos se pueden administrar oralmente así como también ruta intravenosa, intramuscular o subcutánea. Los portadores sólidos incluyen almidón, lactosa, fosfato de dicalcio, celulosa microcristalina, sucrosa y caolín, mientras los portadores líquidos incluyen agua estéril, polietilen glicoles, tensoactivos no iónicos y aceites comestibles tales como almidón, maní y aceites de sésamo como son apropiados a la naturaleza del ingrediente activo y la forma particular de administración deseada. Los adyuvantes empleados de costumbre en la preparación de las composiciones farmacéuticas pueden ser ventajosamente incluidos tal como agentes saborizantes, agentes clonantes, agentes preservantes y antioxidantes, por ejemplo, vitamina E, ácido ascórbico, BHT y BHA.

Una composición farmacéutica preferida de los compuestos de la invención desde el punto de vista de facilidad de preparación y administración son composiciones sólidas, particularmente, tabletas y cápsulas de llenado en duro o cápsulas de llenado en líquido. Se prefiere la administración oral de los compuestos.

Estos compuestos activos pueden ser administrados parenteralmente o intraperitonealmente. Las soluciones o suspensiones de estos compuestos activos como base libre o sal farmacológicamente aceptable se puede preparar en agua adecuadamente mezclada con un tensactivo tal como hidróxi-propilcelulosa. Las dispersiones también se pueden preparar en glicerol líquido, polietilen glicoles y mezclas de estos en aceites. Bajo condiciones ordinarias de almacenamiento y uso, estas preparaciones contienen un preservativo para evitar el crecimiento de microorganismos.

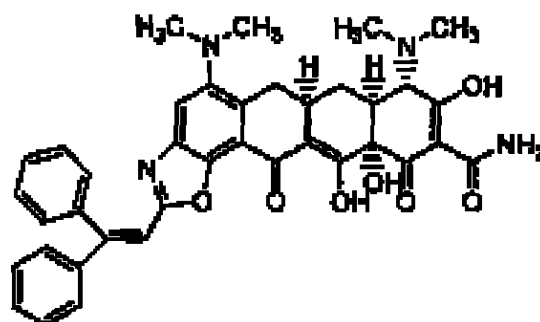
Las formas farmacéuticas adecuadas para uso inyectable incluyen soluciones acuosas estériles o dispersiones o polvos estériles para la preparación extemporánea de soluciones estériles o dispersiones. En todos los casos, la forma debe ser estéril y debe ser fluida de tal forma que exista fácil aplicación con jeringas. Debe ser estable bajo las condiciones de elaboración y almacenamiento y debe ser preservada contra la acción de contaminación en microorganismos tales como bacterias y hongos. El portador puede ser un medio solvente o de dispersión que contiene, por ejemplo, agua, etanol, poliel (por ejemplo, glicerol, propilen glicol y polietilen glicol líquido), mezclas adecuadas de estas y aceites vegetales.

La invención será más completamente descrita en conjunto con los siguientes ejemplos específicos que no deben ser considerados como limitantes del alcance de la invención.

Ejemplo de procedimiento A

EJEMPLO 1

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-2-(2,2-difenilvinil)-
3,11a,12-trihidroxi-11,13-dioxo-6,6a,7,7a,8,11,11a,13-
octahidrotetraceno [2,1-d] [1,3] oxazol-10-carboxamida



Una sal de sulfato de 9-aminociclinolona (0.200g, 0.748 mmol) se disuelve en DMF anhidro y se trata con β -fenilcinnamaldehído (0.779g, 3.74 mmol, 5 equivalentes) La solución se trata con DDQ (0.045 g, 0.374 mmol, 0.5 equivalentes) y se agita a temperatura ambiente durante 5 min. La espectrometría de masa ES+ muestra una proporción 1:1 del producto y el material de partida. Una segunda porción de DDQ (0.068 g, 0.300 mmol, 0.4 equivalentes) se agrega. Después de aproximadamente 5 minutos, se agrega acetonitrilo (7.5 mL), y la mezcla de reacción completa se vierte lentamente en éter (750 mL.) El sólido rosa se remueve mediante filtración y se lava con éter fresco para producir 0.480 g del producto crudo. Este material se disuelve en agua (75 mL) para dar una solución a pH 2.2, que se extrae con diclorometano (2 X 100 mL.) El pH de la capa acuosa se eleva a 3.0 con amonio acuoso, y la solución es de nuevo extraída con diclorometano (2 X 100 mL). Los cuatro

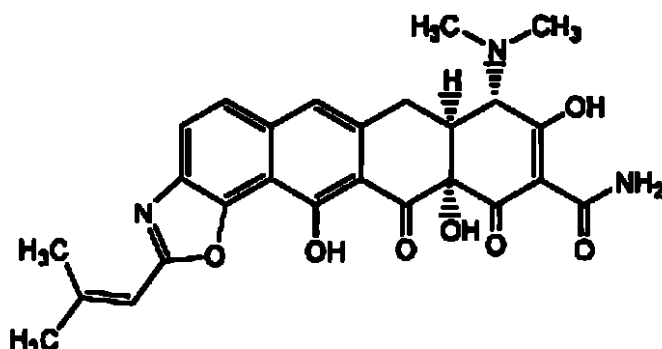
extractos orgánicos se secan con (Na_2SO_4), filtrados y concentrados a un volumen de aproximadamente 2 mL. Se agrega una porción pequeña de metanol (1 mL), y la solución concentrada se trata gota a gota con HCl 1M en éter. El precipitado sólido se filtra, se lava con éter fresco y se seca bajo vacío en producto como su sal HCl.

Señales ^1H RMN seleccionadas δ 4.26 (s, 1H), 7.13 (s, 1H), 7.26-7.45 (m, 6H), 7.63 (s, 1H), 9.08 (s, 1H), 9.54 (s, 1H).

Los compuestos de esta invención listados adelante en los Ejemplos 2 a 37 se preparan substancialmente siguiendo el método descrito en detalle anteriormente en el Ejemplo 1 utilizando procedimiento A.

EJEMPLO 2

(7aS, 8S, 11aS) - 8 - (dimetilamino) - 9, 11a, 13 - trihidroxi - 2 - (2 - metil - 1 - propenil) - 11, 12 - díoxo - 7, 7a, 8, 11, 11a, 12 - hexahidronaftaceno [2, 1 - d] [1, 3] oxazol - 10 - carboxamida



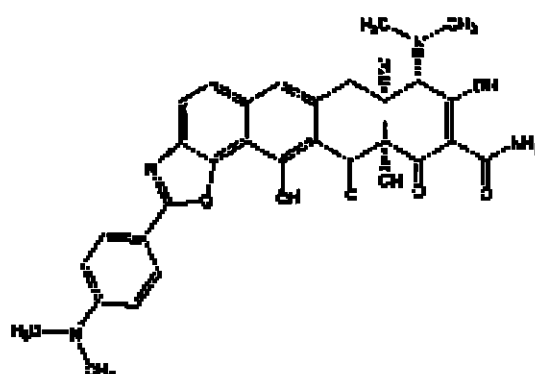
MS m/z 492 ($M+H$)

HRMS: calculado para $C_{18}H_{26}N_2O_7$, 491.16925; encontrado (ESI+),

492.1765.

EJEMPLO 3

(7aR,8S,11aS)-8-(dimetilamino)-2-[4-(dimetilamino)fenil]-
9,11a,13-trihidroxí-11,12-dioxo-7,7a,8,11,11a,12-
hexahidronaftaceno [2,1-d] [1,3]oxazol-10-carboxamida

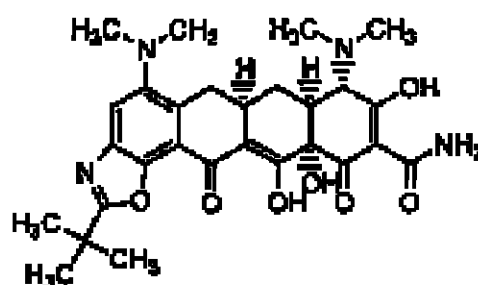


HRMS: calculado para $C_{30}H_{33}N_2O_7$, 566.1958; encontrado (ESI+),

567.2030.

EJEMPLO 4

(6aR,7aR,8S,11aS)-2-tert-butí-5,8-bis(dimetilamino)-9,11a,12-
trihidroxí-11,13-dioxo-6,6a,7,7a,8,11,11a,13-
octahidrotetraceno [2,1-d] [1,2]oxazol-10-carboxamida



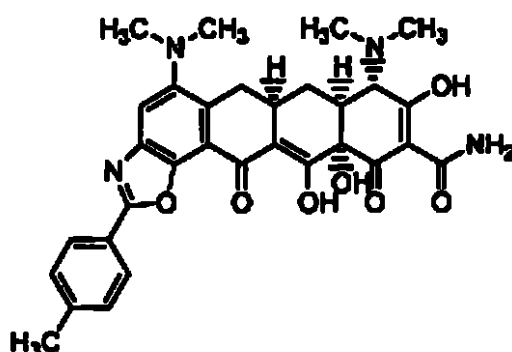
MS (ESI) m/z 539.3 (M+H);

MS (ESI) m/z 270.4 (M+2H);

HRMS: calculado para $C_{28}H_{34}N_4O_7 \cdot HCl$, 574.2194; encontrado (ESI-),
537.23462;

EJEMPLO 5

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-9,11a,12-trihidróxi-2-(4-metilfenil)-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida



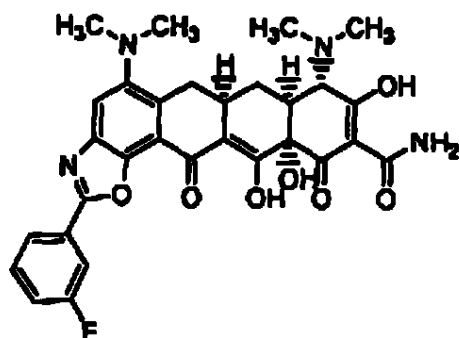
MS (ESI) m/z 573.3 (M+H);

MS (ESI) m/z 287 (M+2H);

HRMS: calculado para $C_{31}H_{32}N_4O_7 \cdot HCl$, 608.2038; encontrado (ESI-),
571.21905;

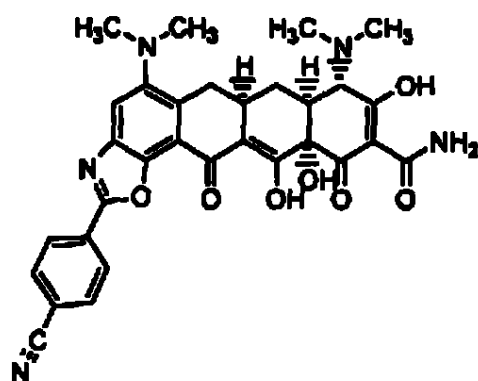
EJEMPLO 6

(7aS,8S,11aS)-5,8-bis(dimetilamino)-2-(3-fluorofenil)-9,11a,13-trihidróxi-11,12-dioxo-7,7a,8,11,11a,12-hexahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida



EJEMPLO 7

(6aR,7aS,8S,11aS)-2-(4-cianofenil)-5,8-bis(dimetilamino)-
9,11a,12-trihidroxi-11,13-dioxo-6,6a,7,7a,8,11,11a,13-
octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida

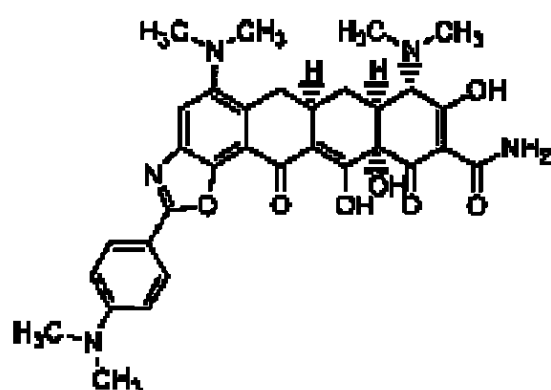


MS (ESI) m/z 584.4 ($M+H$);

HRMS: calculado para $C_{31}H_{29}N_5O_7 \cdot HCl$, 619.1834; encontrado (ESI-),
582.19817;

EJEMPLO 8

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-2-(4-(
(dimetilamino)fenil)-9,11a,12-trihidroxi-11,13-dioxo-
6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-
carboxamida



MS (ESI) m/z 502.2 ($M+H$);

MS (ESI) m/z 351.5 ($M+2H$);

HRMS: calculado para $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_7 \cdot \text{HCl}$, 637.2303; encontrado (ESI-),

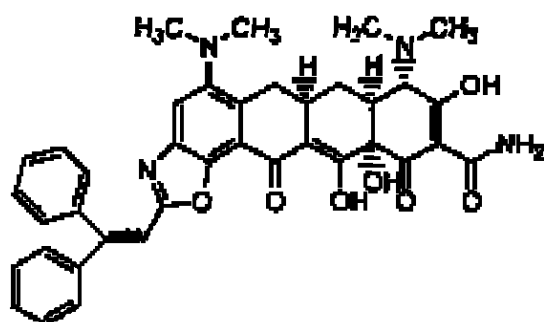
630.24521;

EJEMPLO 9

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -2- (2,2-difenilvinil) -

9,11a,12-trihidroxí-11,13-dioxo-6,6a,7,7a,8,11,11a,13-

octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida



MS (ESI) m/z 661.3 ($M+H$);

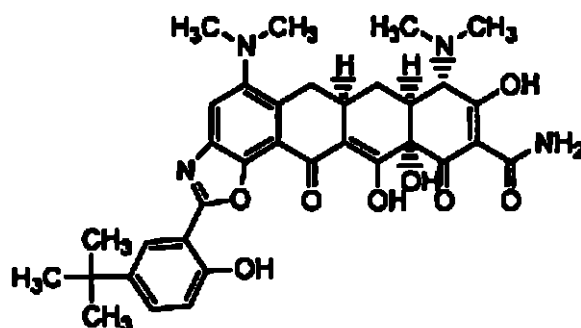
MS (ESI) m/z 331.3 ($M+2H$);

HRMS: calculado para $\text{C}_{30}\text{H}_{25}\text{N}_4\text{O}_7 \cdot \text{HCl}$, 696.2351; encontrado (ESI-),

699.24957;

EJEMPLO 10

(6aR,7aS,8S,11aS)-2-(5-tert-butil-2-hidroxifenil)-5,8-bis(dimetilamino)-9,11a,12-trihidroxi-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida



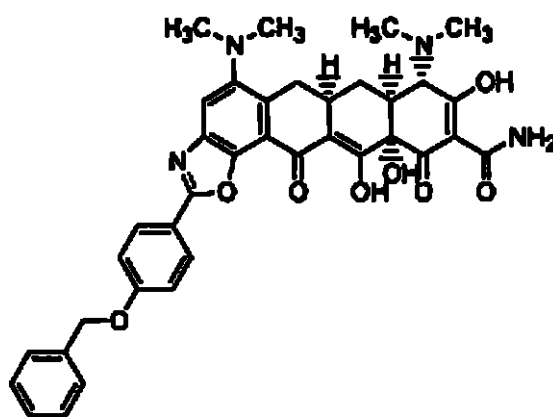
MS (ESI) m/z 631.4 (M+H);

HRMS: calculado para $C_{34}H_{39}N_4O_5 \cdot HCl$, 666.2456; encontrado (ESI+),

631.27753;

EJEMPLO 11

(6aR,7aS,8S,11aS)-2-[4-(benciloxi)fenil]-5,8-bis(dimetilamin)-9,11a,12-trihidroxi-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida

