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8-21084

Industria y Comercio

SUPERINTENDENCIA

INVENTARIO ✓

Delegatura de Propiedad Industrial
Division de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCION

08-21084

21 EXPEDIENTE No

54 TITULO "DERIVADOS DE GLICILCICLINAS SUSTITUIDOS CON
9-AMINOCARBONILO"

51 CLASIFICACION INTERNACIONAL A G. K 31/165

71 SOLICITANTE WYETH

DOMICILIO NUEVA JERSEY, ESTADOS UNIDOS DE AMERICA

74 APODERADO ALVARO CORREA ORDOÑEZ

TP No 20 281

22 BOGOTA, D C, FEBRERO 28, 2008

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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Act. 411 PRESENTACION Folios: 583

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

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C.C.

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Cual

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3

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5

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7

Clasificación Internacional (51)

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8

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9

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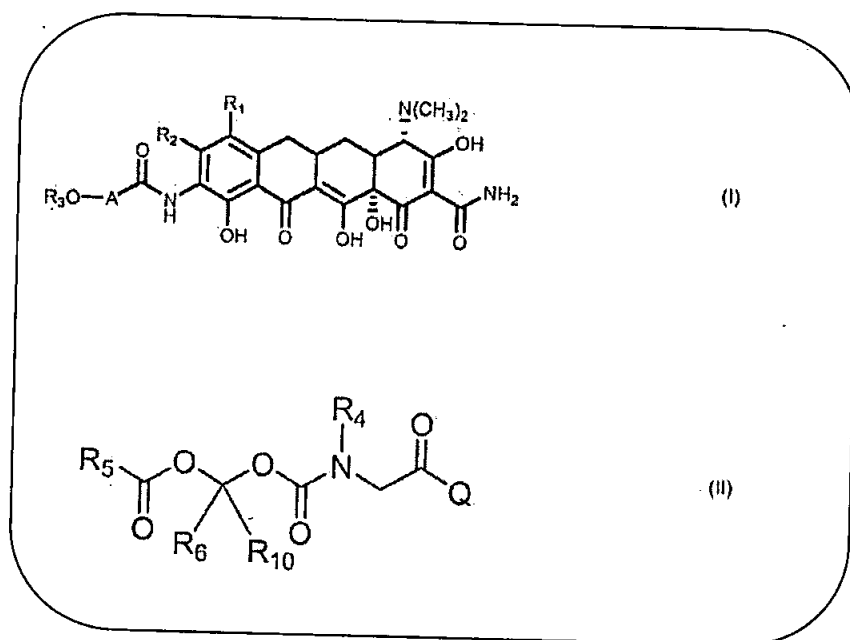
10

ANEXOS

- ☒ 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
- ☐ Arte 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: Extractos, reporte de búsqueda y opinión escrita y notificación de presentación de documento de prioridad

11

FIGURA CARATERISTICA



12

Solicito la concesión de la patente,

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FIRMA:

C.C. 79.143.366 de Usaquén

T.P. 20.281

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

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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	533781	01/02/2008	45,800,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		1 TRAMITES DE SOL. DE PATENTE DE IN	501,000.00
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(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
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GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP,
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GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

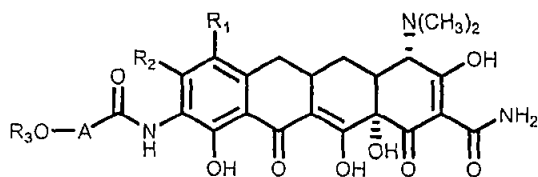
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

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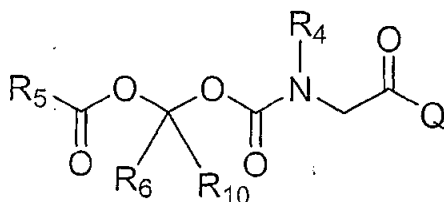
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCLINES



(I)

(57) Abstract: This invention provides compounds of Formula (I) having the structure where R₁, R₂, R₃ and A are defined in the specification or a pharmaceutically acceptable salt thereof useful as antibacterial agents. Compounds according to Formula (II): where Q, R₄, R₅, and R₆ and A are defined in the specification are useful as chemical intermediates.



(II)

WO 2007/027599 A1

9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCLINES

This application claims priority from U.S. Application No.60/713,112 filed August 31, 2005 the entire disclosure of which is incorporated herein by reference.

5 FIELD OF THE INVENTION

The present invention relates to 9-aminocarbonylsubstituted derivatives of glycylicyclines which are useful as antibiotic agents and exhibit antibacterial activity against a wide spectrum of organisms including organisms which are resistant to
10 tetracyclines and other antibiotics.

BACKGROUND OF THE INVENTION

Since 1947 a variety of tetracycline antibiotics have been synthesized and
15 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
20 of these antibiotics. There are two major mechanisms of bacterial resistance to tetracyclines: a) energy-dependent 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
25 interacts with the 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,
30 Haemophilus and 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. Salyers, 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 26,253 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.

Duggar, U.S. Pat. No. 2,482,055, discloses the preparation of Aureomycin.RTM. by fermentation which have antibacterial activity. Growich et al., U.S. Pat. No. 3,007,965, disclose improvements to the fermentation preparation. Beereboom et al., U.S. Pat. No. 3,043,875 discloses tetracycline derivatives Boothe et al., U.S. Pat. No. 3,148,212, reissued as U.S. Pat. No. RE 26,253, and Petisi 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. Petisi 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. 3,360,557 discloses 9- hydroxytetracyclines which have been found to possess antibacterial activity. Zambrano, U.S. Pat. No. 3,360,561 discloses a process for preparing 9-nitrotetracyclines. Martell et al., U.S. Pat. No. 3,518,306 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-substitutedamino-6-demethyl-6-deoxytetracyclines which have broad spectrum antibacterial activity.

Despite the advances being made to overcome the resistance of tetracycline resistant bacteria, there remains a need for newer and better antibiotics to overcome

the increasing incidence of resistance. The present invention provides such antibiotics.

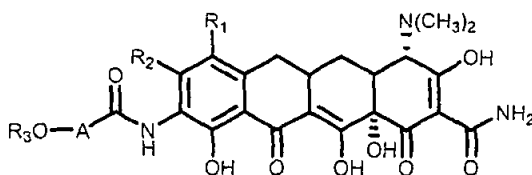
In summary, none of the above patents teach or suggest the novel derivatives of glycylcyclines of this application.

SUMMARY OF THE INVENTION

10 This invention is concerned with 9-aminocarbonylsubstituted derivatives of glycylicyclines represented by Formula I which have antibacterial activity; with methods of treating infectious diseases in humans and other animals when administering these new compounds; with pharmaceutical preparations containing these compounds; and with novel processes for the production of compounds of Formula I.

15

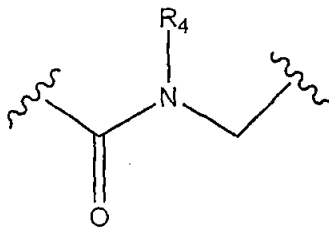
In accordance with the present invention, there is provided compounds represented by Formula (I);



(1)

20

wherein:



A is a moiety

or is absent;

25 R₁ is selected from hydrogen, -OH, amino, -NR₇R₈, halogen,

alkyl of 1 to 12 carbon atoms, optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon atoms, phenyl, hydroxyl, alkoxy of 1 to 12 carbon atoms, N-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon atoms, heterocyclyl of 3 to 8 ring atoms, aryl, aryloxy and N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl, aryloxy and aryl of N-(alkyl of 1 to 12 carbon atoms)-aryl may optionally be substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, alkenyl of 2 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group phenyl, heteroaryl, halogen, amino, cyano, alkyl, hydroxyl, alkoxy, aryl, alkynyl and N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl and aryl of N-(alkyl of 1 to 12 carbon atoms)-aryl may optionally be substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, and alkynyl of 2 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, alkyl, hydroxyl, and alkoxy;

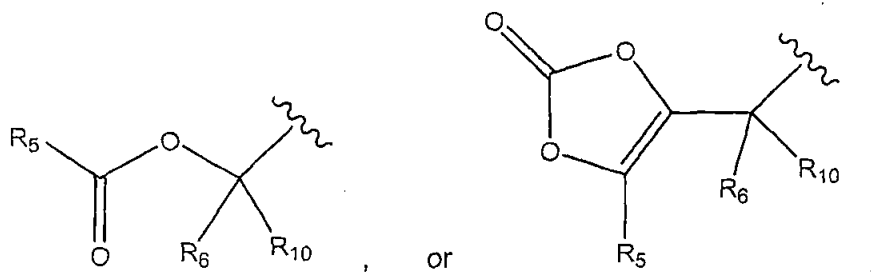
R₂ is selected from hydrogen, halogen, alkyl of 1 to 12 carbon atoms, optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon atoms, phenyl, hydroxyl, alkoxy of 1 to 12 carbon atoms, N-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon atoms, heterocyclyl of 3 to 8 ring atoms, aryl, aryloxy and N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl, aryloxy and aryl of N-(alkyl of 1 to 12 carbon atoms)-aryl may optionally be substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, alkenyl of 2 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group phenyl, heteroaryl, halogen, amino, cyano, alkyl, hydroxyl, alkoxy, aryl, alkynyl and N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl and aryl of N-(alkyl of 1 to 12

carbon atoms)-aryl may optionally be substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, and

5 alkynyl of 2 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, alkyl, hydroxyl, and alkoxy;

R₃ is the moiety R₉,

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R₄ is selected from hydrogen, alkyl of 1 to 12 carbon atoms, optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon atoms, phenyl, hydroxyl, alkoxy of 1 to 12 carbon atoms, N-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon atoms, heterocyclyl of 3 to 8 ring atoms, aryl, aryloxy and N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl, aryloxy and aryl of N-(alkyl

15 of 1 to 12 carbon atoms)-aryl may optionally be substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl,

20 alkenyl of 2 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group phenyl, heteroaryl, halogen, amino, cyano, alkyl, hydroxyl, alkoxy, aryl, alkynyl and N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl and aryl of N-(alkyl of 1 to 12 carbon atoms)-aryl may optionally be substituted with 1 to 3 substituents independently selected from halogen, nitro,

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cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, alkynyl of 2 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, alkyl, hydroxyl, and alkoxy, aryl of 6, 10 or 14 carbon atoms said aryl optionally substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, N-(alkyl of 1 to 12 carbon atoms)-aryl, said aryl optionally substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, aralkyl of 7 to 16 carbon atoms optionally substituted, aroyl of 7 to 13 carbon atoms optionally substituted, SR³, heteroaryl optionally substituted and heteroarylcarbonyl optionally substituted;

R₅ is selected from alkyl of 1 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon atoms, phenyl, hydroxyl, alkoxy of 1 to 12 carbon atoms, N-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon atoms, heterocyclyl of 3 to 8 ring atoms, aryl of 6, 10 or 14 carbon atoms, aryloxy and N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl, aryloxy and aryl of N-(alkyl of 1 to 12 carbon atoms)-aryl, may be optionally substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, aralkyl of 7 to 16 carbon atoms optionally substituted, aroyl, -CH₂(CO)OCH₂aryl, said aryl optionally substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryloxy and phenyl, alkenyl of 2 to 12 carbon atoms optionally substituted, heteroaryl optionally substituted, aryl of 6, 10 or 14 carbon atoms

optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted, cycloalkyl 3 to 6 ring atoms, aryl-CH=CH-, cycloalkyl-alkyl; and adamantyl;

5 R_6 is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon atoms, phenyl, hydroxyl, alkoxy of 1 to 12 carbon atoms, N-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon atoms, heterocyclyl of 3 to 8 ring atoms, aryl, aryloxy and N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl, aryloxy and aryl of N-(alkyl
10 of 1 to 12 carbon atoms)-aryl may optionally be substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, $\text{CH}_3\text{-C(O)-NH-}$, aralkyl, aryloxy, heterocyclyl and phenyl, and cycloalkyl of 3 to 6 carbon atoms;

15 R_7 and R_8 are each independently H or alkyl of 1 to 12 carbon atoms or R_7 and R_8 when optionally taken together with the nitrogen atom to which each is attached form a 3 to 8 membered heterocyclyl ring;

20 R_9 is aralkyl of 7 to 16 carbon atoms optionally substituted or alkyl of 1 to 12 carbon atoms;

R_{10} is H or alkyl of 1 to 12 carbon atoms;

or a pharmaceutically acceptable salt thereof.

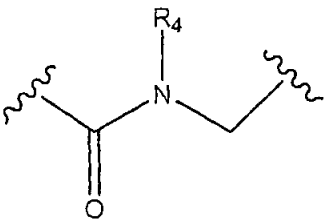
25 An embodiment of this invention provides compounds of Formula I wherein R_1 is - NR_7R_8 , R_7 is hydrogen, R_8 is methyl, ethyl, n-propyl, n-butyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl or a pharmaceutically acceptable salt thereof.

30 Another embodiment of this invention provides compounds of Formula I wherein R_1 is - NR_7R_8 , R_7 is methyl or ethyl, R_8 is methyl, ethyl, n-propyl, 1-methylethyl, n-propyl, 1-methylpropyl, or 2-methylpropyl or a pharmaceutically acceptable salt thereof.

A further embodiment of this invention provides compounds of Formula I wherein R_1 is $-NR_7R_8$, R_7 and R_8 are taken together with the nitrogen atom to which each is attached form a 3 to 8 membered heterocyclyl ring or a pharmaceutically acceptable salt thereof.

Another embodiment of this invention provides compounds of Formula I wherein R_2 is H or a pharmaceutically acceptable salt thereof.

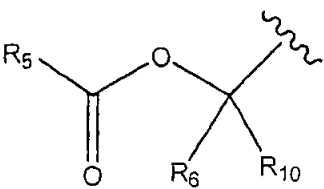
Another embodiment of this invention provides compounds of Formula I wherein A is a moiety



or a pharmaceutically acceptable salt thereof.

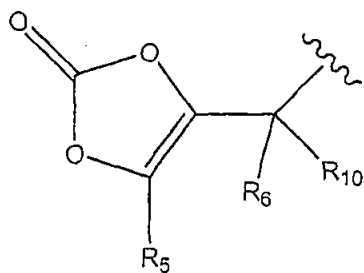
A further embodiment of this invention provides compounds of Formula I wherein A is absent or a pharmaceutically acceptable salt thereof.

A further embodiment of this invention provides compounds of Formula I wherein R_3 is a moiety



or a pharmaceutically acceptable salt thereof.

A further additional embodiment of this invention provides compounds of Formula I wherein R₃ is a moiety

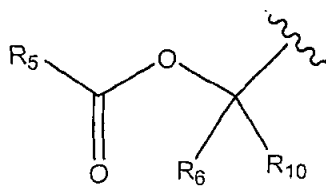


5

or a pharmaceutically acceptable salt thereof.

An embodiment of this invention provides compounds of Formula I wherein R₃ is a moiety

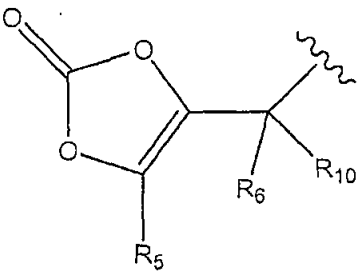
10



15 and R₆ and R₁₀ are H or a pharmaceutically acceptable salt thereof.

An additional embodiment of this invention provides compounds of Formula I wherein R₃ is a moiety

20

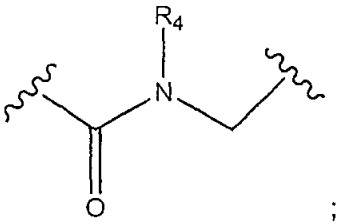


and R₆ and R₁₀ are H or a pharmaceutically acceptable salt thereof.