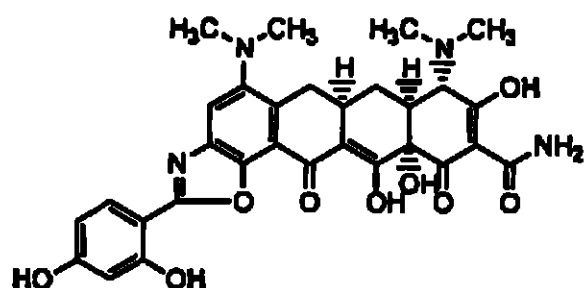


MS (ESI) m/z 665.2 (M+H);

HRMS: calculado para $C_{27}H_{36}N_4O_8 \cdot HCl$, 700.2300; encontrado (ESI+),
665.26096;

EJEMPLO 12

(6aR,7aS,8S,11aS)-2-(2,4-dihidroxifenil)-5,8-bis(dimetilamino)-
9,11a,12-trihidroxil-11,13-dioxo-6,6a,7,7a,8,11,11a,13-
octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida

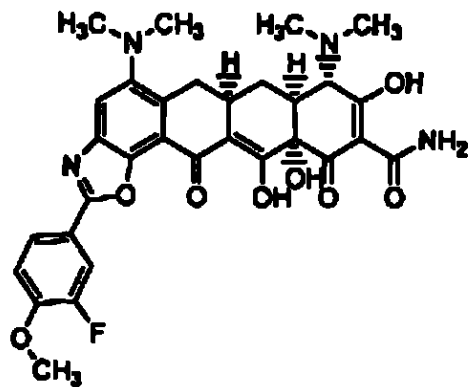


MS (ESI) m/z 591.2 (M+H);

HRMS: calculado para $C_{30}H_{30}N_4O_9 \cdot HCl$, 626.1760; encontrado (ESI-),
589.1927;

EJEMPLO 13

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-2-(3-fluoro-4-
metoxifenil)-9,11a,12-trihidroxil-11,13-dioxo-
6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-
carboxamida



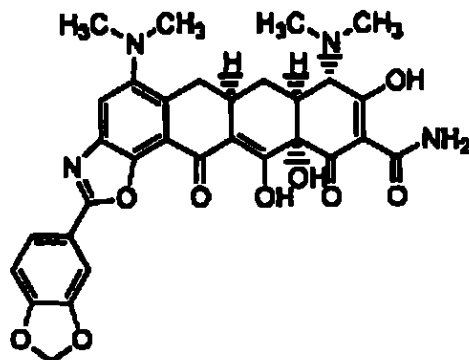
MS (ESI) m/z 607.3 (M+H);

MS (ESI) m/z 304 (M+2H);

HRMS: calculado para C₃₁H₃₁FN₄O₆ · HCl, 642.1893; encontrado (ESI-), 605.20519;

EJEMPLO 14

(6aR, 7aS, 8S, 11aS) -2-(1,3-benzodioxol-5-il) -5,8-bis(dimetilamino) -
9,11a,12-trihidróxi-11,13-dioxo-6,6a,7,7a,8,11,11a,13-
octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida



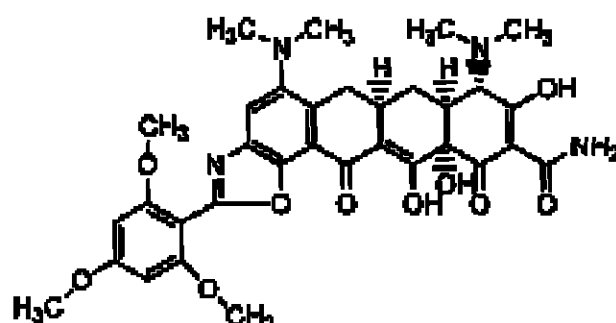
MS (ESI) m/z 603.3 (M+H);

MS (ESI) m/z 302.1 (M+2H);

HRMS: calculado para C₃₁H₃₁N₄O₆ · HCl, 638.1780; encontrado (ESI+),
603.20953;

EJEMPLO 15

(6*S*R, 7*a*S, 8*S*, 11*a*S) -5, 8-bis(dimetilamino) -9, 11*a*, 12-trihidroxí-
11, 13-dioxo-2-(2, 4, 5-trimetoxifenil) -6, 6*a*, 7, 7*a*, 8, 11, 11*a*, 13-
octahidrotetraceno[2, 1-*d*] [1, 3]oxazol-10-carboxamida

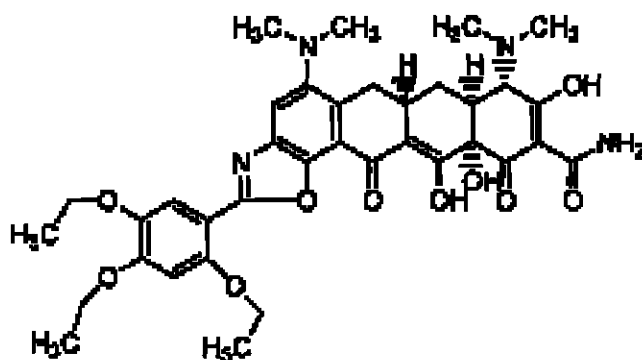


MS (ESI) m/z 649.2 (M+H);

HRMS: calculado para $C_{33}H_{34}N_4O_{10} \cdot HCl$, 684.2198; encontrado (ESI-
, 647.23441;

EjemPlo 16

(6*a*R, 7*a*S, 8*S*, 11*a*S) -5, 8-bis(dimetilamino) -9, 11*a*, 12-trihidroxí-
11, 13-dioxo-2-(2, 4, 5-trietoxifenil) -6, 6*a*, 7, 7*a*, 8, 11, 11*a*, 13-
octahidrotetraceno[2, 1-*d*] [1, 3]oxazol-10-carboxamida



MS (ESI) m/z 691.3 (M+H);

HRMS: calculado para $C_{36}H_{42}N_4O_{10} \cdot HCl$, 726.2668; encontrado

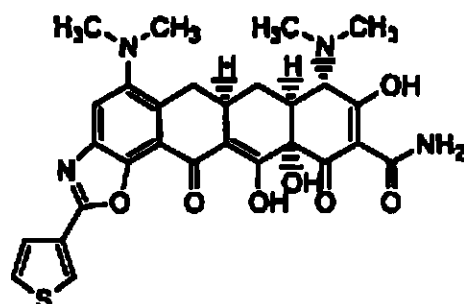
(ESI+), 691.29817;

EJEMPLO 17

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-9,11a,12-trihidroxí-

11,13-dioxo-2-tien-3-il-6,6a,7,7a,8,11,11a,13-

octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida



MS (ESI) m/z 565.2 (M+H);

MS (ESI) m/z 263.4 (M+2H);

HRMS: calculado para $C_{28}H_{28}N_4O_7S \cdot HCl$, 600.1445; encontrado (ESI-

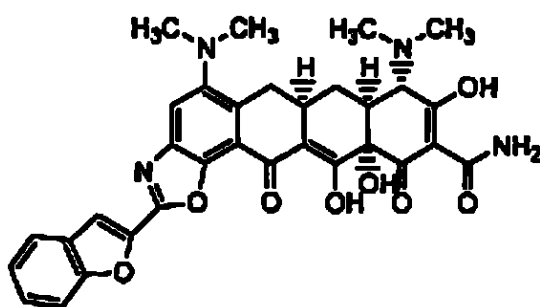
), 563.15992;

EJEMPLO 18

(6aR,7aS,8S,11aS)-2-(1-benzofuran-2-il)-5,8-bis(dimetilamino)-

9,11a,12-trihidroxí-11,13-dioxo-6,6a,7,7a,8,11,11a,13-

octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida

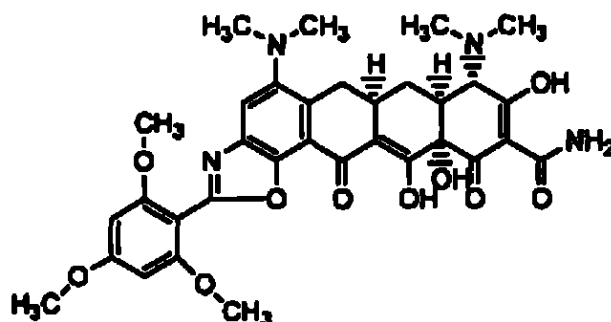


MS (ESI) m/z 599.3 (M+H);

HRMS: calculado para $C_{32}H_{32}N_4O_8 \cdot HCl$, 634.1830; encontrado (ESI-),
597.19811;

EJEMPLO 19

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-9,11a,12-trihidroxi-2-(1-metil-1H-indol-2-il)-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida



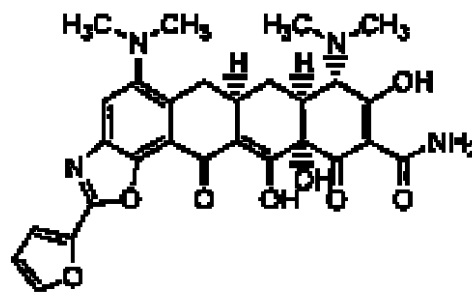
MS (ESI) m/z 612.2 (M+H);

HRMS: calculado para $C_{33}H_{33}N_5O_7 \cdot HCl$, 647.2147; encontrado (ESI+),
612.24406;

EJEMPLO 20

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-2-(2-furil)-9,11a,12-

trihidroxí-11,13-dioxo-6,6a,7,7a,8,11,11a,13-
octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida

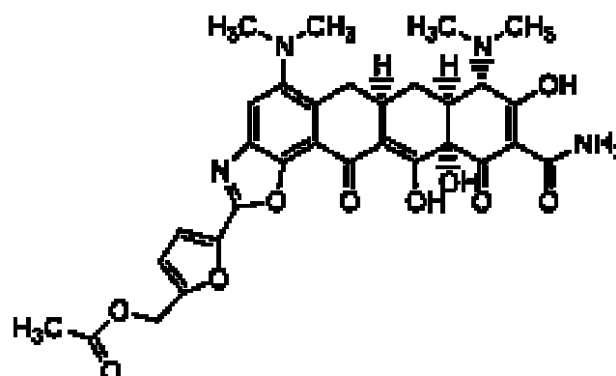


MS (ESI) m/z 549.3 (M+H),

HRMS: calculado para $C_{28}H_{23}N_4O_5 \cdot HCl$, 584.1674; encontrado (ESI-),
547.1922,

EXEMPLO 21

Acetato de {5-[(6aR,7aS,8S,11aS)-10-(aminocarbonil)-5,5-bis(dimetilamino)-9,11a,12-trihidroxí-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-2-il]-2-furil}metilo

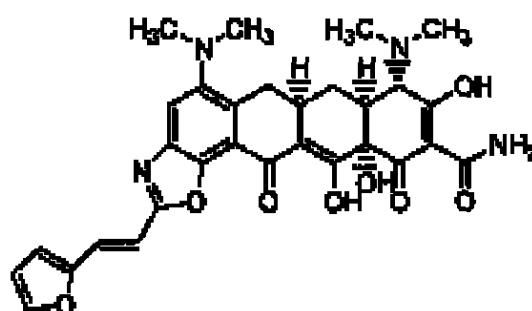


MS (ESI) m/z 621.2 (M+H),

HRMS: calculado para $C_{32}H_{23}N_4O_7 \cdot HCl$, 656.1885; encontrado
(ESI+), 621.21807,

EJEMPLO 22

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-2-[(E)-2-(2-furil)etenil]-9,11a,12-trihidroxi-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida



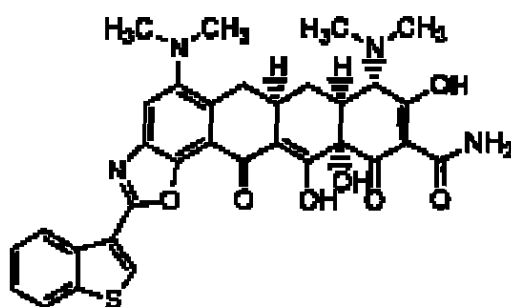
MS (ESI) m/z 575.2 (M+H);

MS (ESI) m/z 288.3 (M+2H);

HRMS: calculado para $C_{30}H_{27}N_4O_5 \cdot HCl$, 610.1830; encontrado (ESI-), 573.1985;

EJEMPLO 23

(6aR,7aS,8S,11aS)-2-(1-benzotien-3-il)-5,8-bis(dimetilamino)-9,11a,12-trihidroxi-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida

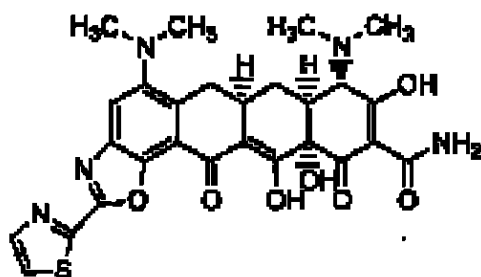


MS (ESI+) m/z 615.1 [(M+R)+];

HRMS: calculado para $C_{22}H_{20}N_4O_7S \cdot HCl$, 650.1602; encontrado
(ESI+), 615.19036;

EJEMPLO 24

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-9,11a,12-trihidroxí-
11,13-dioxo-2-(1,3-tiazol-2-il)-6,6a,7,7a,8,11,11a,13-
octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida



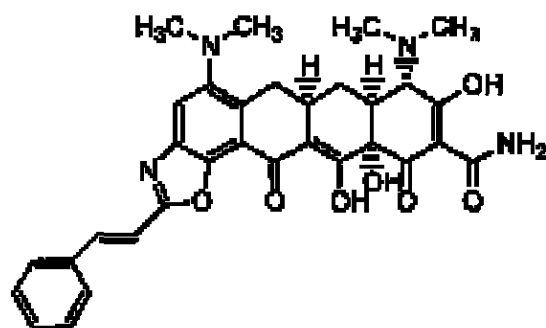
MS (ESI) m/z 546.4 (M+H);

MS (ESI) m/z 263.6 (M+2H);

HRMS: calculado para $C_{22}H_{22}N_4O_7S \cdot HCl$, 601.1398; encontrado
(ESI+), 566.16973;

EJEMPLO 25

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-9,11a,12-trihidroxí-
11,13-dioxo-2-[(E)-2-feniletanil]-6,6a,7,7a,8,11,11a,13-
octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida



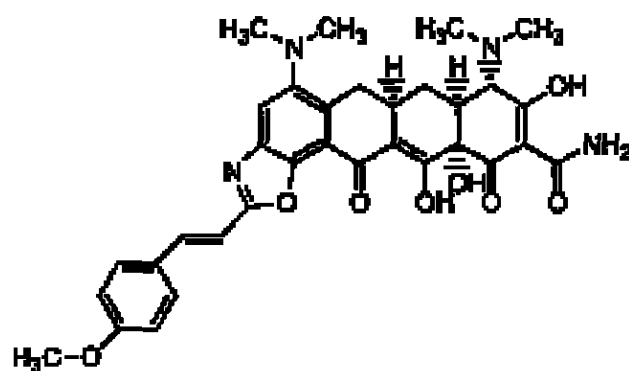
MS (ESI) m/z 585.4 (M+H);

MS (ESI) m/z 293.3 (M+2H);

HRMS: calculado para $C_{32}H_{42}N_4O_7 \cdot HCl$, 620.2038; encontrado (ESI+),
585.2329;

EJEMPLO 26

(6aR, 7aS, 8S, 11aS) -5,8-bis(dimetilamino) -9,11a,12-trihidroxí-2-
[(E)-2-(4-metoxifenil)etenil] -11,13-dioxo-6,6a,7,7a,8,11,11a,13-
octahidrotetraceno [2,1-d] [1,3]oxazol-10-carboxamida