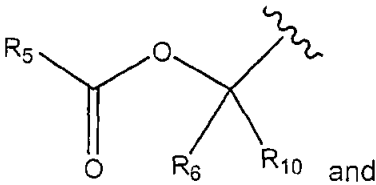
5

A further embodiment of this invention provides compounds of Formula I wherein R₃ is R₉ or a pharmaceutically acceptable salt thereof.

10 An additional embodiment of this invention provides compounds of Formula I wherein A is the moiety,



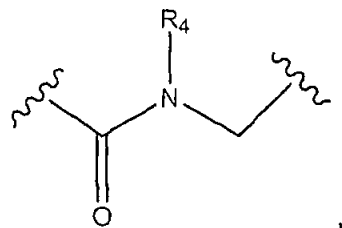
15 R₃ is the moiety



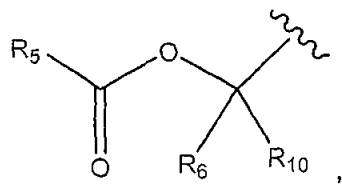
R₅ is aryl of 6 carbon atoms or a pharmaceutically acceptable salt thereof.

20

A further embodiment of this invention provides compounds of Formula I wherein A is the moiety



5 R₃ is the moiety ,



10 R₄ is 1,1-dimethylethyl and

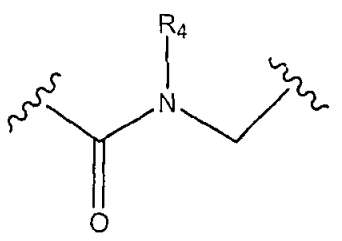
R₅ is aryl of 6 carbon atoms or a pharmaceutically acceptable salt thereof.

15 An additional embodiment of this invention provides compounds of Formula I

wherein:

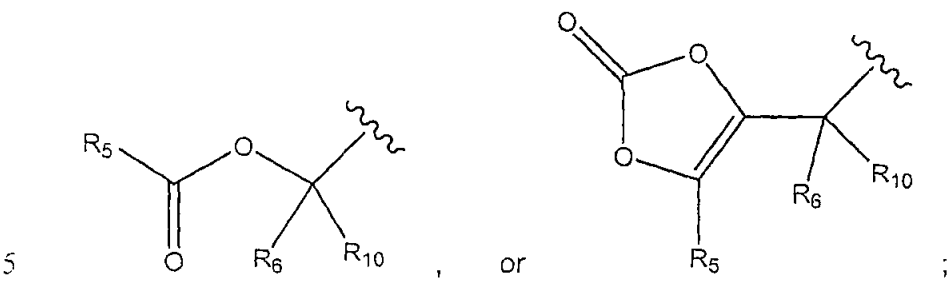
A is a moiety

20



R₁ is -NR₇R₈;

R₂ is hydrogen;
R₃ is the moiety



R₄ is selected from alkyl of 1 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon atoms, phenyl, hydroxyl, alkoxy of 1 to 12 carbon atoms, N-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon atoms, heterocyclyl of 3 to 8 ring atoms, aryl, and aryloxy wherein said aryl and aryloxy is optionally substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryloxy and phenyl;

15 R₅ is selected from alkyl of 1 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon atoms, phenyl, hydroxyl, alkoxy of 1 to 12 carbon atoms, N-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon atoms, heterocyclyl of 3 to 8 ring atoms, aryl of 6, 10 or 14 carbon atoms, and aryloxy wherein said aryl, aryloxy and aryl of N-(alkyl of 1 to 12 carbon atoms)-aryl, may be optionally substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, aralkyl of 7 to 16 carbon atoms optionally substituted, aroyl, -CH₂(CO)OCH₂aryl, said aryl optionally substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryloxy and

phenyl, heteroaryl optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, cycloalkyl 3 to 6 ring atoms, aryl-CH=CH-, cycloalkyl-alkyl; and adamantyl;

5 R₆ is hydrogen;

R₇ and R₈ are each independently H or alkyl of 1 to 12 carbon atoms;

10 R₉ is aralkyl of 7 to 16 carbon atoms optionally substituted or alkyl of 1 to 12 carbon atoms;

R₁₀ is H;

or a pharmaceutically acceptable salt thereof.

15

Further embodiments of the invention are the following specifically preferred compounds of Formula I or pharmaceutically acceptable salts thereof:

20 (((2-(((7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl 2-methylpropanoate,

25 (((2-(((7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl 4-methoxybenzoate,

30 (((2-(((7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl 4-methylbenzoate,

- (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(butyl)amino]carbonyl)oxy)methyl 4-fluorobenzoate,
- 5 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(propyl)amino]carbonyl)oxy)methyl 4-methylbenzoate,
- 10 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(propyl)amino]carbonyl)oxy)methyl 4-methoxybenzoate,
- 15 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(propyl)amino]carbonyl)oxy)methyl cyclobutanecarboxylate,
- 20 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(propyl)amino]carbonyl)oxy)methyl 4-fluorobenzoate,
- 25 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(propyl)amino]carbonyl)oxy)methyl 2-methylpropanoate,
- 30 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(propyl)amino]carbonyl)oxy)methyl phenylacetate,

19

(([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl](butyl)amino]carbonyl)oxy)methyl phenylacetate,

- 5 (([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl](butyl)amino]carbonyl)oxy)methyl pivalate,

- 10 (([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl](butyl)amino]carbonyl)oxy)methyl heptanoate,

- 15 (([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl](butyl)amino]carbonyl)oxy)methyl cyclobutanecarboxylate,

- 20 (([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl](propyl)amino]carbonyl)oxy)methyl heptanoate,

- 25 (([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl](butyl)amino]carbonyl)oxy)methyl 4-tert-butylbenzoate,

- 30 (([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl](butyl)amino]carbonyl)oxy)methyl 1,1'-biphenyl-4-carboxylate,

(([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl](butyl)amino]carbonyl)oxy)methyl 3,5-dimethylbenzoate,

20

- (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl 1,1'-biphenyl-4-carboxylate,
 5
 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl 3,5-dimethylbenzoate,
 10
 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl 4-tert-butylbenzoate,
 15
 1-(((2-(((7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(butyl)amino]carbonyl}oxy)ethyl acetate,
 20
 (((2-(((7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl cyclohexanecarboxylate,
 25
 (((2-(((7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl cyclohexanecarboxylate,
 30
 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl 3,3-dimethylbutanoate,
 30
 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl 3,3-dimethylbutanoate,

- (([(2-([(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(propyl)amino]carbonyl)oxy)methyl 2,2-dimethylbutanoate,
- 5 (([(2-([(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(butyl)amino]carbonyl)oxy)methyl cyclopentylacetate,
- 10 (((2-([(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(butyl)amino]carbonyl)oxy)methyl adamantane-1-carboxylate,
- 15 (((2-([(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(propyl)amino]carbonyl)oxy)methyl cyclopentylacetate,
- 20 (((2-([(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(propyl)amino]carbonyl)oxy)methyl adamantane-1-carboxylate,
- 25 (((2-([(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 3,3-dimethylbutanoate,
- 30 (((2-([(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 4-tert-butylbenzoate,
- 30 (((2-([(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 2,2-dimethylbutanoate,

(([(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 2-methylpropanoate,

5 (([(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl cyclopentanecarboxylate,

10 (([(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 4-methylbenzoate,

15 (([(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl heptanoate, and

20 (([(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 4-methoxybenzoate.

Further embodiments of the invention are the following specifically preferred compounds of Formula I or pharmaceutically acceptable salts thereof:

25 benzyl 2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl(propyl)carbamate,

30 ethyl 2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl(propyl)carbamate, and

23

isobutyl 2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl(propyl)carbamate.

- 5 Additional further embodiments of the invention are the following specifically preferred compounds of Formula I or pharmaceutically acceptable salts thereof:

10 {{{(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl thiophene-2-carboxylate,

15 {{{(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl thiophene-2-carboxylate,

20 {{{(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl thiophene-3-carboxylate,

25 {{{(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl thiophene-3-carboxylate,

30 {{{(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl 2-furoate, and

35 {{{(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl 2-furoate.

Further embodiments of the invention are the following specifically preferred compounds of Formula I or pharmaceutically acceptable salts thereof:

24

- 5
(((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl propionate,
- 10
(((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl cyclohexanecarboxylate,
- 15
(((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 3,5-dimethylbenzoate,
- 20
(((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 4-fluorobenzoate,
- 25
(((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 3-methylbutanoate,
- 30
(((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl cyclopentylacetate,
- 35
(((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 4-(trifluoromethyl)benzoate,
- 40
(((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl cyclopropanecarboxylate,

- (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl adamantane-1-carboxylate,
- 5 butyl 2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl(tert-butyl)carbamate,
- isobutyl 2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl(tert-butyl)carbamate,
- 10 methyl 2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl(tert-butyl)carbamate,
- 15 methyl 2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl(tert-butyl)carbamate,
- (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl pentanoate,
- 20 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl cyclobutanecarboxylate,
- 25 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 3-cyclohexylpropanoate,
- 30 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl (4-fluorophenoxy)acetate,

26

- (([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl cyclohexylacetate,
- 5 (([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 2,6-dimethylbenzoate,
- 10 (([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl phenylacetate,
- 15 (([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl pivalate,
- 20 (([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 1,1'-biphenyl-4-carboxylate,
- 25 (([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 1-naphthoate,
- 30 (([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 2-naphthoate,
- (([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 2,6-difluorobenzoate,

22

- (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 2-fluorobenzoate,
- 5 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 2-(trifluoromethyl)benzoate,
- 10 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 1,1'-biphenyl-2-carboxylate,
- 15 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 2,4,6-trimethylbenzoate,
- 20 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 4-isopropoxybenzoate,
- 25 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 3,4,5-trimethoxybenzoate,
- 30 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl (2E)-3-phenylprop-2-enoate,

(((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl [3,5-bis(trifluoromethyl)phenyl]acetate,

5

(((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 4-(heptyloxy)benzoate,

10 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 2-(2-phenylethyl)benzoate,

15 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 4-(dodecyloxy)benzoate,

20 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 4-(acetylamino)benzoate,

25 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl anthracene-9-carboxylate,

30 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 4-benzoylbenzoate, and

30 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl diphenylacetate.

29

Additional further embodiments of the invention are the following specifically preferred compounds of Formula I or pharmaceutically acceptable salts thereof:

5 [[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}carbonyl)oxy]methyl 4-fluorobenzoate,

10 [[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}carbonyl)oxy]methyl 3,5-dimethylbenzoate,

15 [[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}carbonyl)oxy]methyl pivalate,

20 [[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}carbonyl)oxy]methyl 3,3-dimethylbutanoate,

25 [[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}carbonyl)oxy]methyl 2,2-dimethylbutanoate,

30 [[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}carbonyl)oxy]methyl 2-ethylbutanoate,

30 [[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}carbonyl)oxy]methyl thiophene-2-carboxylate,

[(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)carbonyl)oxy]methyl cyclopentylacetate, and

- 5 [(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)carbonyl)oxy]methyl 4-tert-butylbenzoate.

Further embodiments of the invention are the following specifically preferred
10 compounds of Formula I or pharmaceutically acceptable salts thereof:

(([(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 1H-indole-2-carboxylate,

15 (([(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl nicotine,

20 (([(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl isonicotinate,

25 (([(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 4-pyrrolidin-1-ylbenzoate,

30 (([(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 3-methyl-1-benzofuran-2-carboxylate,

(((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 1-methyl-1H-indole-3-carboxylate,

5 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl quinoline-2-carboxylate,

10 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 1-benzofuran-2-carboxylate, and

15 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl-1-methyl-1H-pyrrole-2-carboxylate.

Further embodiments of the invention are the following specifically preferred compounds of Formula I or pharmaceutically acceptable salts thereof:

20 (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-(((7S,10aR)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl(propyl)carbamate,

25 (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-(((7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl(butyl)carbamate,

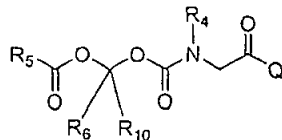
30 (2-oxo-5-phenyl-1,3-dioxol-4-yl)methyl 2-(((7R,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl(propyl)carbamate,

[5-(4-methoxyphenyl)-2-oxo-1,3-dioxol-4-yl]methyl 2-[[[(7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl(propyl)carbamate,

- 5 (2-oxo-5-phenyl-1,3-dioxol-4-yl)methyl 2-[[[(7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl(butyl)carbamate and

- 10 [5-(4-methoxyphenyl)-2-oxo-1,3-dioxol-4-yl]methyl 2-[[[(7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl(butyl)carbamate.

An additional embodiment of this invention are compounds represented by Formula (II):



(II)

wherein:

- 25 R_4 is selected from hydrogen, alkyl of 1 to 12 carbon atoms, optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon atoms, phenyl, hydroxyl, alkoxy of 1 to 12 carbon atoms, N-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon atoms, heterocycl of 3 to 8 ring atoms, aryl, aryloxy and N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl, aryloxy and aryl of N-(alkyl of 1 to 12 carbon atoms)-aryl may optionally be substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl,
- 30

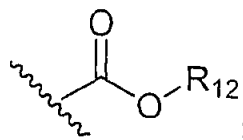
- alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl,
 alkenyl of 2 to 12 carbon atoms optionally substituted with 1 to 3 substituents
 independently selected from the group phenyl, heteroaryl, halogen, amino, cyano,
 5 alkyl, hydroxyl, alkoxy, aryl, alkynyl and N-(alkyl of 1 to 12 carbon atoms)-aryl,
 wherein said aryl and aryl of N-(alkyl of 1 to 12 carbon atoms)-aryl may optionally be
 substituted with 1 to 3 substituents independently selected from halogen, nitro,
 cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino,
 carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl
 10 and phenyl, alkynyl of 2 to 12 carbon atoms optionally substituted with 1 to 3
 substituents independently selected from the group halogen, amino, cyano, alkyl,
 hydroxyl, and alkoxy, aryl of 6, 10 or 14 carbon atoms said aryl optionally substituted
 with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl,
 hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl,
 15 alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl,
 N-(alkyl of 1 to 12 carbon atoms)-aryl, said aryl optionally substituted with 1 to 3
 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl,
 alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl,
 aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, aralkyl of 7 to 16
 20 carbon atoms optionally substituted, aroyl of 7 to 13 carbon atoms optionally
 substituted, SR³, heteroaryl optionally substituted and heteroarylcarbonyl optionally
 substituted;
- 25 R₅ is selected from alkyl of 1 to 12 carbon atoms optionally substituted with 1 to 3
 substituents independently selected from the group halogen, amino, cyano, cycloalkyl
 of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon atoms, phenyl, hydroxyl, alkoxy of 1 to
 12 carbon atoms, N-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon
 atoms, heterocyclyl of 3 to 8 ring atoms, aryl of 6, 10 or 14 carbon atoms, aryloxy and
 30 N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl, aryloxy and aryl of N-(alkyl of
 1 to 12 carbon atoms)-aryl, may be optionally substituted with 1 to 3 substituents
 independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl,
 alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-

- C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, aralkyl of 7 to 16 carbon atoms optionally substituted, aroyl, -CH₂(CO)OCH₂aryl, said aryl optionally substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryloxy and phenyl, alkenyl of 2 to 12 carbon atoms optionally substituted, heteroaryl optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted, cycloalkyl 3 to 6 ring atoms, aryl-CH=CH-, cycloalkyl-alkyl; and adamantyl;
- 10 R₆ is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon atoms, phenyl, hydroxyl, alkoxy of 1 to 12 carbon atoms, N-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon atoms, heterocyclyl of 3 to 8 ring atoms, aryl, aryloxy and
- 15 N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl, aryloxy and aryl of N-(alkyl of 1 to 12 carbon atoms)-aryl may optionally be substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, and cycloalkyl of 3 to 6 carbon
- 20 atoms;

R₁₀ is H or alkyl of 1 to 12 carbon atoms;

- 25 Q is -OR₁₁, Cl, Br or I;

R₁₁ is H, benzyl optionally substituted with nitro or a moiety of the formula

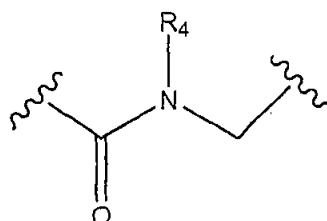


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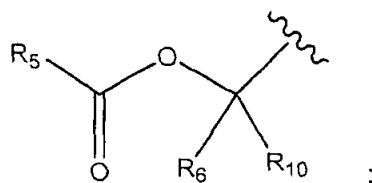
R₁₂ is alkyl of 1 to 6 carbon atoms.

The compounds having Formula II are useful as chemical intermediates for making the compounds having formula I and the pharmaceutically acceptable salt thereof wherein: A is a moiety

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and R₃ is the moiety



10 where R₄ and R₅ are as defined above.

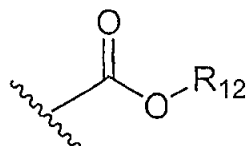
An embodiment of the invention provides compounds of Formula II wherein R₄ is t-butyl, R₅ is alkyl of 1 to 6 carbon atoms, and R₁₁ is benzyl optionally substituted with
15 nitro.

Another embodiment of the invention provides compounds of Formula II wherein R₄ is alkyl of 1 to 6 carbon atoms, R₅ is phenyl optionally substituted and R₁₁ is benzyl optionally substituted with nitro.

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An embodiment of the invention provides compounds of Formula II wherein R₅ is alkyl of 1 to 6 carbon atoms, R₄ is t-butyl and R₁₁ is H.

A further embodiment of the invention provides compounds of Formula II wherein R₅ is alkyl of 1 to 6 carbon atoms, R₄ is t-butyl, Q is -OR₁₁, R₁₁ is
25



and R₁₂ is alkyl of 1 to 6 carbon atoms.

Another embodiment of the invention provides compounds of Formula II wherein R₆
5 and R₁₀ are H.

Further embodiments of the invention provides the following specifically preferred
compounds of Formula II or pharmaceutically acceptable salts thereof.

10 ({{{[2-(benzyloxy)-2-oxoethyl]}(tert-butyl)amino]carbonyl}oxy)methyl 4-tert-
butylbenzoate,

{{[2-(benzyloxy)-2-oxoethyl]}(tert-butyl)amino]carbonyl}oxy)methyl 2,2-
dimethylbutanoate,

15 {{{[2-(benzyloxy)-2-oxoethyl]}(tert-butyl)amino]carbonyl}oxy)methyl 2-
methylpropanoate,

{{[2-(benzyloxy)-2-oxoethyl]}(tert-butyl)amino]carbonyl}oxy)methyl
20 cyclopentanecarboxylate,

{{[2-(benzyloxy)-2-oxoethyl]}(tert-butyl)amino]carbonyl}oxy)methyl 4-methylbenzoate,

{{[2-(benzyloxy)-2-oxoethyl]}(tert-butyl)amino]carbonyl}oxy)methyl heptanoate,

25 {{{[2-(benzyloxy)-2-oxoethyl]}(tert-butyl)amino]carbonyl}oxy)methyl propionate,

{{[2-(benzyloxy)-2-oxoethyl]}(tert-butyl)amino]carbonyl}oxy)methyl
cyclohexanecarboxylate,

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- (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino)carbonyl)oxy)methyl 3,5-dimethylbenzoate,
- (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino)carbonyl)oxy)methyl 4-fluorobenzoate,
- (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino)carbonyl)oxy)methyl 3-methylbutanoate,
- benzyl N-(tert-butyl)-N-(((cyclopentylacetyl)oxy)methoxy)carbonyl)glycinate,
- (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino)carbonyl)oxy)methyl 4-(trifluoromethyl)benzoate,
- (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino)carbonyl)oxy)methyl cyclopropanecarboxylate,
- (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino)carbonyl)oxy)methyl adamantane-1-carboxylate,
- (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino)carbonyl)oxy)methyl pentanoate,
- (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino)carbonyl)oxy)methyl cyclobutanecarboxylate,
- (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino)carbonyl)oxy)methyl 3-cyclohexylpropanoate,
- benzyl N-(tert-butyl)-N-(((4-fluorophenoxy)acetyl)oxy)methoxy)carbonyl)glycinate,
- benzyl N-(tert-butyl)-N-(((cyclohexylacetyl)oxy)methoxy)carbonyl)glycinate,
- (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino)carbonyl)oxy)methyl 2,6-dimethylbenzoate,

- benzyl N-(tert-butyl)-N-({[(phenylacetyl)oxy]methoxy}carbonyl)glycinate,
- ({{[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl pivalate,
- 5 ({{[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 1-benzofuran-2-carboxylate,
- ({{[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 1-methyl-1H-pyrrole-2-carboxylate,
- 10 ({{[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 1,1'-biphenyl-4-carboxylate,
- ({{[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 4-methoxybenzoate,
- 15 ({{[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 1H-indole-2-carboxylate,
- 20 benzyl N-(tert-butyl)-N-({[(diphenylacetyl)oxy]methoxy}carbonyl)glycinate,
- ({{[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 1-naphthoate,
- 25 ({{[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 2-naphthoate,
- ({{[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 1-methyl-1H-indole-3-carboxylate,
- 30 ({{[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl quinoline-2-carboxylate,
- ({{[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl nicotinate,

- (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl isonicotinate,
- 5 (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 2,6-difluorobenzoate,
- (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 2-fluorobenzoate,
- 10 (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 2-(trifluoromethyl)benzoate,
- (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 4-(1H-pyrrol-1-yl)benzoate,
- 15 (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 1,1'-biphenyl-2-carboxylate,
- (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 2,4,6-trimethylbenzoate,
- 20 (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 4-isopropoxybenzoate,
- (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 3,4,5-trimethoxybenzoate,
- 25 (((2-(benzyloxy)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 3,5-dimethoxybenzoate,
- 30 3-phenyl-acrylic acid (benzyloxycarbonylmethyl-tert-butyl-carbamoyloxy)-methyl ester,

- ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 3-methyl-1-benzofuran-2-carboxylate,
- 5 benzyl N-([[[[3,5-bis(trifluoromethyl)phenyl]acetyl]oxy]methoxy]carbonyl)-N-(tert-butyl)glycinate,
- ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 4-(heptyloxy)benzoate,
- 10 ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 2-(2-phenylethyl)benzoate,
- ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 4-(dodecyloxy)benzoate,
- 15 ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 4-(acetylamino)benzoate,
- ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl anthracene-9-carboxylate and
- 20 ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 4-benzoylbenzoate.
- 25 Additional embodiments of the invention are the following specifically preferred compounds of Formula II or pharmaceutically acceptable salts thereof.
- N-(tert-butyl)-N-([[(4-tert-butylbenzoyl)oxy]methoxy]carbonyl)glycine,
- 30 N-(tert-butyl)-N-([[(isobutyryloxy)methoxy]carbonyl]glycine,
- N-(tert-butyl)-N-([[(cyclopentylcarbonyl)oxy]methoxy]carbonyl)glycine,

- N-(tert-butyl)-N-({[(4-methylbenzoyl)oxy]methoxy}carbonyl)glycine,
- N-(tert-butyl)-N-({[(heptanoyloxy)methoxy]carbonyl)glycine,
- 5 N-(tert-butyl)-N-({[(propionyloxy)methoxy]carbonyl)glycine,
- N-(tert-butyl)-N-({[(cyclohexylcarbonyl)oxy]methoxy}carbonyl)glycine,
- N-(tert-butyl)-N-({[(3,5-dimethylbenzoyl)oxy]methoxy}carbonyl)glycine,
- 10 N-(tert-butyl)-N-({[(4-fluorobenzoyl)oxy]methoxy}carbonyl)glycine,
- N-(tert-butyl)-N-({[(3-methylbutanoyl)oxy]methoxy}carbonyl)glycine,
- 15 N-(tert-butyl)-N-({[(cyclopentylacetyl)oxy]methoxy}carbonyl)glycine,
- N-(tert-butyl)-N-({[(4-(trifluoromethyl)benzoyl]oxy]methoxy}carbonyl)glycine,
- N-(tert-butyl)-N-({[(cyclopropylcarbonyl)oxy]methoxy}carbonyl)glycine,
- 20 N-({[(1-adamantylcarbonyl)oxy]methoxy}carbonyl)-N-(tert-butyl)glycine,
- N-(tert-butyl)-N-({[(pentanoyloxy)methoxy]carbonyl)glycine,
- 25 N-(tert-butyl)-N-({[(cyclobutylcarbonyl)oxy]methoxy}carbonyl)glycine,
- N-(tert-butyl)-N-({[(3-cyclohexylpropanoyl)oxy]methoxy}carbonyl)glycine,
- N-(tert-butyl)-N-({[(4-fluorophenoxy)acetyl]oxy]methoxy}carbonyl)glycine
- 30 N-(tert-butyl)-N-({[(cyclohexylacetyl)oxy]methoxy}carbonyl)glycine,
- N-(tert-butyl)-N-({[(2,6-dimethylbenzoyl)oxy]methoxy}carbonyl)glycine,

- N-(tert-butyl)-N-({[(phenylacetyl)oxy]methoxy}carbonyl)glycine,
- N-(tert-butyl)-N-({[(2,2-dimethylpropanoyl)oxy]methoxy}carbonyl)glycine,
- 5 N-({[(1-benzofuran-2-ylcarbonyl)oxy]methoxy}carbonyl)-N-(tert-butyl)glycine,
- N-(tert-butyl)-N-({[(1-methyl-1H-pyrrol-2-yl)carbonyl]oxy}methoxy)carbonyl]glycine,
- 10 N-({[(1,1'-biphenyl-4-ylcarbonyl)oxy]methoxy}carbonyl)-N-(tert-butyl)glycine,
- N-(tert-butyl)-N-({[(4-methoxybenzoyl)oxy]methoxy}carbonyl)glycine,
- N-(tert-butyl)-N-({[(1H-indol-2-ylcarbonyl)oxy]methoxy}carbonyl)glycine,
- 15 N-(tert-butyl)-N-({[(diphenylacetyl)oxy]methoxy}carbonyl)glycine,
- N-(tert-butyl)-N-({[(1-naphthoyloxy)methoxy]carbonyl)glycine,
- 20 N-(tert-butyl)-N-({[(2-naphthoyloxy)methoxy]carbonyl)glycine,
- N-(tert-butyl)-N-({[(1-methyl-1H-indol-3-yl)carbonyl]oxy}methoxy)carbonyl]glycine,
- N-(tert-butyl)-N-({[(quinolin-2-ylcarbonyl)oxy]methoxy}carbonyl)glycine,
- 25 N-(tert-butyl)-N-({[(pyridin-3-ylcarbonyl)oxy]methoxy}carbonyl)glycine,
- N-(tert-butyl)-N-({[(isonicotinoyloxy)methoxy]carbonyl)glycine,
- 30 N-(tert-butyl)-N-({[(2,6-difluorobenzoyl)oxy]methoxy}carbonyl)glycine,
- N-(tert-butyl)-N-({[(2-fluorobenzoyl)oxy]methoxy}carbonyl)glycine,

- N-(tert-butyl)-N-([2-(trifluoromethyl)benzoyl]oxy)methoxy)carbonyl]glycine,
- N-(tert-butyl)-N-([4-(pyrrolidin-1-yl)benzoyl]oxy)methoxy)carbonyl]glycine,
- 5 N-([1,1'-biphenyl-2-ylcarbonyl]oxy)methoxy)carbonyl]-N-(tert-butyl)glycine,
- N-(tert-butyl)-N-([mesitylcarbonyl]oxy)methoxy)carbonyl]glycine,
- N-(tert-butyl)-N-([4-isopropoxybenzoyl]oxy)methoxy)carbonyl]glycine,
- 10 N-(tert-butyl)-N-([3,4,5-trimethoxybenzoyl]oxy)methoxy)carbonyl]glycine,
- N-(tert-butyl)-N-([3,5-dimethoxybenzoyl]oxy)methoxy)carbonyl]glycine,
- 15 N-(tert-butyl)-N-([(2E)-3-phenylprop-2-enoyl]oxy)methoxy)carbonyl]glycine,
- N-(tert-butyl)-N-([3-methyl-1-benzofuran-2-yl]carbonyl]oxy)methoxy)carbonyl]glycine,
- 20 N-([3,5-bis(trifluoromethyl)phenyl]acetyl]oxy)methoxy)carbonyl]-N-(tert-butyl)glycine,
- N-(tert-butyl)-N-([4-(heptyloxy)benzoyl]oxy)methoxy)carbonyl]glycine,
- 25 N-(tert-butyl)-N-([2-(2-phenylethyl)benzoyl]oxy)methoxy)carbonyl]glycine,
- N-(tert-butyl)-N-([4-(dodecyloxy)benzoyl]oxy)methoxy)carbonyl]glycine,
- N-([4-(acetylamino)benzoyl]oxy)methoxy)carbonyl]-N-(tert-butyl)glycine,
- 30 N-([9-anthrylcarbonyl]oxy)methoxy)carbonyl]-N-(tert-butyl)glycine and
- N-([4-benzoylbenzoyl]oxy)methoxy)carbonyl]-N-(tert-butyl)glycine

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A further embodiment of the invention is the following specifically preferred compound of Formula II or pharmaceutically acceptable salts thereof.

- 5 3,3-Dimethyl-butyric acid [tert-butyl-(2-isobutoxycarbonyloxy-2-oxo-ethyl)-carbamoyloxy]-methyl ester.

Definitions

For the compounds of the invention defined above and referred to herein, unless
5 otherwise noted, the following terms are defined:

The term alkyl means a straight or branched alkyl moiety of 1 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon
10 atoms, phenyl, hydroxyl, alkoxy of 1 to 12 carbon atoms, N-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon atoms, heterocyclyl of 3 to 8 ring atoms, aryl, aryloxy and N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl, aryloxy and aryl of N-(alkyl of 1 to 12 carbon atoms)-aryl may optionally be substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl,
15 alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl. In some embodiments of the invention alkyl is a moiety of 1 to 6 carbon atoms. In other embodiments of the invention alkyl is a moiety of 1 to 3 carbon atoms. In other embodiments of the invention alkyl is 1,1-dimethylethyl also termed t-butyl. In some
20 embodiments of the invention when alkyl is a methyl group wherein optional substitution is two independent phenyl rings. Non-limiting examples of alkyl are methyl, ethyl, n-propyl, 1-methylethyl, n-butyl, 1-methylpropyl, 2-methylpropyl and 1,1-dimethylethyl.

25 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 independently substituted with 1 to 3 substituents selected from the group phenyl, heteroaryl, halogen, amino, cyano, alkyl, hydroxyl, alkoxy, aryl, alkynyl and N-(alkyl of 1 to 12 carbon atoms)-aryl,
30 wherein said aryl and aryl of N-(alkyl of 1 to 12 carbon atoms)-aryl may optionally be substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl

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and phenyl. In some embodiments of the invention alkenyl is a vinyl moiety $\text{CH}_2=\text{CH}-$.

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As used herein the term alkoxy refers to alkyl-O- wherein alkyl is hereinbefore defined. Non limiting examples include: methoxy and ethoxy.

- 10 As used herein the term aryl means an aromatic moiety having 6, 10 or 14 carbon atoms preferably 6 to 10 carbon atoms, optionally substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, $\text{CH}_3\text{-C(O)-NH-}$, aralkyl, aryloxy, heterocyclyl and phenyl. In particular, aryl is phenyl or
- 15 naphthyl optionally substituted with 1 to 3 substituents.