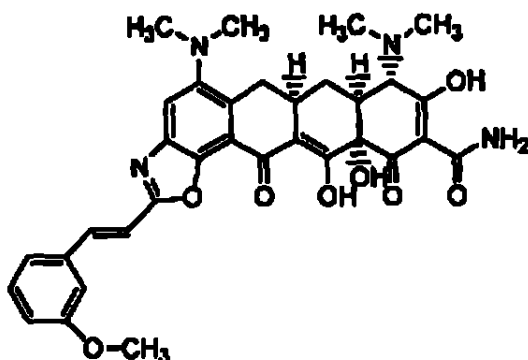
MS (ESI) m/z 615.3 (M+H);

MS (ESI) m/z 308.3 (M+2H);

HRMS: calculado para $C_{33}H_{44}N_4O_8 \cdot HCl$, 650.2143; encontrado (ESI+),
615.24413;

EJEMPLO 27

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-9,11a,12-trihidroxi-2-
[(E)-2-(3-metoxifenil)etenil]-11,13-dioxo-6,6a,7,7a,8,11,11a,13-
octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida



MS (ESI) m/z 615.4 (M+H);

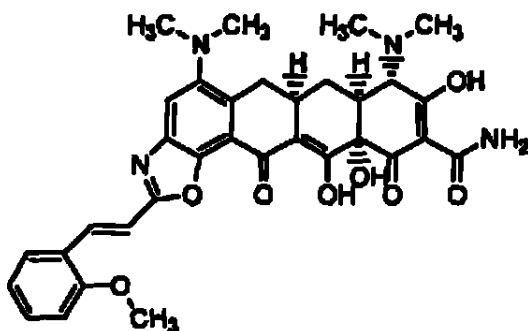
MS (ESI) m/z 308.3 (M+2H);

HRMS: calculado para $C_{33}H_{34}N_4O_8 \cdot HCl$, 650.2143; encontrado (ESI+),

615.24419;

EJEMPLO 28

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-9,11a,12-trihidroxi-2-
[(E)-2-(2-metoxifenil)etenil]-11,13-dioxo-6,6a,7,7a,8,11,11a,13-
octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida



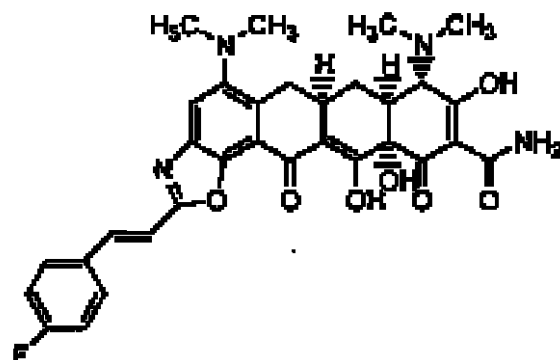
MS (ESI) m/z 615.3 (M+H);

MS (ESI) m/z 308.3 (M+2H);

HRMS: calculado para $C_{13}H_{16}N_4O_7 \cdot HCl$, 650.2143; encontrado (ESI+),
615.24408;

EJEMPLO 29

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-2-[(E)-2-(1-fluorofenil)etenil]-9,11a,12-trihidroxí-11,13-dioxo-
6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-
carboxamida



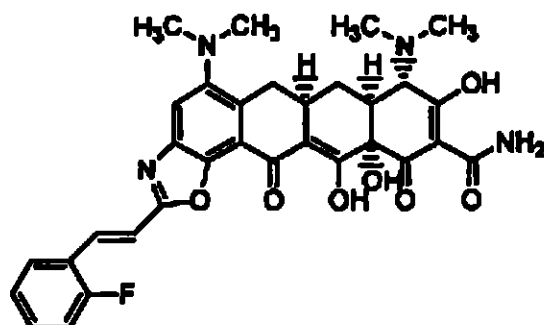
MS (ESI) m/z 603.3 (M+H);

MS (ESI) m/z 302.3 (M+2H);

HRMS: calculado para $C_{32}H_{31}FN_4O_7 \cdot HCl$, 638.1944; encontrado
(ESI+), 603.22476;

EJEMPLO 30

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-2-[(E)-2-(2-fluorofenil)etenil]-9,11a,12-trihidroxí-11,13-dioxo-
6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-
carboxamida



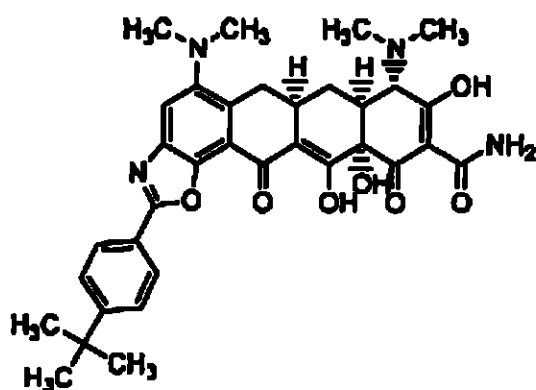
MS (ESI) m/z 603.2 (M+H);

MS (ESI) m/z 302.3 (M+2H);

HRMS: calculado para $C_{32}H_{31}FN_4O_7 \cdot HCl$, 636.1944; encontrado
(ESI+), 603.22469;

EJEMPLO 31

(6aR, 7aS, 8S, 11aS) -2-(4-tert-butilfenil)-5,8-bis(dimetilamino)-
9,11a,12-trihidroxil-11,13-dioxo-6,6a,7,7a,8,11,11a,13-
octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida



MS (ESI) m/z 615.3 (M+H);

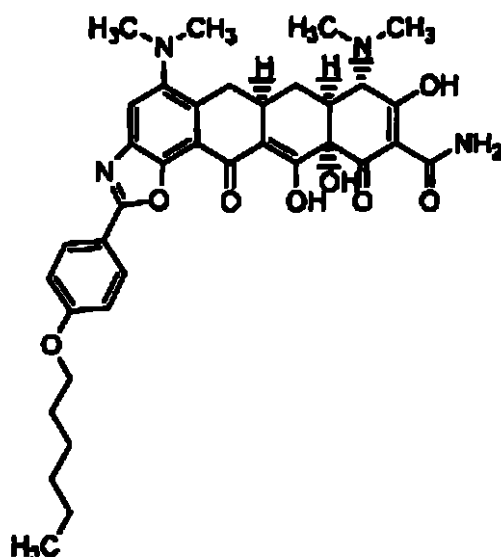
MS (ESI) m/z 308.3 (M+2H);

HRMS: calculado para $C_{34}H_{39}N_4O_7 \cdot HCl$, 650.2507; encontrado (ESI+),

615.28057;

EJEMPLO 32

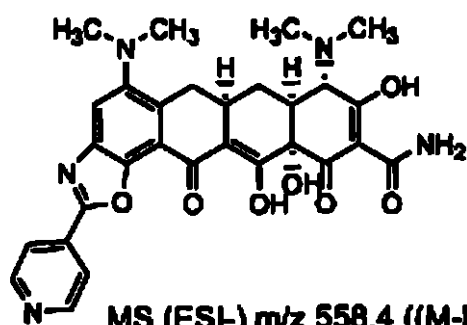
(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -2 - [4 - (hexiloxi) fenil] -
9, 11a, 12-trihidroxil-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-
octahidrotetraceno [2, 1-d] [1, 3] oxazol-10-carboxamida

MS (ESI) m/z 659.4 (M+H);MS (ESI) m/z 330.4 (M+2H);

HRMS: calculado para $C_{36}H_{42}N_4O_8 \cdot HCl$, 694.2769; encontrado (ESI+),
659.30693;

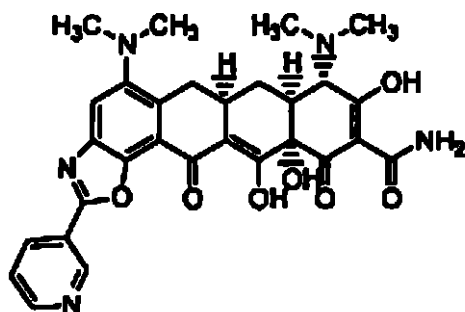
EJEMPLO 33

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -9, 11a, 12-trihidroxil-
11, 13-dioxo-2-piridin-4-il-6, 6a, 7, 7a, 8, 11, 11a, 13-
octahidrotetraceno [2, 1-d] [1, 3] oxazol-10-carboxamida



EJEMPLO 34

(6aR,7aS,8S,11aS)-5,6-bis(dimetilamino)-9,11a,12-trihidroxí-
11,13-dioxo-2-piridin-3-il-6,6a,7,7a,8,11,11a,13-
octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida



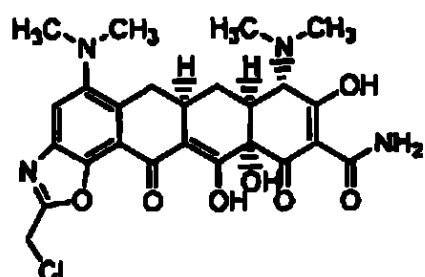
MS (ESI) m/z 560.3 (M+H);

MS (ESI) m/z 280.7 (M+2H);

HRMS: calculado para $C_{29}H_{29}N_5O_7 \cdot HCl$, 595.1834; encontrado (ESI+),
560.21353;

EJEMPLO 35

(6aR,7aS,8S,11aS)-2-(clorometil)-5,8-bis(dimetilamino)-9,11a,12-
trihidroxí-11,13-dioxo-6,6a,7,7a,8,11,11a,13-
octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida

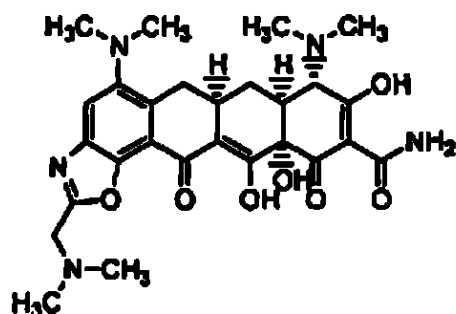


MS (ESI) m/z 531.2 (M+H);

MS (ESI) m/z 266.3 (M+2H);

EJEMPLO 36

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-2-[(dimetilamino)metil]-9,11a,12-trihidroxí-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida



MS (ESI) m/z 540.4 (M+H);

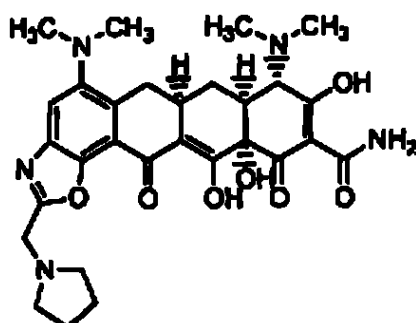
MS (ESI) m/z 270.7 (M+2H);

HRMS: calculado para $C_{27}H_{33}N_5O_7 \cdot HCl$, 575.2147; encontrado (ESI+),
540.24506;

EJEMPLO 37

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-9,11a,12-trihidroxí-

11,13-dioxo-2-(pirrolidin-1-ilmetil)-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida



MS (ESI) m/z 566.4 (M+H);

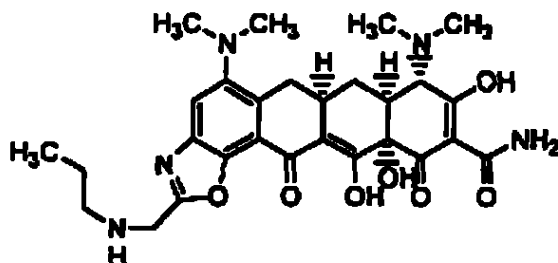
MS (ESI) m/z 283.9 (M+2H);

HRMS: calculado para $C_{29}H_{25}N_5O_7 \cdot HCl$, 601.2303; encontrado (ESI+),
566.26066;

Ejemplo de procedimiento B

EJEMPLO 38

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-9,11a,12-trihidroxí-
11,13-dioxo-2-[(propilamino)metil]-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida



Sal de sulfato de 9-aminominociclina (1.0 g, 1.50 mmol) es
disuelta en DMF (50 mL) y tratada con una solución de 2-cloro-

1,1,1-trimetoxietano (0.463 g, 3.00 mmol, 2 equivalentes). La reacción es agitada a temperatura ambiente hasta que la espectrometría de masa muestra la conversión al derivado de clorometilbenzoxazol. La solución es antes tratada con *n*-propilamina (10 mL, exceso) y agitada hasta que la espectrometría de masa, nos muestra la conversión al *n*-propilaminometilbenzoxazol. La mezcla es concentrada bajo presión reducida para remover el exceso de *n*-propilamina, y luego es vertida lentamente en éter (1 L) y HCl/éter es agregado para precipitar la sal. El sólido es enjuagado con éter fresco y secado bajo vacío. El sólido crudo es disuelto en agua (100 mL) para dar una solución a un pH 2. El pH es elevado sucesivamente por 0.05 unidades con amonio acuoso, y extraído con diclorometano. Las fracciones extraídas a un pH entre 4-4.5 son combinadas, secadas (Na_2SO_4), filtradas y concentradas cerca al secado. Un volumen pequeño de metanol es agregado a la solución y tratada con un 1M HCl en éter. El sólido precipitado es recolectado por filtración, lavado con éter fresco y secado bajo vacío para producir 0.067 g del producto como su sal de HCl.

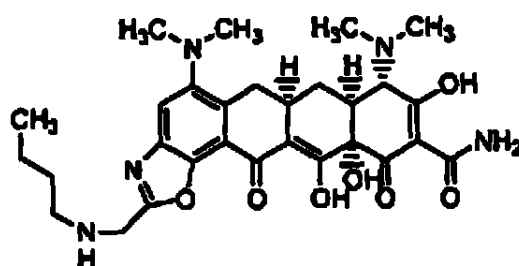
Señales seleccionadas del ^1H NMR: δ 0.94 (t, 3H), 1.73 (m, 2H), 4.31 (s, 1H), 4.65 (s, 2H), 7.78 (s, 1H), 9.15 (s, 1H), 9.67 (s, 1H).

Los compuestos de esta invención listados enseguida en los ejemplos 39 a 41 son preparados sustancialmente siguiendo el método descrito en detalle aquí anteriormente en el ejemplo 38 en el procedimiento B.