The term aralkyl as used herein of 7 to 16 carbon atoms means an alkyl substituted with an aryl group in which the aryl and alkyl group are as defined herein. Non-limiting exemplary aralkyl groups include benzyl and phenethyl and the like.

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Perhaloalkyl as used herein means an alkyl moiety of 1 to 6 carbon atoms in which each hydrogen atom is substituted with a halogen atom, an exemplary example is trifluoromethyl.

- 25 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
- 30 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.

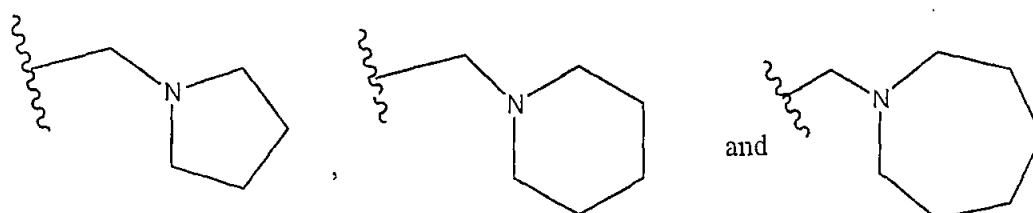
As used herein the term cycloalkyl means a saturated monocyclic ring having from 3 to 6 carbon atoms. Exemplary cycloalkyl rings include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. In an embodiment of the invention cycloalkyl is a moiety of 5 or 6 carbon atoms.

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.

- 10 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 or bicyclic aromatic rings of 8 to 20 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 independently selected from the group alkyl, halogen, cyano, nitro, hydroxy, amino, alkylamino, dialkylamino, alkoxy, aryloxy, -CH₂OCOCH₃ and carboxy. Non-limiting heteroaryl moieties optionally substituted include: furanyl, benzofuranyl, benzothienyl, thienyl, pyridinyl, quinolinyl, tetrazolyl, imidazo, thiazolyl and the like.
- 15
- 20 Where terms are used in combination, the definition for each individual part of the combination applies unless defined otherwise. For instance, aralkyl refers to an aryl group, and alkyl refers to the alkyl group as defined above. Also, aryloxy refers to a arylO- group.
- 25 The term heteroarylcarbonyl means a heteroaryl-C(O)- group in which the heteroaryl group is as previously defined.

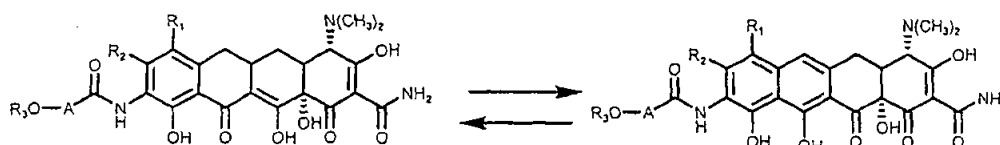
The term heterocyclyl as used herein represents a saturated ring of 3 to 8 ring atoms containing 1 to 3 heteroatoms selected from nitrogen, oxygen and sulfur. In some embodiments of the invention a saturated ring of 5 or 6 ring atoms is preferred. Representative examples are pyrrolidyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, aziridinyl, tetrahydrofuranyl and the like.

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



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 included within the scope of the present invention. For instance, compounds of

10 Formula (I) which exist as tautomers are depicted below:



The present invention accordingly provides a pharmaceutical composition

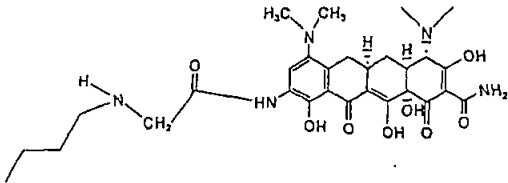
15 which comprises a compound of this invention in combination or association with a pharmaceutically acceptable carrier. In particular, the present invention provides a pharmaceutical composition which comprises an effective amount of a compound of this invention and a pharmaceutically acceptable carrier.

20 Proton sponge is [1,8-bis(dimethylamino)naphthalene, N,N,N',N'-tetramethyl-1,8-naphthalenediamine].

Alkali metal carbonate includes lithium, potassium and sodium carbonate.

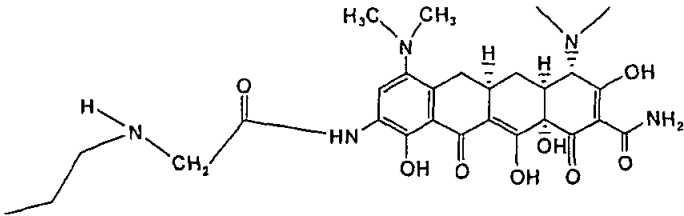
25 DMPU is 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone.

N-butyl-glycylcycline (N-bu-glycyl) is



N-propyl-glycylcycline (N-prop-glycyl) is

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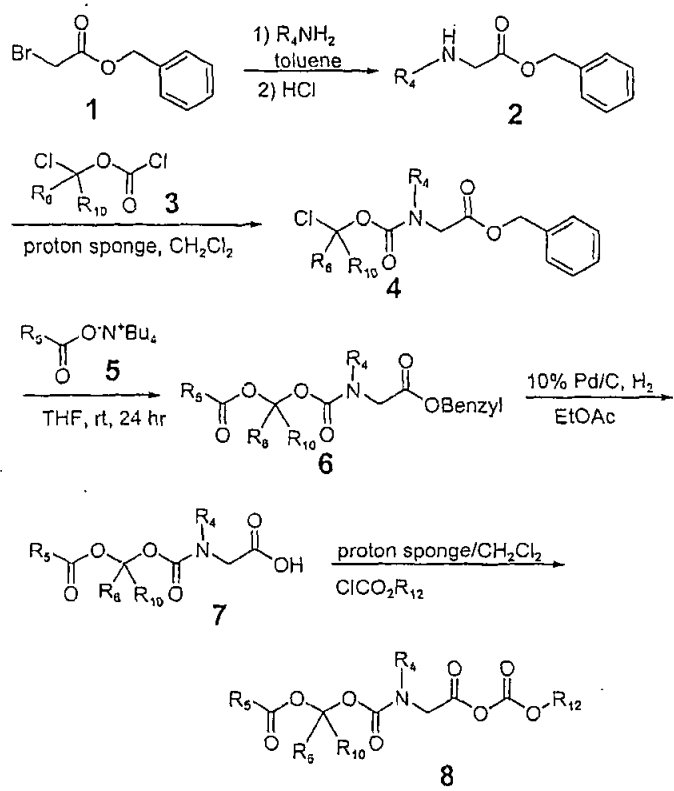


DESCRIPTION OF THE PREFERRED EMBODIMENTS

The compounds of this invention may be prepared according to the following schemes: (1) from commercially available starting materials or: (2) from known starting materials which can be prepared as described in literature procedures or: (3) from new intermediates described in the schemes and experimental procedures.

The synthesis of acyloxy intermediate 8 is shown in Scheme 1. Reaction of amine R_4NH_2 , preferably t-butylamine, with ester 1 provides the substituted amino ester 2. Preparation of the intermediate 4 is accomplished by using Proton Sponge as base to effect the acylation of substituted amino ester 2 with chloromethyl chloroformate 3. Treatment of intermediate 4 with the tetrabutylammonium salt 5 of carboxylic acids gives the benzyl protected acyloxy intermediate 6. The benzyl protecting group is removed by catalytic reduction to give carboxylic acid 7 which is activated to a mixed anhydride with chloroformate $ClCO_2R_{12}$ where R_{12} is alkyl of 1 to 6 carbon atoms, for example iso-butyl chloroformate to give acyloxycarbamate intermediate 8. In an alternate route, silyl esters may optionally be used in place of the benzyl ester of intermediate 4, treating with the appropriate carboxylic acid followed by deblocking the silyl ester with tetrabutylammonium fluoride or magnesium bromide to afford carboxylic acid 7. Optionally, carboxylic acid 7 may be activated through the use of coupling agents not limited to di-t-butyl dicarbonate (Boc_2O); e.g., benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (also known as Bop); benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (also known as PyBop); O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluorophosphate (HBTU); Bromotris-pyrrolidino-phosphonium hexafluorophosphate; 2-Chloro-N-methylpyridinium iodide (CMPI); dicyclohexylcarbodiimide (DCC); 1,3-diisopropylcarbodiimide (DIC); 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDC); or Carbonyl diimidazole.

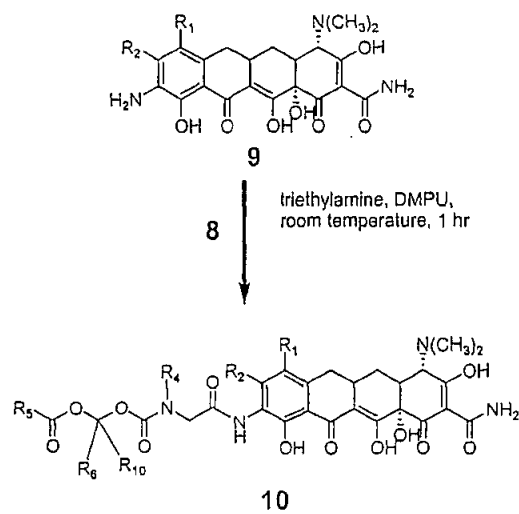
SCHEME 1



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As shown in Scheme 2, reaction of activated acyloxycarbamate intermediate 8 with 7,8-disubstituted-9-aminotetracycline 9 in the presence of triethylamine and DMPU gives acyloxycarbamate 10.

Scheme 2



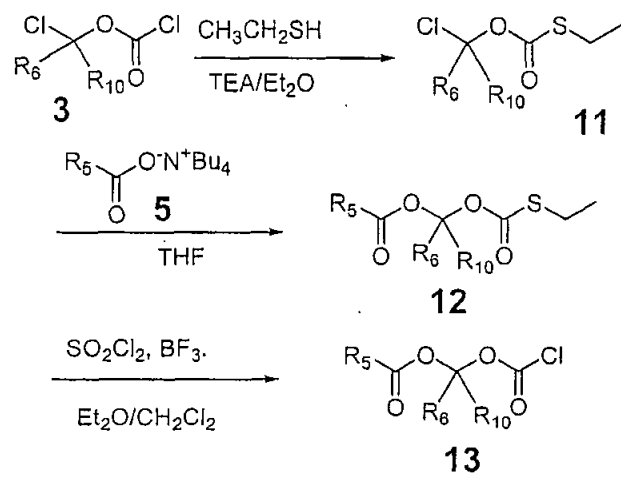
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Additional acyloxy carbamate compounds may be synthesized via routes as shown in Schemes 3 and 4. Treatment of chloromethyl chloroformate 3 with ethanethiol in the presence of triethylamine (TEA) gives carbonothioate 11. Compound 12 is prepared by reacting carbonothioate 11 with carboxylic acid tetrabutylammonium salt 5 in tetrahydrofuran. Chlorination of compound 12 with sulfuryl chloride in the presence of catalytic amount of boron trifluoroetherate affords chloro intermediate 13 (using the methods described in M. Folkmann and F.J. Lund, Synthesis, December 1990, 1159-1166).

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Scheme 3

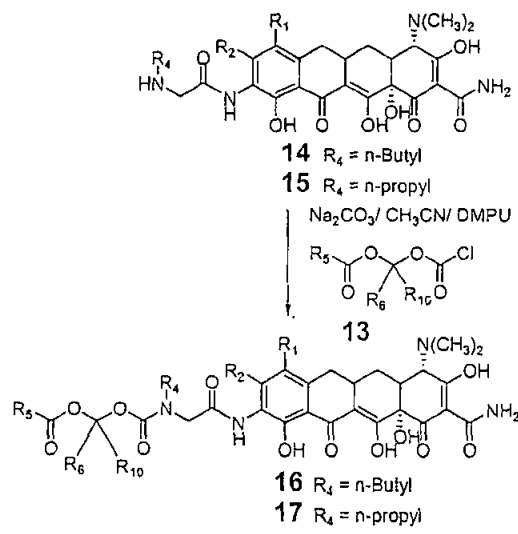


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As further seen in Scheme 4 acyloxycarbamates 16 and 17 where R_4 is preferably n-butyl or n-propyl are synthesized by treatment of either 14 or 15 where R_4 is preferably n-butyl or n-propyl with the chloro intermediate 13 to give

10 acyloxycarbamates 16 and 17 respectively.

Scheme 4



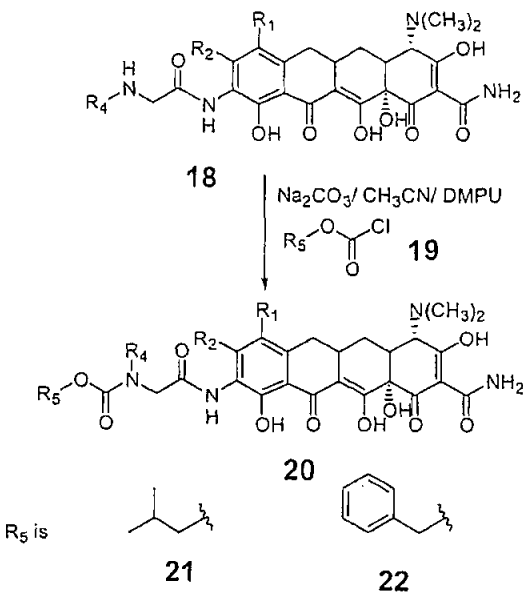
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5^u

As shown in Scheme 5, carbamates of glycylicycline where R₄ is preferably propyl 18 may also be prepared by reaction with chloro intermediate 19 in the presence of an alkali metal carbonate preferably sodium carbonate, and DMPU in acetonitrile to afford preferred compounds (21 and 22).

5

Scheme 5



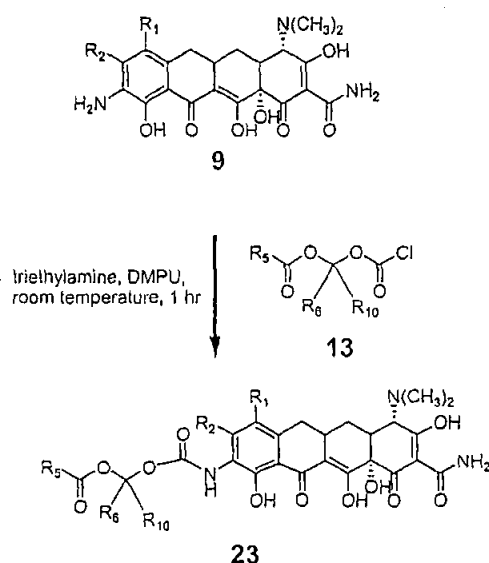
10

R₄ is preferably propyl

15

55

Scheme 6



- 5 As shown in Scheme 6, reaction of chloro intermediate 13 with 7,8-disubstituted-9-aminotetracycline 9 in the presence of triethylamine and DMPU gives carbamate 23.

- As further shown in Scheme 7, compounds of Formula I may generally be prepared
- 10 by removal of the benzyl protecting group from benzyl protected acyloxy intermediate 24 to give carboxylic acid 25 which is activated to a mixed anhydride with a chloroformate $ClCO_2R_{12}$ where R_{12} is alkyl of 1 to 6 carbon atoms, for example isobutyl chloroformate to give acyloxycarbamate intermediate 26. Further reaction of
- 15 intermediate 26 in the presence of triethylamine and DMPU affords compounds of Formula (I).

5x

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 judgement 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.

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. In all cases, the salt formation occurs with the C(4)-dimethylamino group. The salts are preferred for oral and parenteral administration.

58

Standard Pharmacological Test Procedures

Methods for in Vitro Antibacterial evaluation

5

The minimum inhibitory concentration (MIC)

Antimicrobial susceptibility testing. The in vitro activities of the antibiotics are 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 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.

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.

Standard Pharmacological Test Procedures

Presented in Tables I-XIII are representative compounds of Formula I which were evaluated against a panel of 40 selected gram-positive and gram-negative bacteria strains by pre-incubation in water, mouse serum or human serum. Representative compounds were first incubated in mouse serum for an hour prior to the in vitro testing against a panel of selected gram-positive and gram-negative bacteria strains. All compounds were also pre-incubated in water for an hour prior to testing as

control. Representative compounds of Formula I were incubated in human serum prior to MIC determination. Representative compounds of Formula I which demonstrated in vivo activity were further subjected to various stability tests. A summary of the in vitro testing data of representative examples of Formula I are shown in Table 1. Expanded in vitro data of selected examples (87 and 27) are shown in Table 2 and 5 respectively. MICs of representative examples of Formula I are further shown in Tables 3 and 4. Table 6 presents in vitro and in vivo activity of representative examples of compounds of Formula I against Staph. aureus Smith in mice. Table 7 presents in vivo (oral, iv) and in vitro (MIC) activity of representative examples of compounds of Formula I against E. coli in mice. Table 8 presents in vivo (oral, iv) and in vitro (MIC) activity of representative examples of compounds of Formula I, against Staph aureus Smith in mice. Table 9 presents in vitro (MIC) activity of representative examples of compounds of Formula I against E. Coli in human serum and water and also also against Staph in human serum and water. Table 10 presents in vivo single oral dose (SOD) and single intravenous dose (SIV) ED₅₀ data for representative examples of compounds of Formula I against Staph. Smith and E. Coli #311 in mammals.

TABLE I
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCLINES OF FORMULA I
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Mouse Serum		Water		Mouse Serum		Water		Mouse Serum		Water	
	Example 1	Example 1	Example 1	Example 1	Example 2	Example 2	Example 2	Example 2	Example 3	Example 3	Example 3	Example 4
E. coli GC 2236	1	16	4	32	1	>64	1	>64	1	64	64	64
E. coli GC 2231	1	64	4	64	2	>64	1	>64	1	64	64	64
E. coli GC 2235	0.50	16	2	64	1	>64	1	>64	1	64	64	64
E. coli GC 2232	0.50	16	2	64	2	>64	2	>64	1	64	64	64
E. coli GC 2233	1	16	1	64	1	>64	1	>64	1	64	64	64
E. coli GC 2234	0.50	16	1	64	1	>64	1	>64	1	64	64	64
E. coli GC 2270	0.50	16	1	64	1	>64	1	>64	1	64	64	64
E. coli GC 2271	0.50	16	1	64	1	>64	1	>64	0.50	64	64	64
E. coli GC 2272	1	16	1	64	1	>64	1	>64	1	64	64	64
E. coli GC 4559	1	32	1	64	2	>64	2	>64	2	>64	>64	>64
E. coli GC 4560	0.50	2	0.25	4	0.50	32	0.25	8	0.25	8	8	8
E. coli GC 6465	8	>64	8	64	8	>64	8	>64	4	>64	>64	>64
E. coli GC 3226	1	32	4	64	2	>64	2	>64	2	64	64	64
E. coli GC 2203	0.50	16	2	64	1	>64	1	>64	1	64	64	64
E. coli GC 1073	1	32	4	64	2	>64	2	>64	1	>64	>64	>64
Salmonella spp. GC 235	1	64	8	>64	2	>64	2	>64	2	>64	>64	>64

15

TABLE I (Cont)
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCCLINES
OF FORMULA I
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Example 1			Example 2			Example 3			Example 4		
	Mouse Serum	Water	Mouse Serum	Water	Mouse Serum	Water	Mouse Serum	Water	Mouse Serum	Water	Mouse Serum	Water
Example 1	Example 1	Example 1	Example 1	Example 1	Example 1	Example 1	Example 1	Example 1	Example 1	Example 1	Example 1	Example 1
Salmonella spp. GC 566	2	64	8	>64	4	>64	4	>64	4	>64	4	>64
S. cholerae GC 1355	8	>64	>64	>64	16	>64	16	>64	8	>64	8	>64
S. typhimurium GC 2172	4	>64	>64	>64	8	>64	8	>64	4	>64	4	>64
P. aeruginosa GC 2214	32	>64	>64	>64	32	>64	32	>64	32	>64	32	>64
S. aureus GC 1131	1	4	2	4	2	4	2	4	1	4	1	4
S. aureus GC 6466	1	1	1	2	1	2	1	2	0.50	2	0.50	2
S. aureus GC 6467	4	4	4	8	4	8	4	32	2	8	2	8
S. aureus GC 1079	2	4	8	8	2	8	2	32	1	4	1	4
S. aureus GC 4536	2	4	2	4	2	4	2	4	1	4	1	4
S. aureus GC 2216	1	4	2	4	1	4	1	4	0.50	4	0.50	4
S. aureus GC 6335	2	4	8	8	2	8	2	8	1	4	1	4
S. aureus GC 6469	2	8	2	4	4	4	4	32	2	16	2	16

TABLE I (Cont)
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYL CYCLINES OF FORMULA I
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Mouse Serum	Water	Mouse Serum	Water	Mouse Serum	Water	Mouse Serum	Water
	Example 1	Example 1	Example 2	Example 2	Example 3	Example 3	Example 4	Example 4
S. epidermidis GC 4935	2	8	8	8	4	8	2	4
E. faecalis GC 4555	1	4	2	4	1	8	1	8
E. faecalis GC 2265	1	4	4	8	2	32	2	8
E. faecalis GC 2267	2	8	4	4	2	32	1	8
E. faecalis GC 2242	1	4	4	4	2	16	1	4
E. faecium GC 4556	1	4	4	8	2	16	1	4
E. faecium GC 2243	1	2	1	4	1	4	0.50	2
S. pneumoniae* GC 4465	0.50	0.25	0.50	0.25	0.12	0.25	<0.06	0.12
S. pneumoniae+ GC 4465	2	2	2	4	1	2	2	4
S. pyogenes GC 4563	0.25	0.50	0.25	0.25	0.12	0.25	0.12	0.25
S. agalactiae GC 4564	0.50	1	2	2	1	2	0.25	0.50
c. albicans GC 3066	>64	>64	>64	>64	>64	>64	>64	>64

TABLE II
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCINES OF FORMULA I
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Mouse Serum Example 5	Water Example 5	Mouse Serum Example 6	Water Example 6	Mouse Serum Example 7	Water Example 7	Mouse Serum Example 8	Water Example 8
E. coli GC 2236	2	16	2	8	0.25	2	1	32
E. coli GC 2231	2	64	2	64	2	16	2	>64
E. coli GC 2235	1	16	1	8	0.50	4	1	16
E. coli GC 2232	2	32	2	32	0.50	4	1	32
E. coli GC 2233	2	32	2	16	0.50	4	1	32
E. coli GC 2234	1	32	1	16	1	4	1	32
E. coli GC 2270	1	16	1	8	0.50	4	1	64
E. coli GC 2271	1	16	1	8	0.50	4	1	32
E. coli GC 2272	1	32	1	16	0.50	4	1	32
E. coli GC 4559	2	32	2	16	1	8	1	64
E. coli GC 4560	0.50	4	0.25	2	0.25	0.50	0.50	4
E. coli GC 6465	8	>64	4	>64	16	>64	8	>64
E. coli GC 3226	2	32	2	16	0.50	8	2	64
E. coli GC 2203	1	32	2	16	0.50	4	1	32
E. coli GC 1073	2	32	2	16	0.50	8	1	32
Salmonella spp. GC 235	2	32	2	16	2	8	4	64
Salmonella spp. GC 566	4	64	4	64	1	16	4	>64

64

TABLE II (Cont)
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYL CYCLINES OF FORMULA I
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Mouse Serum Example 5	Water	Mouse Serum Example 5	Water	Mouse Serum Example 6	Water	Mouse Serum Example 6	Water	Mouse Serum Example 7	Water	Mouse Serum Example 7	Water	Mouse Serum Example 8	Water	Mouse Serum Example 8
<i>S. cholerae</i> GC 1355	16	>64	16	>64	16	>64	16	>64	16	>64	16	>64	32	>64	>64
<i>S. typhimurium</i> GC 2172	8	>64	8	>64	8	>64	4	>64	4	>64	8	>64	8	>64	>64
<i>P. aeruginosa</i> GC 2214	32	>64	32	>64	32	>64	16	>64	16	>64	32	>64	32	>64	>64
<i>S. aureus</i> GC 1131	0.50	1	0.50	1	0.50	1	1	1	1	1	1	1	1	2	2
<i>S. aureus</i> GC 6466	0.25	0.50	0.25	1	0.25	1	0.50	0.50	0.50	0.50	0.50	0.50	0.50	1	1
<i>S. aureus</i> GC 6467	2	4	2	4	2	4	4	4	4	4	4	4	4	8	8
<i>S. aureus</i> GC 1079	2	2	2	4	2	4	1	4	1	4	2	4	2	4	4
<i>S. aureus</i> GC 4536	1	1	0.50	2	0.50	2	1	1	1	1	0.50	1	0.50	2	2
<i>S. aureus</i> GC 2216	0.50	2	0.50	2	0.50	2	0.50	0.50	0.50	0.50	0.50	0.50	0.50	4	4
<i>S. aureus</i> GC 6335	0.50	1	0.50	2	0.50	2	1	1	1	1	1	1	1	4	4
<i>S. aureus</i> GC 6469	2	4	2	4	2	4	2	4	2	4	2	4	2	8	8
<i>S. epidermidis</i> GC 4935	1	2	1	4	1	4	2	4	2	2	2	2	2	8	8

TABLE II (Cont)
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCLOLINES OF FORMULA I
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Mouse Serum		Water		Mouse Serum		Water		Mouse Serum		Water		Mouse Serum		Water	
	Example 5	Example 6	Example 5	Example 6	Example 6	Example 7	Example 7	Example 8	Example 8	Example 8	Example 8	Example 8	Example 8	Example 8	Example 8	Example 8
E. faecalis GC 4555	1	4	1	4	0.50	1	0.50	1	0.50	8						
E. faecalis GC 2265	2	4	2	4	1	2	1	2	2	8						
E. faecalis GC 2267	2	4	1	4	1	2	1	2	2	8						
E. faecalis GC 2242	1	2	1	2	1	1	1	1	1	4						
E. faecium GC 4556	1	2	1	2	0.50	1	0.50	1	1	4						
E. faecium GC 2243	0.50	1	0.50	2	0.25	0.12	0.25	0.12	0.25	2						
S. pneumoniae* GC 4465	<0.06	0.12	0.12	0.25	0.25	0.25	0.25	0.12	<0.06	0.25						
S. pneumoniae+ GC 4465	2	4	2	2	4	2	4	2	1	4						
S. pyogenes GC 4563	0.12	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.12	0.50						
S. agalactiae GC 4564	0.50	0.50	0.50	0.50	0.25	0.50	0.25	0.50	0.25	0.50						
c. albicans GC 3066	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64						

TABLE III
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCLINES OF FORMULA I
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Mouse Serum Example 9	Water Example 9	Mouse Serum Example 10	Water Example 10	Mouse Serum Example 11	Water Example 11	Mouse Serum Example 12	Water Example 12
E. coli GC 2236	1	8	0.50	8	0.50	8	1	16
E. coli GC 2231	2	64	2	32	2	64	2	64
E. coli GC 2235	0.50	4	0.25	4	0.25	4	1	16
E. coli GC 2232	1	8	0.50	8	1	16	0.50	32
E. coli GC 2233	0.50	4	0.50	8	0.25	8	1	32
E. coli GC 2234	0.50	8	0.50	8	0.50	16	1	16
E. coli GC 2270	0.50	4	0.50	8	0.50	8	0.50	32
E. coli GC 2271	0.50	8	0.25	8	0.25	4	0.50	16
E. coli GC 2272	0.50	8	0.50	8	0.25	4	1	16
E. coli GC 4559	1	8	0.50	16	0.50	32	1	64
E. coli GC 4560	0.25	1	0.12	0.12	0.12	0.12	0.25	1
E. coli GC 6465	4	>64	8	>64	8	>64	8	>64
E. coli GC 3226	2	16	0.50	16	0.50	>64	2	64
E. coli GC 2203	0.50	4	0.50	8	0.25	16	1	32
E. coli GC 1073	1	8	0.50	16	0.50	16	1	64
Salmonella spp. GC 235	1	8	0.50	32	0.50	64	1	64
Salmonella spp. GC 566	2	64	2	>64	2	>64	4	>64
S. choleraeius GC 1355	64	>64	16	>64	32	>64	16	>64

TABLE III (Cont)

ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCLINES OF FORMULA I

MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Mouse Serum	Water	Mouse Serum	Water	Mouse Serum	Water	Mouse Serum	Water	Mouse Serum	Water
Example 9	Example 9	Example 9	Example 10	Example 10	Example 11	Example 11	Example 12	Example 12	Example 12	Example 12
S. typhimurium GC 2172	8	>64	4	>64	4	>64	4	>64		
P. aeruginosa GC 2214	16	>64	16	>64	16	>64	32	>64		
S. aureus GC 1131	<0.06	0.25	0.12	0.12	0.25	0.25	1	2		
S. aureus GC 6466	0.12	0.12	0.12	0.12	0.25	0.25	0.50	1		
S. aureus GC 6467	1	2	2	2	4	4	4	16		
S. aureus GC 1079	2	1	0.50	1	2	4	2	8		
S. aureus GC 4536	0.50	0.50	0.25	0.50	0.50	0.50	1	2		
S. aureus GC 2216	0.25	0.50	0.25	0.50	0.50	0.50	1	4		
S. aureus GC 6335	0.25	0.50	0.25	0.50	1	1	1	2		
S. aureus GC 6469	1	2	1	2	4	4	4	16		
S. epidermidis GC 4935	0.25	1	0.50	1	1	2	4	8		
E. faecalis GC 4555	0.50	2	0.50	1	0.50	1	0.50	4		

TABLE III (Cont)
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCLOLINES OF FORMULA I
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	MouseSerum Example 9	Water Example 9	Mouse Serum Example 10	Water Example 10	Mouse Serum Example 11	Water Example 11	Mouse Serum Example 12	Water Example 12
E. faecalis GC 2265	1	2	1	1	2	4	2	8
E. faecalis GC 2267	1	2	1	2	2	2	2	8
E. faecalis GC 2242	0.50	1	0.25	0.50	0.25	0.50	2	4
E. faecium GC 4556	0.25	0.50	0.25	0.50	0.25	0.50	1	4
E. faecium GC 2243	0.25	0.50	<0.06	0.12	0.12	0.25	0.50	4
S. pneumoniae* GC 4465	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	0.12
S. pneumoniae+ GC 4465	2	2	1	1	2	2	4	8
S. pyogenes GC 4563	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	0.12	0.25
S. agalactiae GC 4564	0.12	0.25	<0.06	0.12	<0.06	<0.06	0.25	0.25
c. albicans GC 3066	>64	>64	>64	>64	>64	>64	>64	>64