(preparado del procedimiento B)

EJEMPLO 39

(6aR,7aS,8S,11aS)-2-[(butilamino)metil]-5,8-bis(dimetilamino)-
9,11a,12-trihidroxí-11,13-dioxo-6,6a,7,7a,8,11,11a,13-
octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida

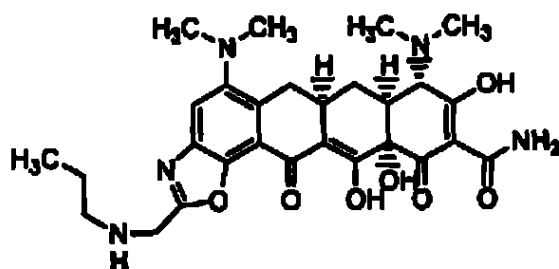
MS (ESI) m/z 568.3 (M+H);MS (ESI) m/z 284.8 (M+2H);MS (ESI) m/z 305.2 (M+ACN+2H);HRMS: calculado para $C_{29}H_{37}N_5O_7 \cdot HCl$, 603.2460; encontrado (ESI+),

569.27616;

(Procedimiento B)

EJEMPLO 40

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-9,11a,12-trihidroxí-
11,13-dioxo-2-[(propilamino)metil]-6,6a,7,7a,8,11,11a,13-
octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida



MS (ESI) m/z 554.3 (M+H);

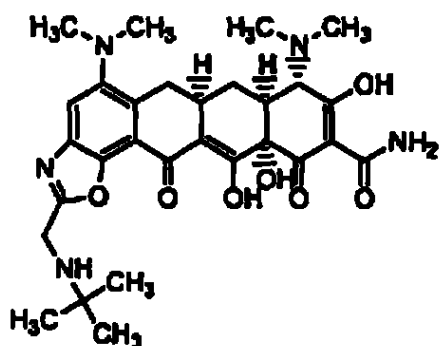
MS (ESI) m/z 277.7 (M+2H);

HRMS: calculado para $C_{28}H_{38}N_5O_7 \cdot HCl$, 589.2303; encontrado (ESI+),
554.2604;

(Procedimiento B)

EJEMPLO 41

(6aR,7aS,8S,11aS) -2- [(tert-butilamino)metil] -5,8-
bis(dimetilamino) -9,11a,12-trihidroxil-11,13-dioxo-
6,6a,7,7a,8,11,11a,13-octahidrotetraceno [2,1-d] [1,3]oxazol-10-
carboxamida



Sal de sulfato de 9-aminoninociclina (1.0 g, 1.50 mmol) es
disuelta en DMF (20 mL) y tratado con una solución de 2-
clorotrimetoxietano (0.35 g, 2.2 mmol, 1.46 equivalentes). La
reacción es agitada a temperatura ambiente hasta que la

espectrometría de masa muestra la conversión al derivado de clorometilbenzoxazol. La solución es antes tratada con t-butilamina (7.3 mL, exceso) y agitada hasta que la espectrometría de masa muestra la conversión al benzoxazol de t-butilaminometilo. La mezcla es concentrada bajo presión reducida para remover el exceso de t-butilamina, y luego se vierte lentamente en éter (1 L) y se agrega HCl/éter para precipitar la sal. El sólido es enjuagado con éter fresco y secado bajo vacío. El sólido crudo es disuelto en agua (100 mL) para dar una solución a un pH 2. El pH es elevado sucesivamente en 0.05 unidades con amoníaco acuoso, y extraído con diclorometano. Las fracciones extraídas de un pH 4 a 4.5 son combinadas, secadas (Na_2SO_4), filtradas y concentradas cerca al secado. Un volumen pequeño de metanol es agregado y la solución es tratada con HCl 1M en éter. El sólido precipitado es recolectado por filtración, lavado con éter fresco y secado bajo vacío para dar el producto como su sal de HCl.

MS (ESI+) m/z 568.4 ((M+H)+);

MS (ESI+) m/z 284.9 ((M+2H)2+);

MS (ESI+) m/z 146.3 ((M'+H)+);

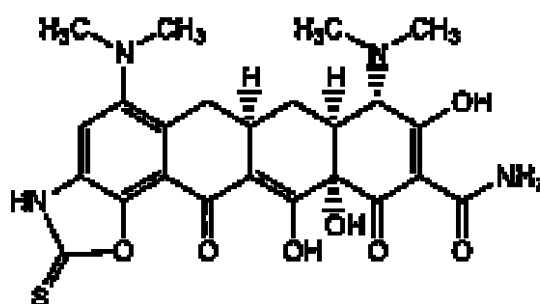
HRMS: calculado para $\text{C}_{23}\text{H}_{37}\text{N}_5\text{O}_7 \cdot \text{HCl}$, 603.2460; encontrado (ESI-),
566.26087;

Ejemplo de procedimiento C

EJEMPLO 42

(6aR, 7aS, 8S, 11aS)-5,8-bis(dimetilamin)-9,11a,12-trihidroxí-

11,13-dioxo-2-tioxo-2,3,6,6a,7,7a,8,11,11a,13-decahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida



A una solución de 9-amino-mino de sulfato (0.668 g, 1 mmol) en DMSO (30 mL) se agregaron 2 equivalentes de 1,1-tiocarbonildimidazol. La reacción es antes agitada a temperatura ambiente durante 2 a 12 horas (seguido por MS(ES)). La mezcla es antes triturada con dietil éter y el sólido es recolectado. El material es usado en la siguiente etapa sin purificación adicional.

MS (ESI) m/z 515.2 (M+H);

HRMS: calculado para $C_{24}H_{26}N_4O_7S \cdot H_2SO_4$, 612.1196; encontrado

(ESI+), 515.15934;

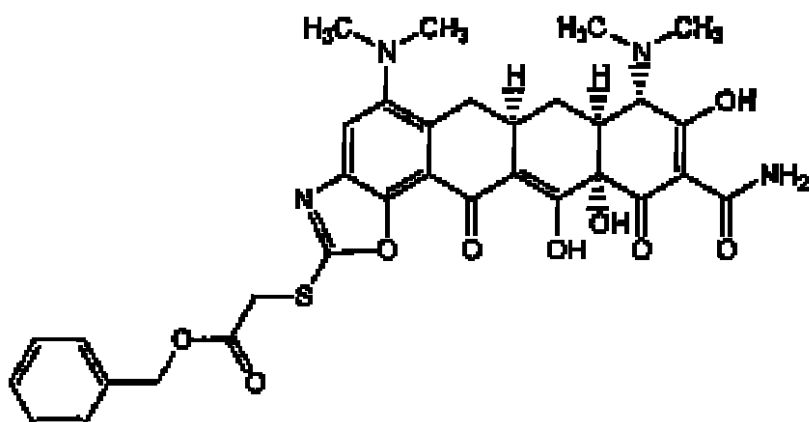
Los compuestos de esta invención listados enseguida en los ejemplos 43 a 44 son preparados sustancialmente siguiendo el método descrito en detalle anterior en el ejemplo 42 en el procedimiento C.

Ejemplo de procedimiento C

(Procedimiento C)

EJEMPLO 43

{ [(6aR,7aS,8S,11aS)-10-(aminocarbonil)-5,6-bis(dimetilamino)-
9,11a,12-trihidroxil-11,13-dioxo-6,6a,7,7a,8,11,11a,13-
octahidrotetraceno[2,1-d][1,3]oxazol-2-il]tio}acetato de bencilo



A una solución de (6aR,7aS,8S,11aS)-5,6-bis(dimetilamino)-
9,11a,12-trihidroxil-11,13-dioxo-2-tioxo-
2,3,6,6a,7,7a,8,11,11a,13-decahidrotetraceno[2,1-d][1,3]oxazol-
10-carboxamida (Ejemplo 42) en N,N-dimetilformamida (DMF) se
agregaron 2 equivalentes de diisopropiletilamina, después de
agitación durante 5 minutos. 1.2 equivalentes de bencil-2-
bromoacetato se agregaron. La mezcla de reacción es agitada
durante una hora y la mezcla es triturada con dietil éter y el
sólido es recolectado. Este es purificado por extracción

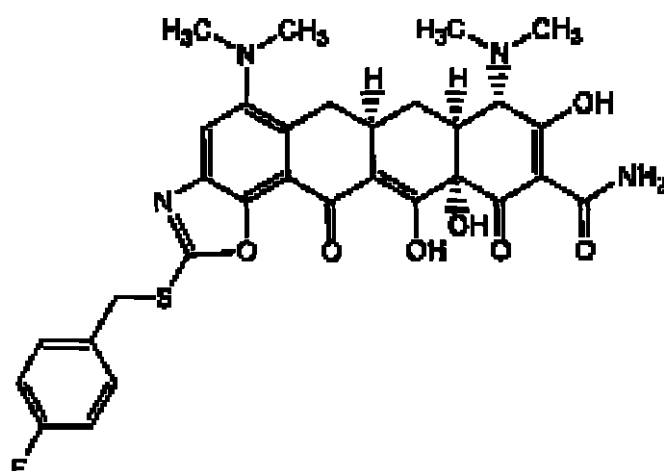
MS (ESI) m/z 663.2 (M+H);

MS (ESI) m/z 332.1 (M+2H);

HRMS: calculado para $C_{33}H_{34}N_4O_7S \cdot HCl$, 658.1813; encontrado
(ESI+), 663.2115;

EJEMPLO 44

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -2- [(4-fluorobenzil) tio] -
9, 11a, 12-trihidroxi-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-
octahidrotetraceno [2, 1-d] [1, 3] oxazol-10-carboxamida



El compuesto del ejemplo es preparado utilizando el
procedimiento D en el Ejemplo 43 utilizando 4-
fluorobenzilbromuro.

MS (ESI) m/z 622.9 (M+H);

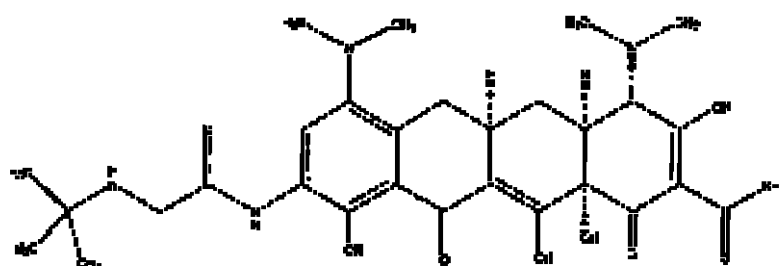
HRMS: calculado para $C_{27}H_{21}FN_4O_7S$ + HCl, 638.1664; encontrado
(ESI+), 623.19629;

Ejemplo de procedimiento D (Compuesto 1 a 4 a 6)

Ejemplo 45

[4S- (4a, 4aa, 5aa, 12aa)] -4, 7-Bis(dimetilamino) -3- [2- (1, 1-
dimetiletilamino) acetilamino] -1, 4, 4a, 5, 5a, 6, 11, 12a-octahidro-
3, 10, 12, 12a-tetrahidroxi-1, 11-dioxo-2-naftacenocarboxamida.

(mono HCl); (base libre)



Sal de sulfato de 9-aminomincicilina (1.0 g, 1.50 mmol) es disuelta en DMF (20 mL) y tratada con una solución de 2-clorometoxietano (0.35 g, 2.2 mmol, 1.47 equivalentes). La reacción es agitada a temperatura ambiente hasta que la espectrometría de masa muestra la conversión al derivado de clorometilbenzoxazol. La solución es antes tratada con *t*-butilamina (7.3 mL, exceso) y agitada hasta que la espectrometría de masa muestra la conversión al benzoxazol de *t*-butilaminometilo. La mezcla es concentrada bajo presión reducida para remover el exceso de *t*-butilamina, y luego se vierte lentamente en éter (1 L) y se agrega HCl/éter para precipitar la sal. El sólido es enjuagado con éter fresco y secado bajo vacío. El sólido crudo es disuelto en agua (100 mL) dando una solución a un pH 2. El pH es elevado sucesivamente en 0.05 unidades con amoníaco acuoso, y extraído con diclorometano. Las fracciones extraídas de un pH 4 a 4.5 son combinadas, secadas (Na₂SO₄), filtradas y concentradas cerca al secado. Un volumen pequeño de metanol es agregado y la solución es tratada con HCl al 1M en éter. El sólido precipitado es recolectado por filtración, lavado con éter fresco y secado bajo vacío para dar el producto como su sal de HCl.

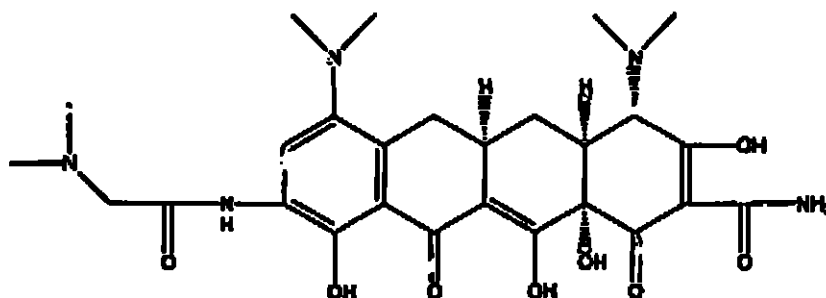
El producto del ejemplo 41 es tratado con ácido acuoso durante 1 hora a 24 horas para dar sal de mono HCl del ejemplo 45.

MS (ESI+) m/z 586.4 ((M+H)+;

Los siguientes ejemplos son preparados por el método similar descrito en el procedimiento D.

Ejemplo 46

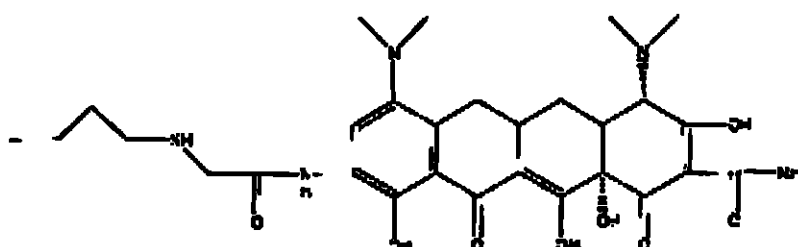
[4S-(4 α ,4a α ,5a α ,12a α)]-4,7-Bis(dimetilamino)-9-
[(dimetilamino)acetilamino]-1,4,4a,5,5a,6,11,12a-octahidro-
3,10,12,12a-tetrahidroxi-1,11-dioxo-2-naftacenocarboxamida.



MS (FAB) m/z 558 ((M+H)+;

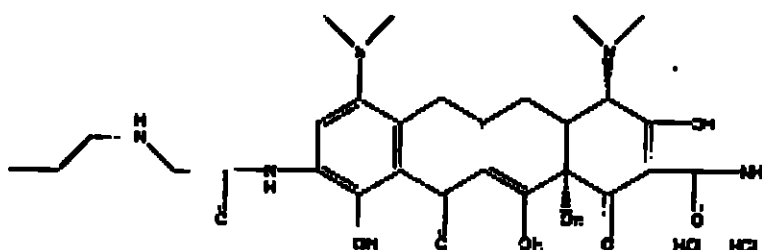
Ejemplo 47

[4S-(4 α ,4a α ,5a α ,12a α)]-4,7-Bis(dimetilamino)-9-[[n-
butilamino)acetil]amino]-1,4,4a,5,5a,6,11,12a-octahidro-
3,10,12,12a-tetrahidroxi-1,11-dioxo-2-naftacenocarboxamida.