TABLE IV
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCLOLINES OF FORMULA I
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Mouse Serum Example 13	Water	Mouse Serum	Water	Mouse Serum	Water	Mouse Serum	Water	Example 15	Example 16	Example 15	Example 16	Example 15	Example 16
		Example 13	Example 14	Example 14	Example 14	Example 15	Example 15	Example 15	Example 15	Example 16	Example 16	Example 16	Example 16	Example 16
E. coli GC 2236	2	8	>64	>64	>64	>64	>64	64	>64	64	>64	>64	>64	>64
E. coli GC 2231	2	16	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2235	2	8	32	>64	64	32	>64	32	64	16	>64	64	64	64
E. coli GC 2232	2	8	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2233	2	8	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2234	1	8	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2270	1	8	>64	>64	>64	64	64	64	64	>64	>64	>64	>64	>64
E. coli GC 2271	2	8	>64	>64	>64	64	64	64	64	>64	>64	>64	>64	>64
E. coli GC 2272	2	8	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 4559	4	16	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 4560	1	4	4	4	4	1	1	1	1	2	2	4	4	4
E. coli GC 6465	8	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 3226	2	16	>64	>64	>64	>64	>64	>64	>64	64	64	>64	>64	>64
E. coli GC 2203	2	8	32	>64	64	32	>64	64	64	16	16	64	64	64
E. coli GC 1073	2	16	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Salmonella spp. GC 235	2	16	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64

TABLE IV (Cont)							
Mouse Serum	Water	Mouse Serum	Water	Mouse Serum	Water	Mouse Serum	Water
Example 13	Example 13	Example 14	Example 14	Example 15	Example 15	Example 16	Example 16
Salmonella spp.							
GC 566	8	64	>64	>64	>64	>64	>64
S. cholerae							
GC 1355	16	>64	>64	>64	>64	>64	>64

TABLE IV (Cont)

ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCLINES OF FORMULA I

MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Mouse Serum		Water		Mouse Serum		Water		Mouse Serum		Water		Mouse Serum		Water	
	Example 13	Example 13	Example 13	Example 13	Example 14	Example 14	Example 14	Example 14	Example 15	Example 15	Example 15	Example 15	Example 16	Example 16	Example 16	Example 16
S. typhimurium GC 2172	8	64			>64			>64					>64			>64
P. aeruginosa GC 2214	32		>64		>64			>64					>64			>64
S. aureus GC 1131	2	2			1			2					2			4
S. aureus GC 6466	1	2			2			8					4			8
S. aureus GC 6467	4	8			2			4					16			8
S. aureus GC 1079	4	4			1			2					2			4
S. aureus GC 4536	1	2			2			2					2			4
S. aureus GC 2216	2	4			2			4					2			4
S. aureus GC 6335	2	4			1			4					4			4
S. aureus GC 6469	4	8			2			4					4			8
S. epidermidis GC 4935	4	8			8			8					16			8
E. faecalis GC 4555	2	4			2			8					4			8

TABLE IV (Cont)

ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCCLINES OF FORMULA I

MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Mouse Serum		Water		Mouse Serum		Water		Mouse Serum		Water		Mouse Serum		Water	
	Example 13	Example 13	Example 13	Example 13	Example 14	Example 14	Example 14	Example 14	Example 15	Example 15	Example 15	Example 15	Example 16	Example 16	Example 16	Example 16
E. faecalis GC 2265	4	8	8	2	8	8	8	8	8	8	8	8	4	4	8	8
E. faecalis GC 2267	4	8	8	2	8	8	8	8	8	8	8	8	4	4	8	8
E. faecalis GC 2242	4	8	8	2	8	8	8	8	8	8	8	8	8	8	8	8
E. faecium GC 4556	2	8	8	4	8	8	8	8	8	8	8	8	4	4	8	8
E. faecium GC 2243	2	4	4	2	4	4	4	4	8	8	8	8	4	4	8	8
S. pneumoniae* GC 4465	0.50	0.50	0.50	2	4	4	4	4	2	2	2	2	4	4	4	4
S. pneumoniae+ GC 4465	8	8	8	4	4	4	4	4	4	4	4	4	8	8	8	8
S. pyogenes GC 4563	0.50	1	1	2	4	4	4	4	2	2	2	2	4	4	8	8
S. agalactiae GC 4564	1	2	2	16	16	16	16	16	8	8	8	8	16	16	16	16
c. albicans GC 3066	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64

22

23

TABLE V

ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYL CYCLINES OF FORMULA I

MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Mouse Serum Example 21	Water Example 21	Mouse Serum Example 22	Water Example 22	Mouse Serum Example 23	Water Example 23	Mouse Serum Example 24	Water Example 24
E. coli GC 2236	1	>64	2	>64	2	>64	1	>64
E. coli GC 2231	1	>64	2	>64	2	>64	2	>64
E. coli GC 2235	0.50	>64	1	>64	1	>64	0.50	>64
E. coli GC 2232	1	>64	2	>64	1	>64	0.50	>64
E. coli GC 2233	1	>64	2	>64	2	>64	1	>64
E. coli GC 2234	0.50	>64	1	>64	1	>64	0.50	>64
E. coli GC 2270	1	>64	1	>64	1	>64	0.50	>64
E. coli GC 2271	0.50	>64	1	>64	1	>64	0.50	>64
E. coli GC 2272	1	>64	1	>64	1	>64	1	>64
E. coli GC 4559	1	>64	2	>64	2	>64	1	>64
E. coli GC 4560	0.25	>64	0.50	>64	0.50	8	0.25	64
E. coli GC 6465	4	>64	8	>64	4	>64	8	>64
E. coli GC 3226	8	>64	8	>64	8	>64	1	>64
E. coli GC 2203	0.50	>64	1	>64	1	>64	0.50	>64
E. coli GC 1073	1	>64	2	>64	1	>64	1	>64
Salmonella spp. GC 235	2	>64	2	>64	2	>64	1	>64
Salmonella spp. GC 566	4	>64	4	>64	4	>64	2	>64
S. cholerae GC 1355	16	>64	16	>64	16	>64	32	>64

TABLE V (CONT)

ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYL CYCLINES OF FORMULA I

MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Mouse Serum		Water		Mouse Serum		Water		Mouse Serum		Water		Mouse Serum		Water	
	Example 21	Example 21	Example 21	Example 21	Example 22	Example 22	Example 22	Example 22	Example 23	Example 23	Example 23	Example 23	Example 24	Example 24	Example 24	Example 24
S. typhimurium GC 2172	4	>64	>64	8	>64	>64	>64	4	>64	>64	>64	>64	8	>64	>64	>64
P. aeruginosa GC 2214	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	16	>64	>64	>64
S. aureus GC 1131	1	64	64	1	64	64	64	1	64	64	64	64	1	64	64	2
S. aureus GC 6466	1	64	64	0.50	64	64	64	0.25	64	64	64	64	0.25	64	64	0.50
S. aureus GC 6467	4	>64	>64	4	>64	>64	>64	4	>64	>64	>64	>64	4	>64	>64	>64
S. aureus GC 1079	4	>64	>64	2	>64	>64	>64	2	>64	>64	>64	>64	2	>64	>64	>64
S. aureus GC 4536	2	32	32	1	32	32	32	1	32	32	32	32	1	32	32	4
S. aureus GC 2216	1	64	64	1	64	64	64	1	64	64	64	64	0.50	64	64	4
S. aureus GC 6335	2	64	64	2	64	64	64	2	64	64	64	64	2	64	64	16
S. aureus GC 6469	4	>64	>64	4	>64	>64	>64	4	>64	>64	>64	>64	4	>64	>64	>64
S. epidermidis GC 4935	2	64	64	2	64	64	64	2	64	64	64	64	2	64	64	16
E. faecalis GC 4555	1	64	64	2	64	64	64	1	64	64	64	64	1	64	64	64
E. faecalis GC 2265	1	64	64	2	64	64	64	1	64	64	64	64	2	64	64	32
E. faecalis GC 2267	2	64	64	4	64	64	64	2	64	64	64	64	4	64	64	64
E. faecalis GC 2242	2	32	32	2	32	32	32	2	32	32	32	32	2	32	32	4
E. faecium GC 4556	2	64	64	2	64	64	64	2	64	64	64	64	1	64	64	32
E. faecium GC 2243	0.50	8	8	1	8	8	8	0.50	8	8	8	8	0.50	8	8	2
S. pneumoniae* GC 4465	0.25	0.50	0.50	0.50	0.50	0.50	0.50	0.12	0.50	0.50	0.50	0.50	<0.06	<0.06	<0.06	<0.06

79

TABLE V (CONT)

ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCCLINES OF FORMULA I

MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Mouse Serum	Water Example	Mouse Serum	Water Example	Mouse Serum	Water	Mouse Serum	Water
	Example 21	21	Example 22	22	Example 23	Example 23	Example 24	Example 24
S. pneumoniae+ GC 4465	4	4	4	16	4	8	2	1
S. pyogenes GC 4563	0.25	0.12	0.50	1	0.12	0.25	<0.06	<0.06
S. agalactiae GC 4564	0.50	8	1	8	0.25	0.25	0.50	8
c. albicans GC 3066	>64	>64	>64	>64	>64	>64	>64	>64

TABLE VI
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCLINES OF FORMULA I
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Mouse Serum Example 25	Water Example 25	Mouse Serum Example 26	Water Example 26	Mouse Serum Example 27	Water Example 27	Mouse Serum Example 28	Water Example 28
E. coli GC 2236	2	64	2	>64	0.50	64	0.50	>64
E. coli GC 2231	2	>64	4	>64	1	>64	1	>64
E. coli GC 2235	1	32	1	64	0.50	64	0.50	>64
E. coli GC 2232	1	>64	1	>64	0.50	64	0.50	>64
E. coli GC 2233	2	32	2	>64	0.50	64	0.50	>64
E. coli GC 2234	1	>64	1	>64	0.50	64	0.25	>64
E. coli GC 2270	1	>64	1	>64	0.50	64	0.50	>64
E. coli GC 2271	1	32	1	>64	0.50	64	0.25	>64
E. coli GC 2272	2	64	2	64	0.50	32	0.50	>64
E. coli GC 4559	2	>64	2	>64	0.50	>64	0.50	>64
E. coli GC 4560	0.50	2	0.50	8	0.25	1	0.25	>64
E. coli GC 6465	8	>64	8	>64	4	>64	8	>64
E. coli GC 3226	2	>64	2	>64	0.50	>64	0.50	>64
E. coli GC 2203	1	>64	1	>64	0.50	>64	0.50	>64
E. coli GC 1073	2	>64	2	>64	0.50	>64	0.50	>64
Salmonella spp. GC 235	2	>64	2	>64	1	>64	0.50	>64
Salmonella spp. GC 566	4	>64	4	>64	1	>64	2	>64
S. cholerae GC 1355	32	>64	32	>64	16	>64	16	>64

27

TABLE VI (CONT)

ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCINES OF FORMULA I

MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Mouse Serum Example 25	Water Example 25	Mouse Serum Example 26	Water Example 26	Mouse Serum Example 27	Water Example 27	Mouse Serum Example 28	Water Example 28
S. typhimurium GC 2172	8	>64	16	>64	4	>64	8	>64
P. aeruginosa GC 2214	32	>64	32	>64	8	>64	16	>64
S. aureus GC 1131	0.50	0.50	0.50	0.50	0.12	0.25	0.50	32
S. aureus GC 6466	0.25	0.25	0.25	0.25	0.12	0.25	0.50	4
S. aureus GC 6467	2	2	1	4	2	2	4	64
S. aureus GC 1079	1	2	1	2	1	2	2	64
S. aureus GC 4536	0.50	0.50	0.25	0.50	0.12	0.12	0.50	32
S. aureus GC 2216	0.50	1	0.50	0.50	0.25	0.25	0.50	32
S. aureus GC 6335	0.50	0.50	0.50	1	0.25	0.50	1	16
S. aureus GC 6469	2	4	1	2	1	2	4	64
S. epidermidis GC 4935	1	2	1	2	0.25	1	1	32
E. faecalis GC 4555	1	2	1	4	0.25	1	0.25	64
E. faecalis GC 2265	2	2	2	8	1	2	2	64
E. faecalis GC 2267	2	4	2	4	1	2	2	64
E. faecalis GC 2242	2	2	2	4	0.50	0.50	0.50	4
E. faecium GC 4556	1	4	1	4	0.50	1	0.50	32
E. faecium GC 2243	0.50	1	1	2	0.12	0.25	0.25	0.25
S. pneumoniae* GC 4465	0.12	0.25	0.25	0.25	<0.06	<0.06	<0.06	<0.06

TABLE VI (CONT)

ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYL CYCLINES OF FORMULA I

MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Mouse Serum Water	Example 25	Mouse Serum Water	Example 26	Mouse Serum Water	Example 27	Mouse Serum Water	Example 28	Water
	Example 25	Example 25	Example 26	Example 26	Example 27	Example 27	Example 28	Example 28	Example 28
S. pneumoniae+ GC 4465	4	4	4	4	1	2	2	0.50	
S. pyogenes GC 4563	0.12	0.25	0.25	<0.06	<0.06	<0.06	<0.06	<0.06	
S. agalactiae GC 4564	0.50	0.50	1	2	0.12	0.12	0.25	0.50	
c. albicans GC 3066	>64	>64	>64	>64	>64	>64	>64	>64	

78

29

TABLE VII
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCINES OF FORMULA I
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Water	Mouse Serum	Mouse Serum	Water	Mouse Serum	Human Serum	Water	Mouse Serum	Human Serum
	Example 42	Example 42	Example 42	Example 43	Example 43	Example 43	Example 44	Example 44	Example 44
E. coli GC 2236	>64	4	>64	>64	0.50	>64	>64	2	>64
E. coli GC 2231	>64	4	>64	>64	0.50	>64	>64	2	>64
E. coli GC 2235	>64	4	>64	>64	0.25	>64	>64	2	>64
E. coli GC 2232	>64	4	>64	>64	0.50	>64	>64	2	>64
E. coli GC 2233	>64	4	>64	>64	0.50	>64	>64	2	>64
E. coli GC 2234	>64	4	>64	>64	0.25	>64	>64	2	>64
E. coli GC 2270	>64	4	>64	>64	0.25	>64	>64	2	>64
E. coli GC 2271	>64	4	>64	>64	0.25	>64	>64	2	>64
E. coli GC 2272	>64	4	>64	>64	0.50	>64	>64	2	>64
E. coli GC 4559	>64	8	>64	>64	0.50	>64	>64	4	>64
E. coli GC 4560	8	2	8	32	<0.06	16	4	2	4
E. coli GC 6465	>64	16	>64	>64	2	>64	>64	8	>64
E. coli GC 3226	>64	16	>64	>64	1	>64	>64	4	>64
E. coli GC 2203	>64	8	>64	>64	0.50	>64	>64	2	>64
E. coli GC 1073	>64	8	>64	>64	0.50	>64	>64	4	>64
Salmonella spp. GC 235	>64	16	>64	>64	0.50	>64	>64	4	>64
Salmonella spp. GC 566	>64	32	>64	>64	2	>64	>64	8	>64

TABLE VII (CONT)

ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCLINES OF FORMULA I

MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Water	Mouse Serum	Mouse Serum	Water	Mouse Serum	Human Serum	Water	Mouse Serum	Human Serum
	Example 42	Example 42	Example 42	Example 42	Example 43	Example 43	Example 43	Example 44	Example 44
S. cholerae GC 1355	>64	64	>64	>64	4	>64	>64	16	>64
S. typhimurium GC 2172	>64	64	>64	>64	2	>64	>64	8	>64
P. aeruginosa GC 2214	>64	>64	>64	>64	16	>64	>64	>64	>64
S. aureus GC 1131	4	2	2	64	1	16	4	2	2
S. aureus GC 6466	4	2	4	64	0.50	16	2	2	2
S. aureus GC 6467	8	4	4	>64	0.50	32	4	2	2
S. aureus GC 1079	4	2	4	64	1	32	4	2	2
S. aureus GC 4536	8	2	4	32	1	16	4	2	2
S. aureus GC 2216	4	2	2	64	0.50	32	2	2	2
S. aureus GC 6335	4	2	4	64	1	64	4	2	4
S. aureus GC 6469	4	2	4	>64	1	32	4	2	2