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30MS (FAB) m/z 586 ((M+H)⁺;

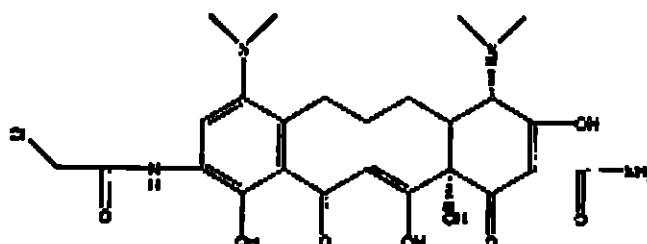
Ejemplo 48

[4S-(4a,4aa,5aa,12aa)]-4,7-Bis(dimetilamino)-9-
 [(propilamino)acetil]amino]-1,4,4a,5,5a,6,11,12a-octahidro-
 3,10,12,12a-tetrahidroxi-1,11-dioxo-2-naftacenocarboxamida

MS (FAB) m/z 572 ((M+H)⁺;

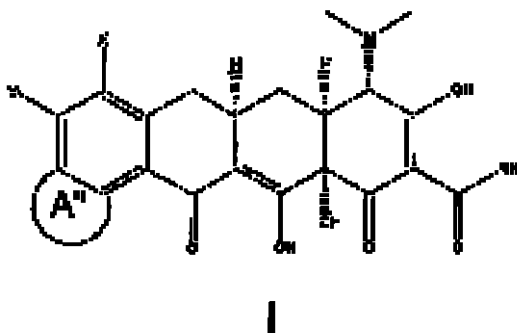
Ejemplo 49

[4S-(4a,4aa,5aa,12aa)]-4,7-Bis(dimetilamino)-9-
 [(cloroacetil]amino]-1,4,4a,5,5a,6,11,12a-octahidro-3,10,12,12a-
 tetrahidroxi-1,11-dioxo-2-naftacenocarboxamida

MS (FAB) m/z 549 ((M+H)⁺;

LO QUE SE REIVINDICA ES:

1. Un compuesto de fórmula (I):



En donde:

X es seleccionado de hidrógeno, amino, $NR^{11}R^{12}$, alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituidos, vinilo opcionalmente sustituido, alquínilo de 2 a 12 átomos de carbono opcionalmente sustituido y halógeno;

A'' es una porción seleccionada del grupo:



R^{11} y R^{12} son cada uno independiente H o alquilo de 1 a 12 átomos de carbono o R^{11} y R^{12} cuando son tomados juntos opcionalmente con el átomo de nitrógeno al cual cada uno

de ellos se liga forma un anillo de hidrocarburo saturado con 3 a 7 miembros

Y es seleccionado de hidrógeno, alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituidos, alquenilo de 2 a 12 átomos de carbono opcionalmente sustituidos, vinilo, alquinilo de 2 a 12 átomos de carbono opcionalmente sustituidos y halógeno;

R es seleccionado de alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos, alquenilo de 2 a 6 átomos de carbono opcionalmente sustituidos, alquinilo de 2 a 12 átomos de carbono opcionalmente sustituidos, $-\text{CH}_2\text{NR}^1\text{R}^2$, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituidos, aralquilo de 7 a 16 átomos de carbono opcionalmente sustituidos, arilo de 7 a 13 átomos de carbono opcionalmente sustituidos, SR^1 , heteroarilo de 5 o 6 átomos de anillo opcionalmente sustituido, que contiene 1 a 4 heteroátomos que pueden ser iguales o diferentes, independientemente seleccionados de nitrógeno, oxígeno y azufre y heterocarilocarbenilo de 5 o 6 anillos de átomos opcionalmente sustituidos que contienen 1 a 4 heteroátomos que pueden ser iguales o diferentes, independientemente seleccionados de nitrógeno, oxígeno y azufre;

R^1 y R^2 son cada uno independientemente H o alquilo de 1 a 12 átomos de carbono o

R^1 y R^2 cuando son tomados juntos opcionalmente con el átomo de nitrógeno al cual estén ligados forma un anillo de hidrocarburo saturado de a 3 a 7 miembros;

R^3 es alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos, $-CH_2$ -arilo opcionalmente sustituido, aralquilo de 7 a 16 átomos de carbono opcionalmente sustituidos, arilo, $-CH_2(CO)OCH_2$ arilo opcionalmente sustituido, $-CH_2$ -alquénilo de 2 a 12 átomos de carbono opcionalmente sustituidos, y $-CH_2$ -alquínilo de 2 a 12 átomos de carbono opcionalmente sustituidos;

Con la condición de que cuando X es NR^1R^2 y R^1 es hidrógeno, entonces R^2 es metilo, etilo, n-propilo, n-butilo, 1-metiletilo, 1-metilpropilo, 2-metilpropilo o 1,1-dimetiletilo;

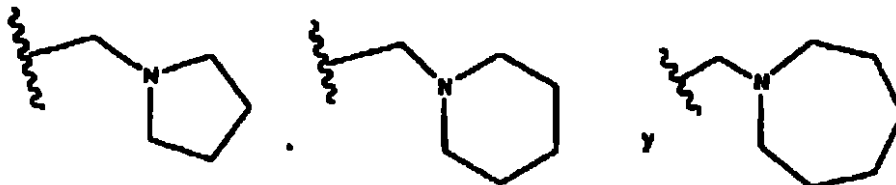
Y que cuando R^1 es metilo o etilo entonces R^2 es metilo, etilo, n-propilo, 1-metiletilo, n-propilo, 1-metilpropilo, o 2-metilpropilo;

O un tautómero o una sal farmacéuticamente aceptable de ellos.

2. Un compuesto de acuerdo con la reivindicación 1 en donde R es fenilo opcionalmente sustituido con 1 a 3 sustituyentes o una sal farmacéuticamente fue aceptable del mismo.

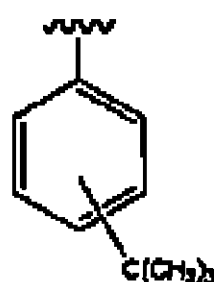
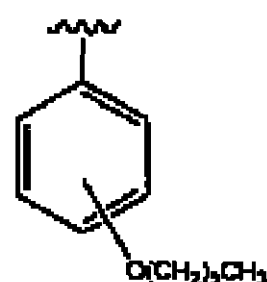
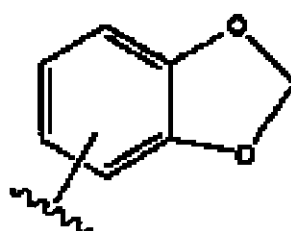
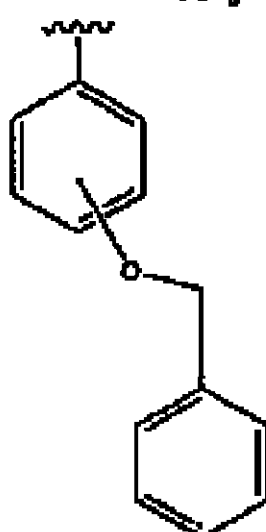
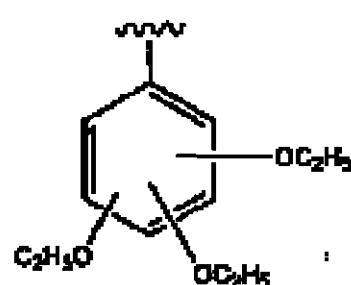
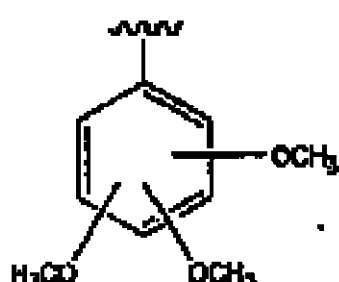
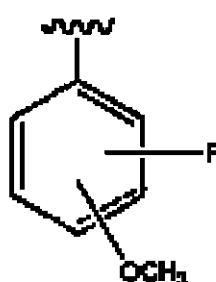
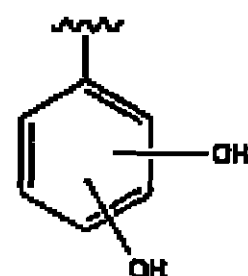
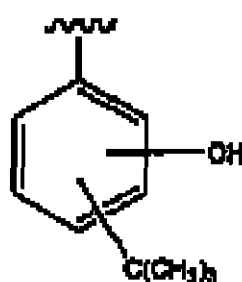
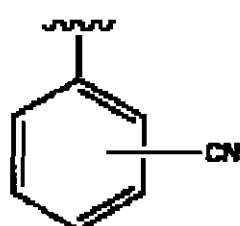
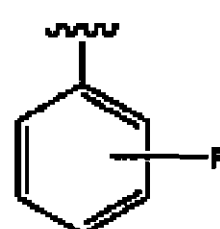
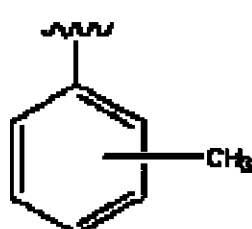
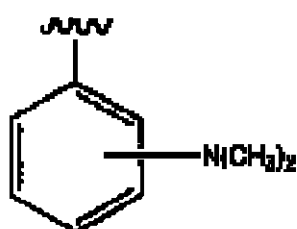
3. Un compuesto de acuerdo con la reivindicación 1 en donde R de Fórmula (I) es seleccionado del grupo alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, y alquil-heterociclilo o una sal farmacéuticamente aceptable de ellos.

4. Un compuesto de acuerdo con la reivindicación 3 en donde alquil-heterociclilo es seleccionado de las porciones del grupo



o una sal farmacéuticamente aceptable del mismo.

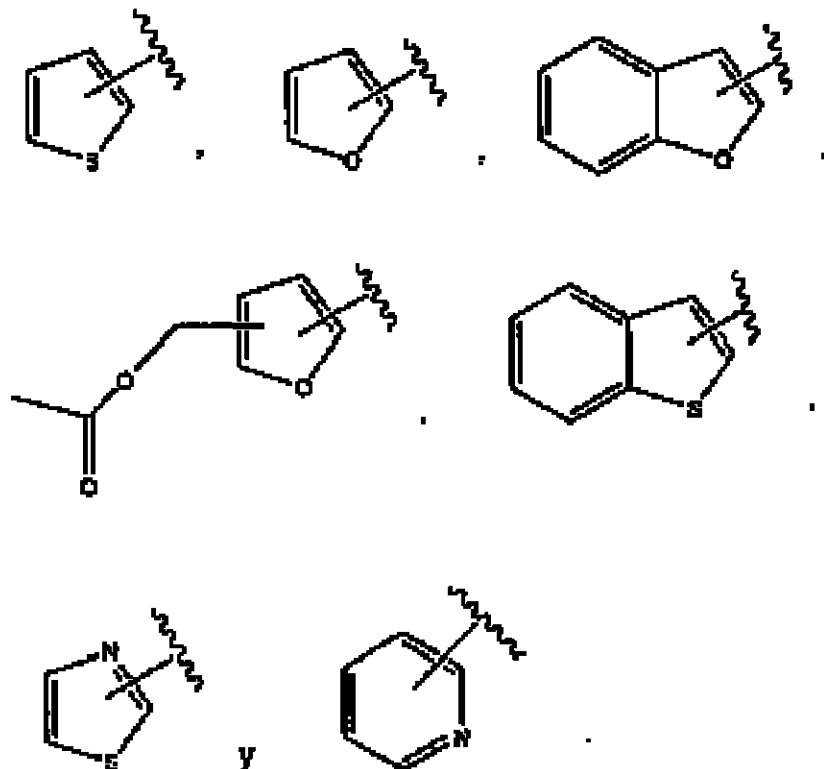
5. Un compuesto de acuerdo con la reivindicación 2 en donde R es seleccionado de las porciones del grupo



o una sal farmacéuticamente aceptable de ellos.

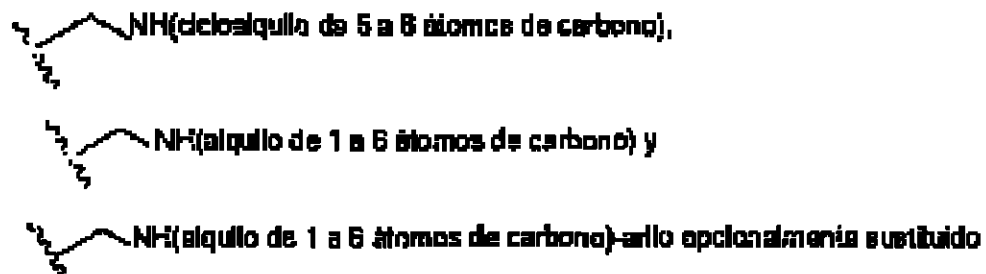
6. Un compuesto de acuerdo con la reivindicación 1 en donde R es heteroarilo o una sal farmacéuticamente aceptable del mismo.

7. Un compuesto de acuerdo con la reivindicación 6 en donde $\bar{R}$ es seleccionado de porciones seleccionadas del grupo.



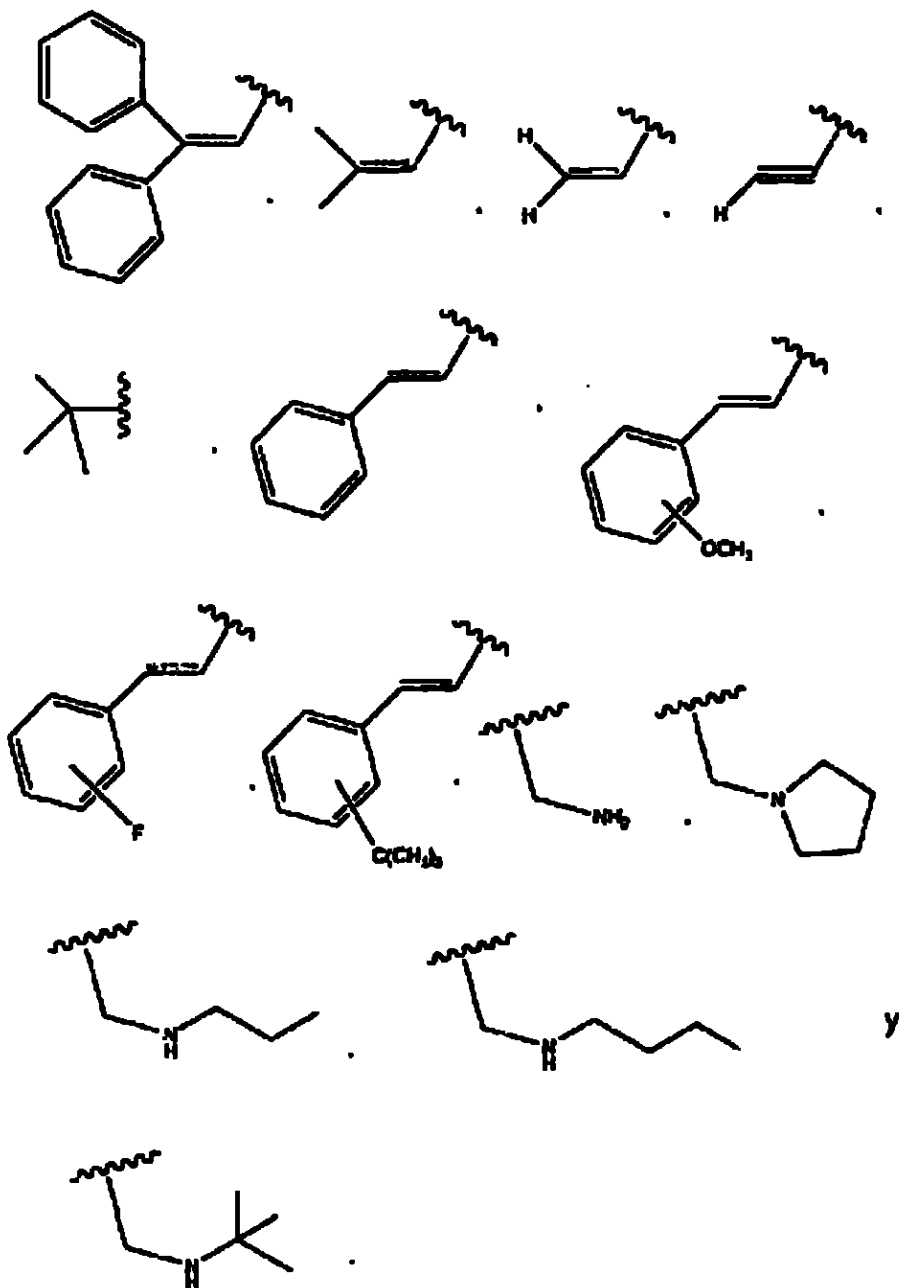
o una sal farmacéuticamente aceptable de ellos.

8. Un compuesto de acuerdo con la reivindicación 1 en donde R es alquilo de 1 a 6 átomos de carbono opcionalmente sustituidos, alquenilo de 2 a 6 átomos de carbono opcionalmente sustituidos,



o una sal farmacéuticamente aceptable de ellos.

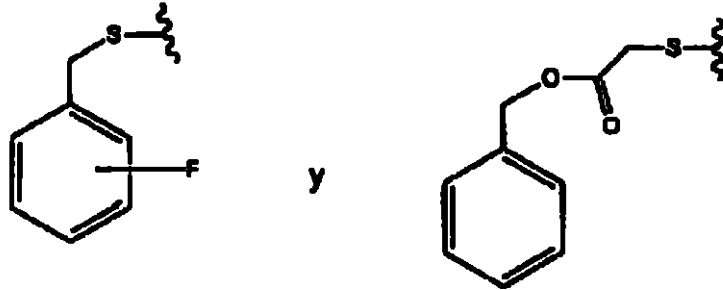
9. Un compuesto de acuerdo con la reivindicación 1 en donde R es seleccionado de las porciones



o una sal farmacéuticamente aceptable de ellos.

10. Un compuesto de acuerdo con la reivindicación 1 en donde R es S-alquilo de 1 a 12 átomos de carbono, S-CH₂-arilo opcionalmente sustituido y S-CH₂(CO)OCH₂arilo opcionalmente sustituido o una sal farmacéuticamente aceptable de ellos.

11. Un compuesto de acuerdo con la reivindicación 10 en donde R es seleccionado de las porciones del grupo



o una sal farmacéuticamente aceptable de ellos.

12. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 11 en donde Y es H.

13. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 12 en donde X es -NMe₂.

14. Un compuesto de acuerdo con la reivindicación 1 seleccionado del grupo:

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -2- (2, 2-difenilvinil) -9, 11a, 12-trihidroxi -11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3]oxazol-10-carboxamida,

(7aS, 8S, 11aS) -3- (dimetilamino) -9, 11a, 13-trihidroxi -2- (2-metil-1-propenil) -11, 12-dioxo-7, 7a, 8, 11, 11a, 12-hexahidronaftaceno[2, 1-d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -2-tert-butyl-5,8-bis(dimetilamin) -

9,11a,12-trihidroxi-11,13-dioxo-6,6a,7,7a,8,11,11a,13-
octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5,8-bis(dimetilamino)-2-[(E)-2-(2-

furil)etenil]-9,11a,12-trihidroxi-11,13-dioxo-
6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-
d][1,3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5,8-bis(dimetilamino)-9,11a,12-

trihidroxi-11,13-dioxo-2-[(E)-2-feniletetil]-
6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-
d][1,3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5,8-bis(dimetilamino)-9,11a,12-

trihidroxi-2-[(E)-2-(4-metoxifenil)etenil]-11,13-dioxo-
6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-
d][1,3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5,8-bis(dimetilamino)-9,11a,12-

trihidroxi-2-[(E)-2-(3-metoxifenil)etenil]-11,13-dioxo-
6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-
d][1,3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5,8-bis(dimetilamino)-9,11a,12-

trihidroxi-2-[(E)-2-(2-metoxifenil)etenil]-11,13-dioxo-
6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-
d][1,3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -2- [(E) -2- (4-fluorofenil) etenil] -9, 11a, 12-trihidroxi-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3] oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -2- [(E) -2- (2-fluorofenil) etenil] -9, 11a, 12-trihidroxi-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3] oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -2- (clorometil) -5, 8-bis(dimetilamino) -9, 11a, 12-trihidroxi-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3] oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -2- [(dimetilamino) metil] -9, 11a, 12-trihidroxi-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3] oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -9, 11a, 12-trihidroxi-11, 13-dioxo-2- (pirrolidin-1-ilmetil) -6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3] oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -9, 11a, 12-trihidroxi-11, 13-dioxo-2- [(propilamino) metil] -6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3] oxazol-10-carboxamida,

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(6aR, 7aS, 8S, 11aS) -2- [(butilamino)metil] -5, 8-
bis(dimetilamino) -9, 11a, 12-trihidroxí-11, 13-dioxo-
6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-
d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -9, 11a, 12-
trihidroxí-11, 13-dioxo-2- [(propilamino)metil] -
6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-
d] [1, 3]oxazol-10-carboxamida y

(6aR, 7aS, 8S, 11aS) -2- [(tert-butilamino)metil] -5, 8-
bis(dimetilamino) -9, 11a, 12-trihidroxí-11, 13-dioxo-
6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-
d] [1, 3]oxazol-10-carboxamida, o una sal
farmacéuticamente aceptable de ellos.

15. Un compuesto de acuerdo con la reivindicación 1
seleccionado a partir del grupo

(7aS, 8S, 11aS) -8- (dimetilamino) -2- [4- (dimetilamino) fenil] -
9, 11a, 13-trihidroxí-11, 12-dioxo-7, 7a, 8, 11, 11a, 12-
hexahidronaftaceno[2, 1-d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -2- tert-butil-5, 8-bis(dimetilamino) -
9, 11a, 12-trihidroxí-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-
octahidrotetraceno[2, 1-d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -9, 11a, 12-trihidroxi-2-(4-metilfenil)-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3]oxazol-10-carboxamida,

(7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -2-(3-fluorofenil)-9, 11a, 13-trihidroxi-11, 12-dioxo-7, 7a, 8, 11, 11a, 12-hexahidrotetraceno[2, 1-d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -2-(4-cianofenil)-5, 8-bis(dimetilamino)-9, 11a, 12-trihidroxi-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5, 8-bis(dimetilamino) -2-[4-(dimetilamino) fenil]-9, 11a, 12-trihidroxi-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -2-(5-tert-butil-2-hidroxifenil)-5, 8-bis(dimetilamino)-9, 11a, 12-trihidroxi-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -2-[4-(benciloxi) fenil]-5, 8-bis(dimetilamino)-9, 11a, 12-trihidroxi-11, 13-dioxo-6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno[2, 1-d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -2- (2,4-dihidroxifenil) -5,8-

bis(dimetilamino) -9, 11a, 12-trihidroxi-11, 13-dioxo-

6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno [2, 1-

d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5,8-bis(dimetilamino) -2- (3-fluoro-4-

metoxifenil) -9, 11a, 12-trihidroxi-11, 13-dioxo-

6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno [2, 1-

d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -2- (1,3-benzodioxol-5-il) -5,8-

bis(dimetilamino) -9, 11a, 12-trihidroxi-11, 13-dioxo-

6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno [2, 1-

d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5,8-bis(dimetilamino) -9, 11a, 12-

trihidroxi-11, 13-dioxo-2- (2,4,6-trimetoxifenil) -

6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno [2, 1-

d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5,8-bis(dimetilamino) -9, 11a, 12-

trihidroxi-11, 13-dioxo-2- (2,4,5-trietoxifenil) -

6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno [2, 1-

d] [1, 3]oxazol-10-carboxamida,

(6aR, 7aS, 8S, 11aS) -5,8-bis(dimetilamino) -9, 11a, 12-

trihidroxi-2- (1-metil-1H-indol-2-il) -11, 13-dioxo-

6, 6a, 7, 7a, 8, 11, 11a, 13-octahidrotetraceno [2, 1-

d] [1, 3]oxazol-10-carboxamida,

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(6aR,7aS,8S,11aS)-2-(4-tert-butylfenil)-5,8-bis(dimetilamino)-9,11a,12-trihidroxi-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida y

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-2-[4-(hexiloxi)fenil]-9,11a,12-trihidroxi-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida

o una sal L farmacéuticamente aceptable de ellos.

16. Un compuesto de acuerdo con la reivindicación 1 seleccionado del grupo:

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-9,11a,12-trihidroxi-11,13-dioxo-2-rien-3-il-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida,

(6aR,7aS,8S,11aS)-2-(1-benzofuran-2-il)-5,8-bis(dimetilamino)-9,11a,12-trihidroxi-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida,

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-2-(2-furil)-9,11a,12-trihidroxi-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida,

acetato de (5-[(6aR,7aS,8S,11aS)-10-(aminocarbonil)-5,8-bis(dimetilamino)-9,11a,12-trihidroxi-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-2-il]-2-furil}metilo,

(6aR,7aS,8S,11aS)-2-(1-benzotien-3-il)-5,8-bis(dimetilamino)-9,11a,12-trihidroxi-11,13-dioxo-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida,

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-9,11a,12-trihidroxi-11,13-dioxo-2-(1,3-tiazol-2-il)-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida,

(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-9,11a,12-trihidroxi-11,13-dioxo-2-piridin-4-il-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida y

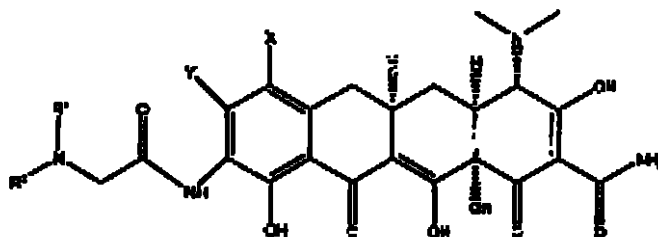
(6aR,7aS,8S,11aS)-5,8-bis(dimetilamino)-9,11a,12-trihidroxi-11,13-dioxo-2-piridin-3-il-6,6a,7,7a,8,11,11a,13-octahidrotetraceno[2,1-d][1,3]oxazol-10-carboxamida

o una sal farmacéuticamente aceptable de los mismos.

17. Una composición farmacéutica que comprende un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 16 o una sal farmacéuticamente aceptable de los mismos en asociación con un vehículo farmacéuticamente aceptable.

18. Un método para el tratamiento o control de infecciones bacterianas en animales de sangre caliente que comprende administrar a dicho animal una cantidad farmacológicamente efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 16 o una sal farmacéuticamente aceptable de los mismos.

19. Un proceso para la preparación de un compuesto de fórmula



o una sal farmacéuticamente aceptable de la misma.

en donde:

X es seleccionado de hidrógeno, amino, $NR^{11}R^{12}$, alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituidos, vinilo, opcionalmente sustituido, alquinilo

de 2 a 12 átomos de carbono opcionalmente sustituidos y halógeno;

R^1 y R^2 son cada uno independientemente H o alquilo de 1 a 12 átomos de carbono o

R^1 y R^2 cuando son tomados juntos opcionalmente con el átomo de nitrógeno al cual cada uno de ellos esta sujeto forma un anillo de hidrocarburo saturado de 3 a 7 miembros;

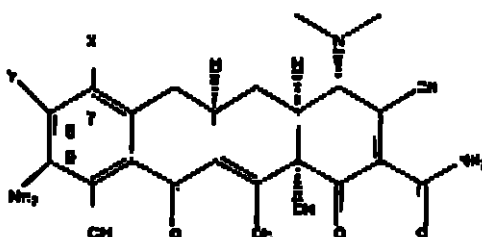
R^{11} y R^{12} son cada uno independientemente H o alquilo de 1 a 12 átomos de carbono o

R^{11} y R^{12} cuando son tomados juntos opcionalmente con el átomo de nitrógeno al cual cada uno de ellos esta sujet forman un anillo de hidrocarburo saturados con 3 a 7 miembros;

Y es seleccionado de hidrógeno, alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituidos, alquenilo de 2 a 12 átomos de carbono opcionalmente sustituidos, vinilo, alquinilo de 2 a 12 átomos de carbon opcionalmente sustituidos y halógeno;

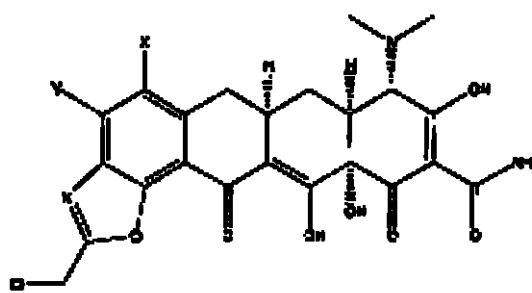
comprende las etapas:

a. hacer reaccionar 9-amino-6-demetil-6-deoxitetraciclina 7-(sustituido)-8-(sustituido)-de fórmula

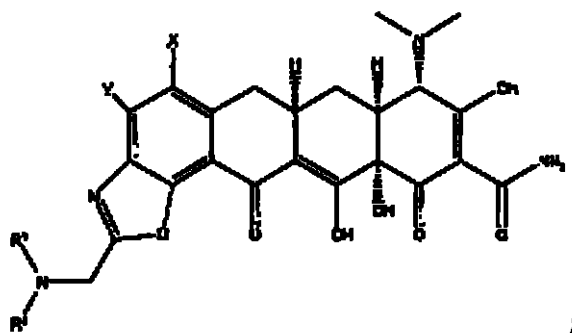


o una sal farmacéuticamente aceptable de la misma.

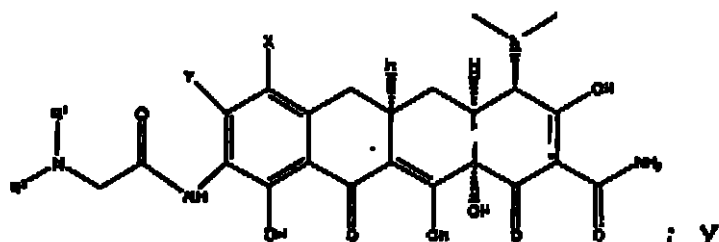
con 2-clorotrimetoxietano en un disolvente aprótico para proporcionar un compuesto de cloro de la fórmula



b. hacer reaccionar el compuesto de cloro con una amina R^1R^2NH para formar una amina sustituida de la fórmula



c. hidrolizar la amina sustituida con ácido para dar un compuesto de la fórmula



d. aislar el compuesto o una sal farmacéuticamente aceptable del mismo.

20. El proceso de acuerdo con la reivindicación 19 en donde X es $N(CH_3)_2$.

21. El proceso de acuerdo con la reivindicación 19 o la reivindicación 20 en donde la amina R^1R^2NH es t-butil amina.

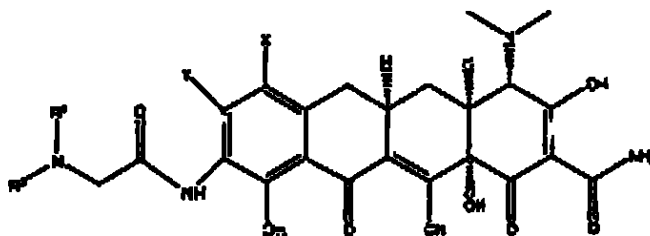
22. el proceso de acuerdo con una cualquiera de las reivindicaciones 19 a 21 en donde el disolvente aprótico es N,N-dimetilformamida.

23. El proceso de acuerdo con una cualquiera de reivindicaciones 19 a 22 en donde [4S-(4 α ,4a α ,5a α ,12a α)]-4,7-Bis(dimetilamino)-9-[2-(1,1-dimetiletilamino)acetilamino]-1,4,4a,5,5a,6,11,12a-octahidro-3,10,12,12a-tetrahidroxi-1,11-dioxo-2-naftacenocarboxamida o una sal farmacéuticamente aceptable del mismo es preparada.

24. Un proceso para la preparación de un compuesto de la fórmula

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en donde:

X es seleccionado de hidrógeno, amino, $\text{NR}^{11}\text{R}^{12}$, alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituidos, vinilo, opcionalmente sustituido, alquinilo de 2 a 12 átomos de carbono opcionalmente sustituidos y halógeno;

R^1 y R^2 son cada uno independientemente H o alquilo con 1 a 12 átomos de carbono o

R^1 y R^2 cuando son tomados juntos opcionalmente con el átomo de nitrógeno al cual ellos están sujetos forma un anillo de hidrocarburo saturado de 3 a 7 miembros;

R^{11} y R^{12} son cada uno independientemente H o alquilo de 1 a 12 átomos de carbono o

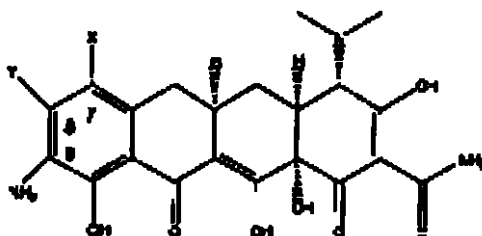
R^{11} y R^{12} cuando son tomados juntos opcionalmente con el átomo de nitrógeno al cual ellos están sujetos forma un anillo de hidrocarburo saturado de 3 a 7 miembros;

Y es seleccionado de hidrógeno, alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituidos, vinilo, alquenilo de 2 a 12 átomos de carbono opcionalmente sustituidos, alquinilo de 2 a 12 átomos de carbono opcionalmente sustituidos y halógeno;

o una sal farmacéuticamente aceptable de los mismos

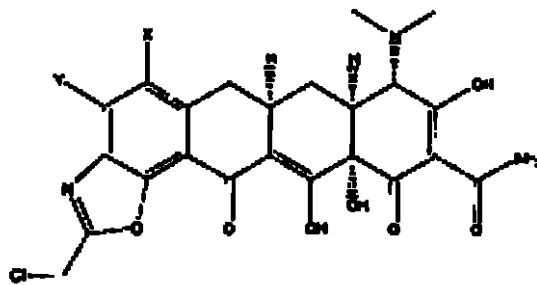
comprende las etapas de:

a. hacer reaccionar 9-amino-6-dimetil-6-deoxitetraciclina 7-(sustituido)-8-(sustituido)-de la fórmula

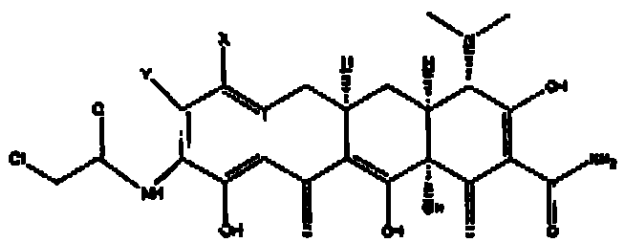


c una sal farmacéuticamente aceptable de la misma.

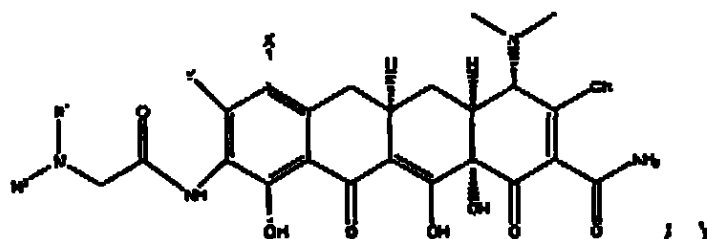
con 2-clorotrimetoxietano en un disolvente aprótico para proporcionar un compuesto de cloro la fórmula



- b. hacer reaccionar el compuesto de cloro con ácido para dar 9-(2-clorometilcarbonilamino)-6-demetil-6-deoxitetraciclina sustituido de la fórmula



- c. hacer reaccionar la 9-(2-clorometilcarbonilamino)-6-demetil-6-deoxitetraciclina sustituido con amina R^1R^2NH para dar un compuesto de la fórmula



- d. aislar el compuesto o una sal farmacéuticamente aceptable del mismo.

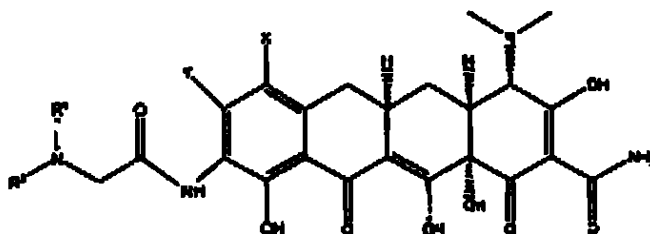
25. El proceso de acuerdo con la reivindicación 24 en donde X es $N(CH_3)_2$.

26. El proceso de acuerdo con la reivindicación 24 o reivindicación 25 en donde la amina R^1R^2NH es t-butil amina.

27. El proces de acuerdo con una cualquiera de las reivindicaciones 24 a 26 en donde el disolvente aprótico es N,N-dimetilformamida.

28. El proceso de acuerdo con una cualquiera de las reivindicaciones 24 a 27 en donde [4S-(4 α ,4 α ,5 α ,12 α)]-4,7-Bis(dimetilamino)-9-[2-(1,1-dimetiletilamino)acetilamino]-1,4,4 α ,5,5 α ,6,11,12 α -octahidro-3,10,12,12 α -tetrahidroxi-1,11-dioxo-2-naftacenocarboxamida o una sal farmacéuticamente aceptable del mismo es preparada.

29. Un compuesto de la fórmula



o una sal farmacéuticamente aceptable de la misma.

en donde:

X es seleccionado de hidrógeno, amino, NR¹¹R¹², alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituidos, vinilo, opcionalmente sustituido, alquinil de 2 a 12 átomos de carbono opcionalmente sustituidos y halógeno;

R^1 y R^2 son cada uno independientemente H o alquilo de 1 a 12 átomos de carbono o

R^1 y R^2 cuando son tomados juntos opcionalmente con el átomo de nitrógeno al cual ellos están sujetos forma un anillo de hidrocarburo saturado de 3 a 7 miembros

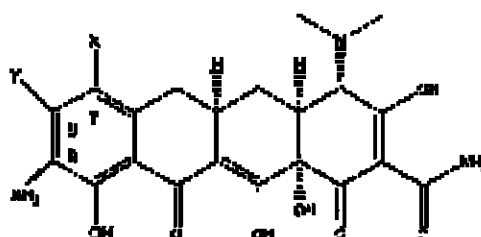
R^{11} y R^{12} son cada uno independientemente H o alquilo de 1 a 12 átomos de carbono o

R^{11} y R^{12} cuando son tomados juntos opcionalmente con el átomo de nitrógeno al cual ellos están sujetos forma un anillo de hidrocarburo saturado de 3 a 7 miembros

Y es seleccionado de hidrógeno, alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituidos, alquenilo de 2 a 12 átomos de carbono opcionalmente sustituidos vinilo, alquinilo de 2 a 12 átomos de carbon opcionalmente sustituidos y halógeno;

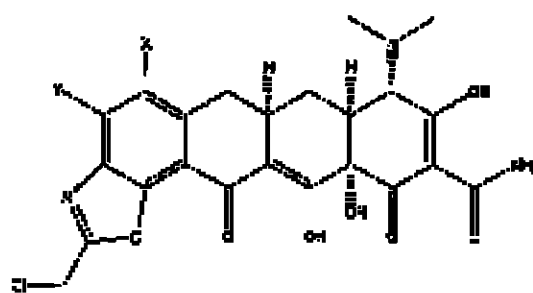
producido por el proceso que comprende las etapas de:

a. hacer reaccionar 9-amino-6-demetil-6-deoxitetraciclina 7-(sustituido)-8-(sustituido)-de fórmula

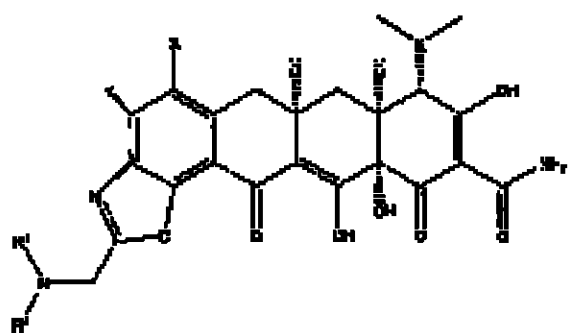


c una sal farmacéuticamente aceptable de la misma.

con 2-clorotrimetoxietano en un disolvente aprótico para proporcionar un compuesto de cloro de la fórmula

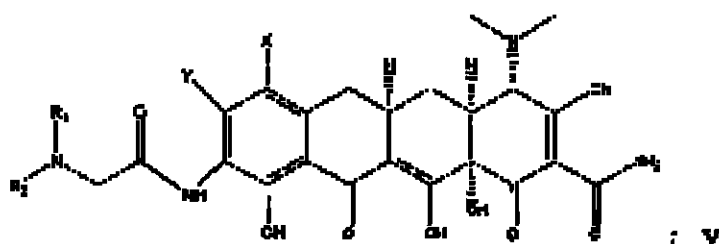


b. hacer reaccionar el compuesto de cloro con una amina R^1R^2NE para formar una amina sustituida de la fórmula



c. hidrolizar la amina sustituida con ácido para dar un compuesto de la fórmula

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d. aislar el compuesto o una sal farmacéuticamente aceptable del mismo.

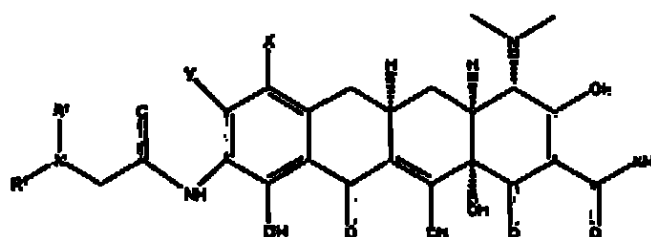
30. El producto producido por el proceso de acuerdo con la reivindicación 29 en donde X es $N(CH_3)_2$.

31. El producto producido por el proceso de acuerdo con la reivindicación 29 o la reivindicación 30 en donde la amina R^1R^2NH es t-butil amina.

32. El producto producido por el proceso de acuerdo con una cualquiera de las reivindicaciones 29 a 31 en donde el disolvente aprótico es N,N-dimetilformamida.

33. El producto producido por el proceso de acuerdo con una cualquiera de las reivindicaciones 29 a 31 que es [4S-(4R,4aR,5aR,12aR)]-4,7-Bis(dimetilamino)-9-[2-(1,1-dimetiletilamino)acetilamino]-1,4,4a,5,5a,6,11,12a-octahidro-3,10,12,12a-tetrahidroxi-1,11-dioxo-2-naftacencarboxamida o una sal farmacéuticamente aceptable del mismo.

34. Un compuesto de la fórmula



en donde:

X es seleccionado de hidrógeno, amino, $\text{NR}^{11}\text{R}^{12}$, alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituidos, vinilo opcionalmente sustituido, alquinilo de 2 a 12 átomos de carbono opcionalmente sustituidos y halógeno;

R^1 y R^2 son cada uno independientemente H o alquilo de 1 a 12 átomos de carbono o

R^1 y R^2 cuando son tomados juntos opcionalmente con el átomo de nitrógeno al cual ellos están sujetos forma un anillo de hidrocarburo saturado de 3 a 7 miembros

R^{11} y R^{12} son cada uno independientemente H o alquilo de 1 a 12 átomos de carbono o

R^{11} y R^{12} cuando son tomados juntos opcionalmente con el átomo de nitrógeno al cual ellos están sujetos forma un anillo de hidrocarburo saturado de 3 a 7 miembros

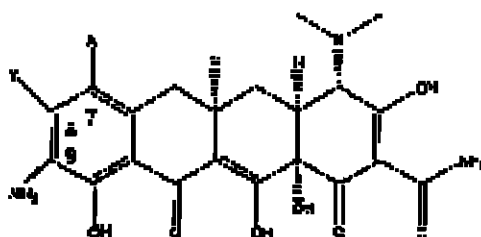
Y es seleccionado de hidrógeno, alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos, arilo de 6, 10 o 14

átomos de carbono opcionalmente sustituidos, alquénilo de 2 a 12 átomos de carbono opcionalmente sustituidos, vinilo, alquinilo de 2 a 12 átomos de carbono opcionalmente sustituidos y halógeno;

o una sal farmacéuticamente aceptable del mismo.

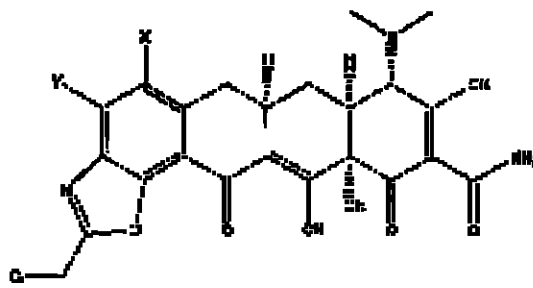
producido por el proceso comprende las etapas:

a. hacer reaccionar 9-amino-6-demetil-5-deoxitetraaciclina 7-(sustituido)-6-(sustituido) de la fórmula

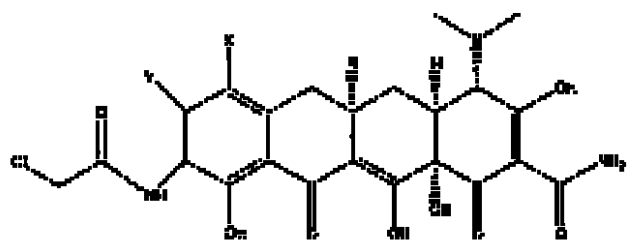


o una sal farmacéuticamente aceptable del mismo.

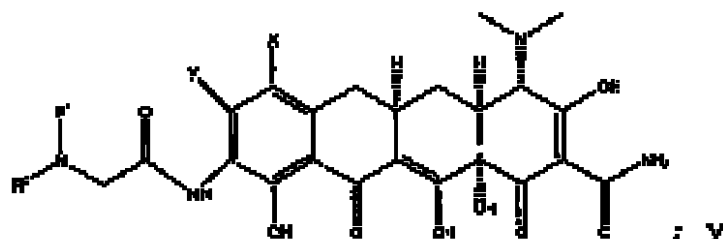
con 2-clorometoxietano en un disolvente aprótico para proporcionar un compuesto de cloro de la fórmula



b. hacer reaccionar el compuesto de cloro con ácido para dar 9-(2-clorometilcarbonilamino)-6-demetil-6-deoxitetraaciclina sustituido de la fórmula



c. hacer reaccionar la 9-(2-clorometilcarbonylamino)-6-demetil-6-deoxitetraciclina sustituido con amina R^1R^2NH para dar un compuesto de la fórmula



d. aislar el compuesto o una sal farmacéuticamente aceptable del mismo.

35. El producto preparado por el proceso de acuerdo con la reivindicación 34 en donde X es $N(CH_3)_2$.

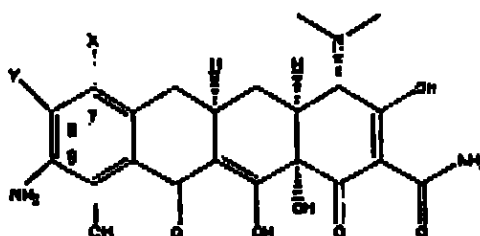
36. El producto preparado por el proceso de acuerdo con la reivindicación 34 o la reivindicación 35 en donde la amina R^1R^2NH es t-butil amina.

37. El producto preparado por el proceso de acuerdo con una cualquiera de las reivindicaciones 32 a 36 en donde el disolvente aprótico es N,N-dimetilformamida.

38. El producto preparado por el proceso de acuerdo con una cualquiera de las reivindicaciones 34 a 37 que es [4S-(4 α ,4a α ,5a α ,12a α)]-4,7-Bis(dimetilamino)-9-[2-(1,1-dimetiletilamino)acetilamino]-1,4,4a,5,5a,6,11,12a-octahidro-3,10,12,12a-tetrahidróxi-1,11-dioxo-2-naftacenocarboxamida o una sal farmacéuticamente aceptable del mismo.

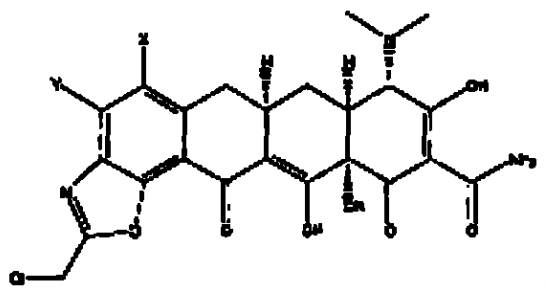
39. Un proceso para preparar un compuesto de la fórmula I de acuerdo con la reivindicación 1 que comprende.

a). hacer reaccionar 9-amino-6-dimetil-6-deoxitetraciclina 7-(sustituido)-8-(sustituido)-de la fórmula



o una sal farmacéuticamente aceptable de la misma.

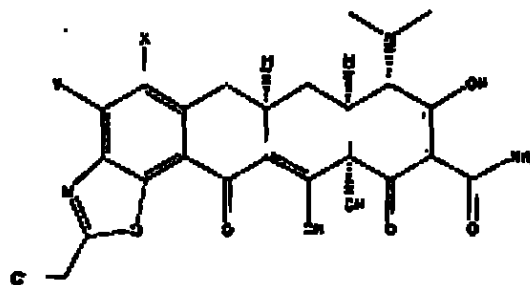
con 2-clorotrimetoxietano en un disolvente aprótico para proporcionar un compuesto de cloro de la fórmula



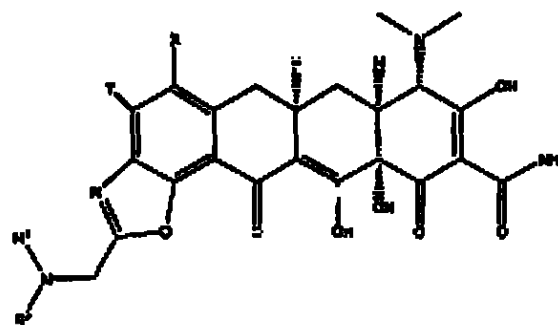
en donde las variables son como se definió en la reivindicación 1;

o

b. hacer reaccionar a compuesto de cloro de fórmula



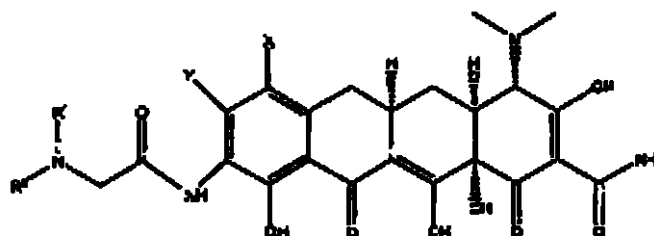
en donde las variables según se definió en la reivindicación 1; con una amina R^1R^2NH para formar una amina sustituida de la fórmula



o

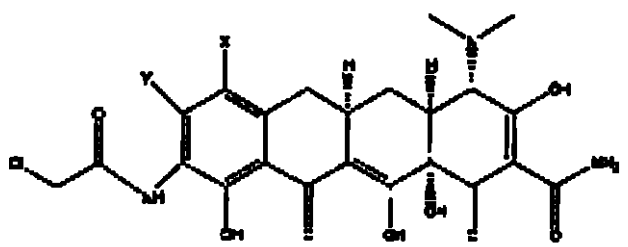
c) convertir un compuesto básico de fórmula I según se definió en la reivindicación 1 a una sal farmacéuticamente aceptable del mismo o viceversa.

40. Un proceso para preparar un compuesto de fórmula:

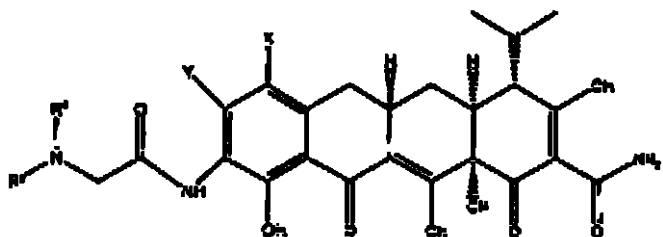


en donde las variables son según se definió en la reivindicación 34 que comprende:

a) hacer reaccionar a 9-(2-clorometilcarbonilamino)-6-demetil-6-deoxitetraclina sustituido de la fórmula

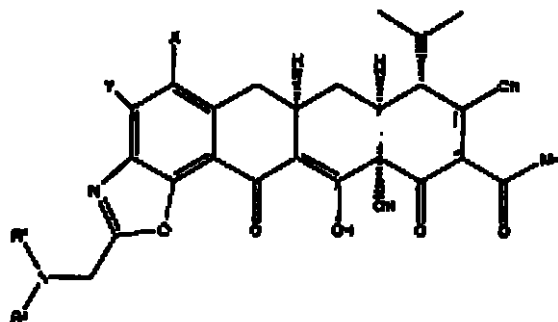


con una amina R^1R^2NH para dar un compuesto de la fórmula



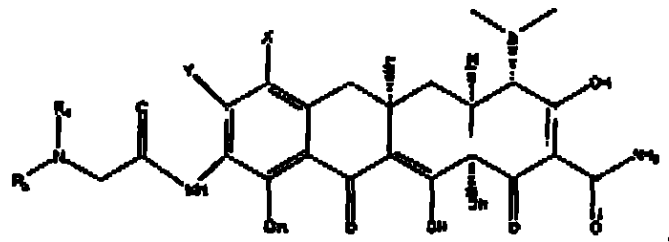
o

b) hidrolizar una amina sustituida de fórmula



en donde las variables son según se definió en la reivindicación 29,

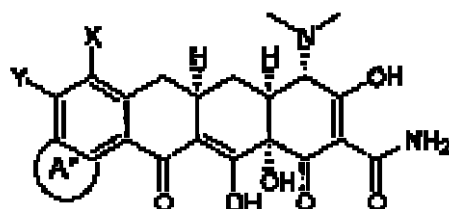
con ácido para dar un compuesto de la fórmula



y si se desea convertir el producto a una sal farmacéuticamente aceptable del mismo.

RESUMEN

Esta invención suministra compuestos de la fórmula:



I

en donde A'', X y Y son según se definió en la especificación.

Estos compuestos son útiles como agentes antibacterianos.

PATENT COOPERATION TREATY

000241

204

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
MYETH
Patent Law Department
Attn: Calnan, William R.
Five Giralda Farms
Madison, New Jersey 07940
UNITED STATES OF AMERICA

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

APR 19 2005

(PCT Rule 44.1)

Date of mailing
(day/month/year) 14/04/2005

Applicant's or agent's file reference

AM101558

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.

PCT/US2004/040450

International filing date
(day/month/year)

07/12/2004

Applicant

MYETH

DUCKETED

DUE DATE

STAT DATE

BY

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 48):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (+41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that an international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ The protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ No decision has been made yet on the protest: the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 90 months from the priority date.

Within 18 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 30 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 18 months.

See the Annex to Form PCT/IB301 and, for details about the applicable time limits, Office by Office, see the PCT Applicant's Guide, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority



European Patent Office, P.O. Box 5818
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 551 epo nl,
Fax: (+31-70) 340-3916

Authorized officer

Federico Bononelli

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the letter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 20 or, where applicable, Article 41.

When?

Within 2 months from the date of issuance of the international search report or 16 months from the priority date, whichever time first expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Examining Authority (Rule 46.2).

Where a demand for international preliminary examination has been filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, as a result of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must accompany the amendments?

Letter (Section 205(a)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. References to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/selected Office, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/selected Office, see Volume II of the PCT Applicant's Guide.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference AMI 01558	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below.	
International application No. PCT/US2004/040850	International filing date (day/month/year) 07/12/2004	(Earliest) Priority Date (day/month/year) 08/12/2003
Applicant MYETH		

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 4 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, see Box No. I.

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

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 No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

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

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D263/52 C07C237/26 A61K31/423 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Maximum documentation searched (classification system followed by classification symbols)

IPC 7 CD7D A61K A61P

Documentation searched other than maximum documentation to the extent that such documents are included in the fields searched

Electronic data bases consulted during the international search (name of data base used, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of documents, with indication, where appropriate, of the relevant passages	Reference to claim No.
A	US 5 494 903 A (HLAVKA ET AL) 27 February 1996 (1996-02-27) cited in the application	1-20, 39, 40
X	examples	29-38
X	SUM ET AL.: J. MED. CHEM., vol. 37, no. 3, 1994, pages 184-188, XP002323590 examples 16-20	29-38
X	EP D 582 788 A (AMERICAN CYANAMID COMPANY) 16 February 1994 (1994-02-16)	29-38
X	page 15; claim 7; examples	40

☐ Further documents are listed in the continuation of loc C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

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

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another claim or other special reason (as specified)

O document relating to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date (date)

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the practice or theory underlying the invention

X document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, even 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

7 April 2005

Date of mailing of the international search report

14/04/2005

Name and mailing address of the ISA

European Patent Office, P.O. Box 5010
NL - 3720 HV Rijswijk
Tel. (+31-70) 343-2000, Tx. RI 661 600 01,
Fax: (+31-70) 348-3910

Authorized officer

Lauro, P

INTERNATIONAL SEARCH REPORT

In relation to patent family members

International Application No.
PCT/US2004/040850000238
26

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5494903	A	27-02-1996	US 5529990 A	25-06-1996
			US 5530117 A	25-06-1996
			AT 211120 T	15-01-2002
			AU 654049 B2	20-10-1994
			AU 2618392 A	08-04-1993
			BR 1100853 A3	07-12-1999
			CA 2079692 A1	05-04-1993
			CN 1072172 A ,C	19-05-1993
			CZ 9202984 A3	12-05-1993
			CZ 9703093 A3	16-09-1998
			DE 69232302 D1	31-01-2002
			DE 69232302 T2	14-08-2002
			DK 536515 T3	08-04-2002
			EP 0536515 A1	14-04-1993
			ES 2168254 T3	16-06-2002
			FI 924454 A	05-04-1993
			HK 1011348 A1	12-04-2002
			HU 63145 A2	28-07-1993
			HU 9500116 A3	28-06-1995
			IL 103320 A	06-12-1998
			IL 119590 A	12-03-1999
			JP 3166863 B2	11-07-2001
			JP 5255219 A	05-10-1993
			KR 269072 B1	16-10-2000
			MX 9205532 A1	01-04-1993
			NO 923857 A	05-04-1993
			NZ 244586 A	26-07-1996
			PL 296143 A1	31-05-1993
			PL 172282 B1	29-08-1997
			PL 175957 B1	31-03-1999
			PL 176333 B1	31-05-1999
			PT 536515 T	31-05-2002
			SG 52361 A1	28-09-1998
			SK 114999 A3	11-07-2000
			SK 298492 A3	08-03-1995
			ZA 9207607 A	13-04-1993
EP 0582788	A	16-02-1994	US 5328902 A	12-07-1994
			AT 168992 T	15-08-1998
			AU 4461293 A	17-02-1994
			CA 2103836 A1	14-02-1994
			CN 1089805 A ,C	16-03-1994
			CZ 9301599 A3	16-03-1994
			DE 69319976 D1	03-09-1998
			DE 69319976 T2	25-03-1999
			DK 582788 T3	01-02-1999
			EP 0582788 A1	16-02-1994
			ES 2119831 T3	16-10-1998
			FI 933565 A	14-02-1994
			HK 1009598 A1	20-04-2000
			HU 64943 A2	28-03-1994
			HU 9500629 A3	28-11-1995
			HU 74001 A2	28-10-1996
			IL 106673 A	20-11-1997
			IL 119118 A	08-02-1998
			JP 3583449 B2	04-11-2004
			JP 6206855 A	26-07-1994
			LV 12350 A ,B	20-10-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

National Application No.

PCT/US2004/040850

000247

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0582788	A	MX 9304647 A1	28-02-1994
		NO 932869 A	14-02-1994
		NZ 248357 A	26-04-1996
		PH 30007 A	29-10-1996
		PL 300063 A1	21-02-1994
		PL 174115 B1	30-06-1998
		PL 173904 B1	29-05-1998
		RU 2125986 C1	10-02-1999
		SG 47559 A1	17-04-1998
		SK 85693 A3	08-06-1994
		US 5401729 A	28-03-1995
		US 5380888 A	10-01-1995
		US 5466684 A	14-11-1995
		US 5495031 A	27-02-1996
		ZA 9305894 A	09-03-1994

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing

(day/month/year) see form PCT/ISA210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/040850

International filing date (day/month/year)
07.12.2004

Priority date (day/month/year)
08.12.2003

International Patent Classification (IPC) or both national classification and IPC
C07D263/52, C07C237/26, A61K31/423, A61P31/04

Applicant
WYETH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA220.

3. For further details, see notes to Form PCT/ISA220.

Name and mailing address of the ISA:



European Patent Office
D-80289 Munich
Tel. +49 89 2399-0 Tx: 623656 eptm d
Fax: +49 89 2399-4465

Authorized Officer

Laur, P

Telephone No. +49 89 2399-8268



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/040850

Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/040850

Re Item V

1. Reference is made to the following documents:

D1: US-A-5 494 903 (HLAVKA ET AL) 27 February 1996 (1996-02-27)

D2: SUM ET AL.: J. MED. CHEM., vol 37, no. 1, 1994, pages 184-188,
XP002323590

D3: EP-A-0 582 788 (AMERICAN CYANAMID COMPANY) 16 February 1994 (1994-02-16)

2. The present application concerns:

a) Oxazole-fused tetracycline derivatives (claims 1-18) and their use as intermediates in the process for preparing 9-aminoacetylamino tetracycline derivatives (claims 19-28)

b) 9-Aminoacetylamino tetracycline derivatives (claims 29-38)

c) Process for preparing oxazole-fused tetracycline derivatives (claims 39-40)

3. **Novelty**

The subject-matter indicated above under point a) is novel over the cited prior art, which does not disclose tetracyclines fused with an oxazole. Claims 1 to 28 are thus novel.

The subject-matter indicated under point b) above is not novel re D1 to D3 which disclose compounds which fall under the definition of the compounds claimed in claims 29-38 of the present application; it is to be pointed out that the fact that the compounds are made according to a novel process does not make the final compounds novel.

As regard the first alternative of the process claimed in claim 40, anticipation is to be found in D3 (see page 15 and claim 7 of D3). Claim 39 is novel in view of the novel oxazole-fused tetracycline intermediate.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/040850

4. Inventive step

Since the prior art does not contain any suggestion which would have led the skilled person to prepare oxazole-fused tetracycline active as antibacterial or to use such compounds as intermediates for a process for the preparation of 9-aminoacetylamino tetracycline derivatives, inventive step can be acknowledged for the subject-matter which is considered to be novel.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

CALNAN, William, H.
Wyeth
Patent Law Department
Five Glaxo Farms
Madison, NJ 07940
ETATS-UNIS D'AMERIQUE

MAR 08 2005

Date of mailing (day/month/year) 24 February 2005 (24.02.2005)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference AM101568	
International application No. PCT/US04/040850	International filing date (day/month/year) 07 December 2004 (07.12.2004)
International publication date (day/month/year)	Priority date (day/month/year) 08 December 2003 (08.12.2003)
Applicant WYETH et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Exam., had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(a) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
3. (If applicable) An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Office, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(e) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
08 December 2003 (08.12.2003)	60/527,928	US	24 January 2005 (24.01.2005)
01 July 2004 (01.07.2004)	60/584,823	US	24 January 2005 (24.01.2005)

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Industria y Comercio

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Febrero 2006

Delegatura de Propiedad Industrial División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

		USUARIO	RADICADOR
PATENTE DE INVENCION ()	MODELO DE UTILIDAD ()	()	()
-Indicación de que se solicita la concesión de una patente.		()	()
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.		()	()
-Descripción de la invención.		()	()
-Dibujos de ser estos pertinentes.		()	()
-Comprobante de Pago de las tasas establecidas.		()	()
COMPLETA ()	INCOMPLETA ()	()	()
DISEÑO INDUSTRIAL ()			
-Indicación de que se solicita el registro de Diseño Industrial.		()	()
-Datos de identificación del solicitante o de la persona que se 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 Diseño Industrial.		()	()
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.		()	()
-Representación gráfica del Esquema Trazado.		()	()
-Comprobante de Pago de las tasas establecidas.		()	()
COMPLETA ()	INCOMPLETA ()	()	()

Firma Responsable:

Fecha:



Junio 2, 2006