81

TABLE VII (CONT)											
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCLOLINES OF FORMULA I											
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)											
Water	Mouse Serum	Mouse Serum	Water	Mouse Serum	Human Serum	Water	Mouse Serum	Human Serum	Water	Mouse Serum	Human Serum
Example 42	Example 42	Example 42	Example 42	Example 43	Example 43	Example 43	Example 43	Example 43	Example 44	Example 44	Example 44
S. epidermidis GC 4935	8	4	32	2	4	4	4	4	4	2	4
E. faecalis GC 4555	4	2	32	0.50	8	8	8	4	4	2	4
E. faecalis GC 2265	8	2	32	0.50	8	8	8	4	4	2	2
E. faecalis GC 2267	4	2	32	0.50	4	4	4	4	4	2	4
E. faecalis GC 2242	8	4	16	0.50	4	4	4	4	4	2	4
E. faecium GC 4556	8	2	16	0.50	8	8	8	4	4	2	4
E. faecium GC 2243	4	2	0.25	0.12	0.25	0.25	0.25	4	4	2	4
S. pneumoniae* GC 4465	4	2	0.50	<0.06	1	1	1	2	2	1	2
S. pneumoniae+ GC 4465	8	4	2	2	2	2	2	4	4	4	4
S. pyogenes GC 4563	4	2	<0.06	<0.06	<0.06	<0.06	<0.06	2	2	1	4
S. agalactiae GC 4564	8	2	2	<0.06	2	2	2	4	4	1	4
c. albicans GC 3066	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64

TABLE VIII
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYL CYCLINES OF FORMULA I
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Water	Mouse Serum	Human Serum	Water	Mouse Serum	Human Serum	Water	Mouse Serum	Human Serum
	Example 45	Example 45	Example 45	Example 46	Example 46	Example 46	Example 47	Example 47	Example 47
E. coli GC 2236	16	1	4	64	0.50	4	>64	1	32
E. coli GC 2231	32	1	4	64	0.50	4	>64	1	32
E. coli GC 2235	16	0.50	4	64	0.50	4	>64	1	16
E. coli GC 2232	16	1	4	64	0.50	4	>64	1	16
E. coli GC 2233	16	1	4	64	0.50	4	>64	0.50	16
E. coli GC 2234	16	0.50	4	64	0.50	4	>64	1	16
E. coli GC 2270	32	0.50	4	>64	0.50	4	>64	0.50	16
E. coli GC 2271	16	0.50	4	64	0.50	4	>64	1	16
E. coli GC 2272	16	1	8	64	1	4	>64	1	16
E. coli GC 4559	64	1	8	>64	1	8	>64	2	64
E. coli GC 4560	2	0.25	0.50	4	0.50	1	16	1	4
E. coli GC 6465	>64	2	16	>64	2	16	>64	2	>64
E. coli GC 3226	64	1	8	>64	1	16	>64	2	32
E. coli GC 2203	32	0.50	4	>64	0.50	8	>64	1	32
E. coli GC 1073	64	1	8	>64	1	8	>64	2	32
Salmonella spp. GC 235	>64	1	8	>64	1	16	>64	2	64
Salmonella spp. GC 566	>64	2	32	>64	2	16	>64	4	>64

TABLE VIII (CONT)

ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYL CYCLINES OF FORMULA I

MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Water		Mouse Serum		Human Serum		Water		Human Serum		Water		Mouse Serum		Human Serum		Water		Mouse Serum		Human Serum	
	Example 45	Example 45	Example 45	Example 45	Example 45	Example 45	Example 46	Example 46	Example 46	Example 46	Example 47	Example 47	Example 47	Example 47	Example 47	Example 47	Example 47	Example 47	Example 47	Example 47	Example 47	Example 47
S. cholerae	>64	4	32	>64	2	32	>64	2	32	>64	4	>64	4	>64	4	>64	4	>64	4	>64	4	>64
S. typhimurium	>64	2	32	>64	2	32	>64	2	32	>64	4	>64	4	>64	4	>64	4	>64	4	>64	4	>64
P. aeruginosa	>64	16	>64	>64	16	>64	>64	16	>64	>64	32	>64	32	>64	32	>64	32	>64	32	>64	32	>64
S. aureus GC 1131	1	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	2	2	2	2	2	2	2	2	2	2	2	2
S. aureus GC 6466	0.50	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	1	1	1	1	1	1	1	1	1	1	1	1
S. aureus GC 6467	2	1	1	1	1	1	1	1	1	1	4	4	4	4	4	4	4	4	4	4	4	4
S. aureus GC 1079	1	0.50	0.12	0.50	0.50	0.50	0.50	0.50	0.50	0.50	2	2	2	2	2	2	2	2	2	2	2	2
S. aureus GC 4536	1	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	4	4	4	4	4	4	4	4	4	4	4	4
S. aureus GC 2216	1	1	0.50	1	0.50	0.50	1	0.50	0.50	0.50	2	2	2	2	2	2	2	2	2	2	2	2
S. aureus GC 6335	2	1	0.50	1	1	0.50	1	1	0.50	0.50	2	2	2	2	2	2	2	2	2	2	2	2
S. aureus GC 6469	1	1	0.50	1	1	0.50	1	1	0.50	0.50	4	4	4	4	4	4	4	4	4	4	4	4
S. epidermidis GC 4935	2	1	1	2	1	1	2	1	1	1	4	4	4	4	4	4	4	4	4	4	4	4

TABLE VIII (CONT)
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCINES OF FORMULA I
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Water		Mouse Serum		Human Serum		Water		Human Serum		Water		Mouse Serum		Human Serum	
	Example 45	Example 45	Example 45	Example 45	Example 46	Example 46	Example 46	Example 46	Example 46	Example 46	Example 47	Example 47	Example 47	Example 47	Example 47	Example 47
E. faecalis GC 4555	2	1	2	2	0.50	0.50	0.50	0.50	0.50	0.50	4	4	1	1	4	4
E. faecalis GC 2265	4	0.50	1	2	0.50	0.50	0.50	0.50	0.50	0.50	4	4	1	1	4	4
E. faecalis GC 2267	2	0.50	1	2	0.50	0.50	0.50	0.50	0.50	0.50	4	4	1	1	4	4
E. faecalis GC 2242	2	1	1	1	0.50	0.50	0.50	0.50	0.50	0.50	4	4	1	1	4	4
E. faecium GC 4556	2	1	1	1	0.50	0.50	0.50	0.50	0.50	0.50	4	4	1	1	4	4
E. faecium GC 2243	2	0.50	1	0.50	0.25	0.25	0.25	0.25	0.25	0.25	2	2	0.50	0.50	2	2
S. pneumoniae* GC 4465	0.50	0.25	0.25	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.50	0.50	0.25	0.25	0.50	0.50
S. pneumoniae+ GC 4465	4	2	2	1	1	1	1	1	1	1	4	4	2	2	2	2
S. pyogenes GC 4563	0.50	0.25	0.25	0.25	0.25	0.12	0.12	0.12	0.25	0.25	0.25	0.25	0.12	0.12	0.25	0.25
S. agalactiae GC 4564	0.50	0.25	0.50	0.25	0.25	0.25	0.25	0.25	0.25	0.25	1	1	0.50	0.50	1	1
c. albicans GC 3066	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64

TABLE IX
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCLYCINES OF FORMULA I
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Water Example 48	Mouse Serum Example 48	Human Serum Example 48	Water Example 49	Mouse Serum Example 49	Human Serum Example 49	Water Example 50	Mouse Serum Example 50	Human Serum Example 50
E. coli GC 2236	64	0.25	16	16	0.50	4	32	1	8
E. coli GC 2231	64	0.50	16	16	0.50	8	64	1	8
E. coli GC 2235	32	0.25	16	8	0.50	4	32	1	4
E. coli GC 2232	64	0.25	16	16	0.50	4	32	1	8
E. coli GC 2233	64	0.25	16	8	0.25	4	32	1	8
E. coli GC 2234	64	0.50	16	16	0.25	4	64	1	8
E. coli GC 2270	64	0.50	16	16	0.50	4	32	1	8
E. coli GC 2271	32	0.25	8	8	0.25	4	32	1	4
E. coli GC 2272	64	0.25	8	8	0.50	2	32	1	4
E. coli GC 4559	>64	0.25	32	16	0.50	8	64	2	16
E. coli GC 4560	2	0.12	1	1	0.12	0.50	4	0.50	2
E. coli GC 6465	>64	2	>64	>64	2	32	>64	2	16
E. coli GC 3226	>64	0.50	32	16	0.50	8	32	1	8
E. coli GC 2203	64	0.25	16	8	0.25	4	32	1	8
E. coli GC 1073	64	0.50	32	32	0.50	8	32	2	8
Salmonella spp. GC 235	>64	0.50	32	32	1	16	>64	2	32
Salmonella spp. GC 566	>64	2	>64	64	2	32	>64	4	32
S. cholerae GC 1355	>64	4	>64	>64	4	64	>64	4	64

TABLE IX (CONT)

ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCLOLINES OF FORMULA I

MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Water		Mouse Serum		Human Serum		Water		Mouse Serum		Human Serum		Water		Mouse Serum		Human Serum	
	Example 48	Example 48	Example 48	Example 48	Example 48	Example 48	Example 49	Example 49	Example 49	Example 49	Example 49	Example 49	Example 50	Example 50	Example 50	Example 50	Example 50	Example 50
S. typhimurium GC 2172	>64	4	>64	>64	>64	>64	>64	4	32	>64	4	32	>64	>64	4	32	>64	>64
P. aeruginosa GC 2214	>64	16	>64	>64	>64	>64	>64	32	>64	>64	32	>64	>64	>64	32	>64	>64	>64
S. aureus GC 1131	0.25	0.25	0.25	0.25	0.25	0.25	0.50	0.50	0.50	0.50	0.50	0.50	1	0.50	0.50	0.50	0.50	0.50
S. aureus GC 6466	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.25	0.25	0.25	0.25	0.25	0.25
S. aureus GC 6467	2	1	0.50	0.50	2	0.50	2	1	1	2	0.25	1	2	0.25	0.25	0.25	0.25	0.25
S. aureus GC 1079	1	0.25	0.25	0.25	0.50	0.25	0.50	0.50	0.50	2	0.50	0.50	2	0.50	0.50	0.50	0.50	0.50
S. aureus GC 4536	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.50	0.25	0.25	0.50	0.25	0.25	0.25	0.25	0.25
S. aureus GC 2216	0.50	0.25	0.25	0.25	0.50	0.25	0.50	0.25	0.25	2	0.25	0.25	2	1	0.25	0.50	0.50	0.50
S. aureus GC 6335	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1
S. aureus GC 6469	1	0.50	1	1	1	1	1	1	1	2	1	1	2	1	1	1	1	1
S. epidermidis GC 4935	1	0.50	0.50	0.50	2	0.50	2	1	1	4	2	1	4	2	2	2	2	2
E. faecalis GC 4555	2	0.12	4	4	4	4	4	0.25	0.50	4	0.25	0.50	4	1	1	2	2	2

TABLE IX (CONT)

ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCLINES OF FORMULA I

MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Water Example 48	Mouse Serum Example 48	Human Serum Example 48	Water Example 49	Mouse Serum Example 49	Human Serum Example 49	Water Example 50	Mouse Serum Example 50	Human Serum Example 50
E. faecalis GC 2265	2	0.50	1	2	0.50	1	4	1	2
E. faecalis GC 2267	2	0.50	1	4	0.50	1	4	1	2
E. faecalis GC 2242	1	0.50	1	2	0.50	1	2	1	1
E. faecium GC 4556	1	0.50	1	2	0.50	1	2	1	1
E. faecium GC 2243	0.50	0.25	0.25	0.50	0.25	0.25	0.50	0.25	0.25
S. pneumoniae* GC 4465	0.12	0.12	0.12	0.12	0.12	0.12	<0.06	<0.06	<0.06
S. pneumoniae+ GC 4465	0.25	0.25	0.25	1	1	1	0.50	0.50	0.50
S. pyogenes GC 4563	0.12	0.12	0.12	0.12	0.12	0.12	0.25	0.12	0.12
S. agalactiae GC 4564	0.12	0.12	0.12	0.25	0.12	0.12	0.25	0.25	0.25
c. albicans GC 3066	>64	>64	>64	>64	>64	>64	>64	>64	>64

83

TABLE X (CONT)

ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYL CYCLINES OF FORMULA I

MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Water		Mouse Serum		Human Serum		Water		Human Serum		Water		Mouse Serum		Human Serum	
	Example 51	Example 51	Example 51	Example 51	Example 51	Example 51	Example 52	Example 52	Example 52	Example 52	Example 53	Example 53	Example 53	Example 53	Example 53	Example 53
P. aeruginosa GC 2214	>64	64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
S. aureus GC 1131	1	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
S. aureus GC 6466	1	0.25	0.25	0.25	0.25	0.25	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
S. aureus GC 6467	2	0.50	1	1	1	1	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
S. aureus GC 1079	2	0.50	1	1	1	1	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
S. aureus GC 4536	1	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
S. aureus GC 2216	1	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
S. aureus GC 6335	1	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
S. aureus GC 6469	2	1	1	1	1	1	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
S. epidermidis GC 4935	4	2	2	2	2	2	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
E. faecalis GC 4555	16	1	8	8	8	8	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
E. faecalis GC 2265	8	1	4	4	4	4	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
E. faecalis GC 2267	16	2	4	4	4	4	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50

89

TABLE X (CONT)

ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCILCYCLINES OF FORMULA I

MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Water	Mouse Serum	Human Serum	Water Example 52	Mouse Serum Example 52	Human Serum Example 52	Water Example 53	Mouse Serum Example 53	Human Serum Example 53

E. faecalis GC 2242	8	2	4	4	0.50	4	2	0.50	2
E. faecium GC 4556	8	2	8	4	0.50	2	2	0.50	2
E. faecium GC 2243	4	1	4	1	0.25	1	0.50	0.25	0.25
S. pneumoniae* GC 4465	1	0.50	2	0.12	<0.06	0.25	0.12	0.12	0.25
S. pneumoniae+ GC 4465	1	1	2	2	1	4	2	2	1
S. pyogenes GC 4563	2	0.50	2	0.25	0.12	0.25	0.25	0.12	0.25
S. agalactiae GC 4564	2	1	4	0.50	0.12	0.50	0.50	<0.06	0.50
c. albicans GC 3066	>64	>64	>64	>64	>64	>64	>64	>64	>64

TABLE XI
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCLOLINES OF FORMULA I
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Water	Mouse Serum	Human Serum	Water	Mouse Serum	Human Serum	Water	Mouse Serum	Human Serum
	Example 58	Example 58	Example 58	Example 59	Example 59	Example 59	Example 60	Example 60	Example 60
E. coli GC 2236	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2231	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2235	>64	>64	>64	>64	>64	>64	>64	64	64
E. coli GC 2232	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2233	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2234	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2270	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2271	>64	>64	>64	>64	>64	>64	>64	64	64
E. coli GC 2272	>64	>64	>64	>64	64	>64	64	32	32
E. coli GC 4559	>64	>64	>64	>64	64	>64	>64	>64	>64
E. coli GC 4560	4	4	4	4	4	4	2	1	1
E. coli GC 6465	>64	>64	>64	>64	32	>64	>64	>64	>64
E. coli GC 3226	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2203	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 1073	>64	>64	>64	>64	>64	>64	>64	>64	>64
Salmonella spp. GC 235	>64	>64	>64	>64	>64	>64	>64	>64	>64
Salmonella spp. GC 566	>64	>64	>64	>64	>64	>64	>64	>64	>64
S. choleraeius GC 1355	>64	>64	>64	>64	>64	>64	>64	>64	>64
S. typhimurium GC 2172	>64	>64	>64	>64	>64	>64	>64	>64	>64

TABLE XI (CONT)

ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCCLINES OF FORMULA I

MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Water	Mouse Serum	Human Serum	Water	Example 59	Mouse Serum	Human Serum	Water	Example 60	Mouse Serum	Human Serum
	Example 58	Example 58	Example 58	Example 58	Example 59	Example 59	Example 59	Example 60	Example 60	Example 60	Example 60
P. aeruginosa GC 2214	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
S. aureus GC 1131	4	2	4	4	4	4	4	8	8	2	2
S. aureus GC 6466	4	2	4	8	8	4	4	8	8	4	4
S. aureus GC 6467	4	2	4	4	4	4	4	8	8	4	4
S. aureus GC 1079	8	2	4	8	8	4	2	4	4	2	2
S. aureus GC 4536	4	2	4	4	4	4	4	4	4	2	2
S. aureus GC 2216	4	2	4	4	4	4	4	4	4	2	2
S. aureus GC 6335	4	4	4	4	4	4	4	8	8	8	8
S. aureus GC 6469	4	2	4	4	4	4	4	4	4	2	2
S. epidermidis GC 4935	8	4	4	4	4	4	4	16	16	8	8
E. faecalis GC 4555	8	4	4	4	4	4	4	4	4	4	2
E. faecalis GC 2265	4	4	4	4	4	4	4	8	8	8	4
E. faecalis GC 2267	4	2	4	4	4	4	4	8	8	8	4
E. faecalis GC 2242	4	2	4	4	4	2	4	8	8	8	4
E. faecium GC 4556	4	2	4	4	4	4	4	4	4	4	4
E. faecium GC 2243	4	2	4	4	4	4	8	4	4	2	2
S. pneumoniae* GC 4465	2	2	4	4	4	4	4	2	2	1	1
S. pneumoniae+ GC 4465	8	4	4	8	8	4	8	4	4	4	2
S. pyogenes GC 4563	4	4	4	4	4	4	4	2	2	1	0.50
S. agalactiae GC 4564	8	8	16	8	8	8	8	4	4	4	4
c. albicans GC 3066	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64

92

93

TABLE XII
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCLOLINES OF FORMULA I
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Water Example 61	Mouse Serum Example 61	Human Serum Example 61	Water Example 62	Mouse Serum Example 62	Human Serum Example 62	Water Example 63	Mouse Serum Example 63	Human Serum Example 63
E. coli GC 2236	16	0.50	4	4	0.50	8	>64	1	>64
E. coli GC 2231	32	1	8	8	0.50	4	>64	1	>64
E. coli GC 2235	16	0.50	4	4	0.50	2	>64	0.50	>64
E. coli GC 2232	16	0.50	4	8	1	2	>64	1	>64
E. coli GC 2233	16	1	8	8	2	4	>64	1	>64
E. coli GC 2234	16	0.50	8	8	1	2	>64	1	64
E. coli GC 2270	16	0.50	4	8	0.50	2	>64	0.50	64
E. coli GC 2271	16	0.50	4	4	1	2	>64	0.50	>64
E. coli GC 2272	8	0.50	4	8	1	4	>64	1	>64
E. coli GC 4559	64	1	8	16	1	8	>64	2	>64
E. coli GC 4560	1	0.25	1	0.50	0.25	0.50	16	0.50	2
E. coli GC 6465	>64	1	32	>64	2	8	>64	2	>64
E. coli GC 3226	32	0.50	8	8	1	4	>64	1	>64
E. coli GC 2203	32	0.50	8	16	1	4	>64	1	>64
E. coli GC 1073	32	0.50	8	16	0.50	4	>64	2	>64
Salmonella spp. GC 235	>64	1	16	>64	1	8	>64	1	>64
Salmonella spp. GC 566	>64	1	32	>64	1	16	>64	1	>64
S. choleraesuis GC 1355	>64	2	64	>64	2	32	>64	2	>64

94

TABLE XII (CONT)
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCLOLINES OF FORMULA I
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Water		Mouse Serum		Human Serum		Water		Mouse Serum		Human Serum		Water		Mouse Serum		Human Serum	
	Example 61	Example 61	Example 61	Example 61	Example 61	Example 61	Example 62	Example 62	Example 62	Example 62	Example 62	Example 62	Example 63	Example 63	Example 63	Example 63	Example 63	Example 63
S. typhimurium GC 2172	>64	1		64	>64	>64	2	16	>64	2	>64	>64			2	>64		
P. aeruginosa GC 2214	>64	8		>64	>64	>64	16	>64	>64	32	>64	>64			32	>64		
S. aureus GC 1131	0.50	0.50		0.50	0.50	0.50	0.50	0.50	0.50	1	0.50	0.50	4		1	1		
S. aureus GC 6466	0.50	0.50		0.50	0.25	0.50	0.50	0.50	0.50	0.50	0.50	0.50	2		0.50	1		
S. aureus GC 6467	1	0.50		0.50	0.50	0.50	1	0.50	0.50	2	0.50	0.50	16		2	4		
S. aureus GC 1079	1	0.25		0.50	0.50	0.50	1	0.50	0.50	8	0.50	0.50	8		1	2		
S. aureus GC 4536	0.50	0.50		0.50	0.50	0.50	0.50	0.50	0.50	4	0.50	0.50	4		1	1		
S. aureus GC 2216	1	0.50		0.50	0.50	0.50	0.50	0.50	0.50	4	0.50	0.50	4		1	1		
S. aureus GC 6335	1	0.50		1	0.50	0.50	1	0.50	0.50	4	0.50	0.50	4		1	1		
S. aureus GC 6469	2	0.50		0.50	1	0.50	1	0.50	0.50	16	0.50	0.50	16		1	2		
S. epidermidis GC 4935	1	0.50		1	0.50	0.50	0.50	0.50	0.50	4	0.50	0.50	4		2	2		
E. faecalis GC 4555	2	1		2	1	1	1	0.50	0.50	1	0.50	0.50	4		1	2		
E. faecalis GC 2265	2	0.50		2	1	1	0.50	0.50	0.50	8	0.50	0.50	8		1	2		
E. faecalis GC 2267	2	0.50		2	1	1	0.50	0.50	0.50	16	0.50	0.50	16		1	2		
E. faecalis GC 2242	2	0.50		2	0.50	0.50	0.50	0.50	0.50	1	0.50	0.50	1		1	1		

TABLE XII (CONT)

ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCLINES OF FORMULA I

MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	Water	Mouse Serum	Human Serum	Water	Mouse Serum	Human Serum	Water	Mouse Serum	Human Serum
	Example 61	Example 61	Example 61	Example 62	Example 62	Example 62	Example 63	Example 63	Example 63
E. faecium GC 4556	2	0.50	2	1	1	1	0.50	1	4
E. faecium GC 2243	0.50	0.25	1	0.50	0.50	0.50	0.50	0.25	0.25
S. pneumoniae* GC 4465	0.12	0.12	0.25	0.12	0.12	0.12	0.12	0.12	0.12
S. pneumoniae+ GC 4465	0.50	0.50	0.50	0.50	1	0.50	0.50	0.50	0.50
S. pyogenes GC 4563	0.50	0.25	0.25	0.25	0.25	0.12	0.12	0.12	0.12
S. agalactiae GC 4564	0.25	0.25	0.50	0.25	0.25	0.12	0.25	0.25	0.25
c. albicans GC 3066	>64	>64	>64	>64	>64	>64	>64	>64	>64

85

TABLE XIII
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYL CYCLINES OF FORMULA I
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	MouseSerum Example 108	Water Example 108	MouseSerum Example 109	Water Example 109	MouseSerum Example 109	Water Example 109	MouseSerum Example 110	Water Example 110
E. coli GC 2236	0.50	2	0.50	1	0.50	2	1	2
E. coli GC 2231	2	4	0.50	1	1	2	4	8
E. coli GC 2235	0.50	1	0.25	0.50	0.50	1	0.50	1
E. coli GC 2232	1	2	0.50	1	0.50	2	1	2
E. coli GC 2233	0.50	1	0.25	0.50	1	2	0.50	1
E. coli GC 2234	0.50	2	0.12	0.25	0.25	2	1	2
E. coli GC 2270	0.50	1	0.25	0.50	0.25	2	1	1
E. coli GC 2271	0.50	0.50	0.12	0.25	0.25	1	1	2
E. coli GC 2272	0.25	0.50	0.25	0.25	0.50	2	1	1
E. coli GC 4559	0.50	1	0.12	0.25	1	2	2	2
E. coli GC 4560	0.12	0.25	<0.06	<0.06	0.25	0.25	0.25	0.50
E. coli GC 6465	8	64	1	4	4	16	64	>64
E. coli GC 3226	0.50	1	0.50	1	1	4	2	4
E. coli GC 2203	0.50	1	0.50	1	0.50	2	1	4
E. coli GC 1073	0.50	2	0.50	1	1	4	2	8
Salmonella spp. GC 235	1	4	1	2	1	4	4	8
Salmonella spp. GC 566	1	8	2	4	2	4	16	32
S. cholerae GC 1355	32	64	8	32	8	32	>64	>64

26

TABLE XIII (CONT.)
ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYL CYCLINES OF FORMULA I
MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	MouseSerum Example 108	Water Example 108	MouseSerum Example 109	Water Example 109	MouseSerum Example 109	Water Example 109	MouseSerum Example 110	Water Example 110
S. typhimurium GC 2172	4	32	4	16	4	16	64	>64
P. aeruginosa GC 2214	16	32	16	>64	32	>64	>64	>64
S. aureus GC 1131	0.25	0.50	1	2	1	4	2	4
S. aureus GC 6466	0.50	1	0.50	1	0.50	4	1	2
S. aureus GC 6467	2	8	2	4	2	8	32	>64
S. aureus GC 1079	2	4	2	4	2	8	16	16
S. aureus GC 4536	0.50	1	1	2	1	4	4	4
S. aureus GC 2216	0.50	1	1	2	0.50	8	2	4
S. aureus GC 6335	1	2	2	4	1	4	8	8
S. aureus GC 6469	0.25	1	1	2	2	8	32	32
S. epidermidis GC 4935	1	2	2	4	2	8	4	8
E. faecalis GC 4555	0.50	0.50	0.50	1	0.50	1	1	2
E. faecalis GC 2265	1	2	1	2	1	4	8	4

TABLE XIII (CONT)

ANTIBACTERIAL ACTIVITY OF 9-AMINOCARBONYLSUBSTITUTED DERIVATIVES OF GLYCYLCYCLOLINES OF FORMULA I

MINIMAL INHIBITORY CONCENTRATION MIC(UG/ML)

	MouseSerum		Water		MouseSeru		Water		MouseSeru		Water		MouseSeru		Water	
	Example 108	Example 109	Example 108	Example 109	Example 108	Example 109	Example 108	Example 109	Example 108	Example 109	Example 108	Example 109	Example 108	Example 109	Example 108	Example 109
E. faecalis GC 2267	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2
E. faecalis GC 2242	0.50	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
E. faecium GC 4556	0.50	1	1	2	1	2	1	2	1	2	1	2	1	2	1	2
E. faecium GC 2243	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
S. pneumoniae* GC 4465	0.12	0.12	<0.06	0.12	<0.06	0.12	<0.06	0.12	<0.06	0.12	<0.06	0.12	<0.06	0.12	<0.06	0.12
S. pneumoniae+ GC 4465	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1
S. pyogenes GC 4563	0.12	0.12	<0.06	0.12	<0.06	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12
S. agalactiae GC 4564	0.12	0.12	0.12	0.25	0.12	0.25	<0.06	0.25	<0.06	0.25	<0.06	0.25	<0.06	0.25	<0.06	0.25
c. albicans GC 3066	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64

Table 1. In vitro activity (MIC)^a of representative examples of formula I

Ex Number	Minimum inhibitory concentration MIC (μg/ml)			
	E.coli (Mouse Serum)	E.coli (Water)	Staph (Mouse Serum)	Staph (Water)
1	0.5-1	16-64	1-4	1-8
2	1-4	32-64	1-8	2-8
3	1-2	>64	1-4	4-32
4	0.5-2	64->64	0.5-2	2-16
5	1-2	16-64	0.25-2	0.5-4
6	1-2	8-64	0.5-2	1-4
7	0.25-2	2-16	0.5-4	0.5-4
8	1-2	16->64	0.5-4	1-8
9	0.5-2	4-64	<0.06-2	0.12-2
10	0.25-2	4-32	0.25-2	0.12-2
11	0.25-2	4->64	0.25-4	0.25-4
12	0.5-2	16-64	0.5-4	1-16
13	1-4	8-16	1-4	2-8
14	32->64	64->64	1-8	2-8
15	32->64	32->64	2-16	4-16
16	16->16	64->64	2-8	4-8
17	0.5-2	32-64	1-4	2-32
18	0.5-2	4-8	1-4	1-4
19	0.5-2	32->64	0.5-4	1-8
20	0.5-2	>64	1-4	64->64
21	0.5-8	>64	1-4	32->64
22	1-8	>64	0.5-4	2->64
23	1-8	>64	0.25-4	0.5-8
24	0.5-2	>64	0.25-4	0.5->64
25	1-2	32->64	0.25-2	0.5-4
26	1-4	64->64	0.25-1	0.25-4
27	0.5-1	32->64	0.12-2	0.12-2
28	0.25-1	>64	0.5-4	4-64
29	0.5-1	>64	0.25-2	1-4
30	0.5-1	32->64	0.25-2	1-8
31	0.5-1	16->64	0.25-2	0.5-4
32	0.5-1	1-4	0.25-2	0.5-4
33	0.5-2	32->64	0.12-2	0.12-2

^a Range of MIC (minimum inhibitory concentration) for E. coli and Staph., including MRSA which are selected from those E. coli and Staph., presented in Tables I-XIII.

Table 1 (Cont)

Ex Number	Minimum inhibitory concentration MIC ^a (μg/ml)			
	E.coli (Mouse Serum)	E.coli (Water)	Staph (Mouse Serum)	Staph (Water)
34	0.5-1	4-16	0.25-4	0.25-4
35	4-8	8-64	2-4	2-4
36	2-8	8-32	2-4	4-16
37	2-4	4-32	1-4	2-4
38	0.5-4	64->64	0.5-2	1-8
39	1-4	16-32	1-4	2-16
40	1-2	16->64	0.25-2	0.25-2
41	0.5-4	16-64	0.5-4	1-8
42	4-16	>64	2-4	4-8
43	0.25-2	>64	0.5-2	32->64
44	2-8	>64	2	2-4
45	0.5-2	16->64	0.25-1	0.5-2
46	0.5-2	64->64	0.25-1	0.25-2
47	0.5-2	>64	1-2	2-4
48	0.25-2	32->64	0.12-2	0.12-2
49	0.25-2	8->64	0.12-1	0.12-2
50	1-2	32-64	0.25-2	0.25-4
51	1-2	>64	0.25-2	1-4
52	0.5-1	4-16	0.5-1	2-4
53	0.25-1	16-64	0.25-1	0.5-2
54	0.5-1	>64	0.5-2	1-4
55	0.5-8	64->64	1-2	2-8
56	0.25-2	8->64	0.25-1	1-4
57	0.5-4	>64	0.5-2	4-16
58	>64	>64	2-4	4-8
59	32->64	>64	4	4-8
60	32->64	64->64	2-8	4-16
61	0.5-1	8->64	0.25-0.5	0.5-2
62	0.5-2	4->64	0.5-1	0.25-1
63	0.5-2	>64	0.5-2	2-16
64	<0.12	<0.12 - 1	<0.12 - 0.25	<0.12 - 0.5
	<0.12 -			
65	0.5	16	<0.12 - 0.5	<0.12 - 1
66	>128	>128	1-16	2-16
	<0.12 -			
67	0.25	8-32	<0.12 - 0.25	<0.12 - 1
68	<0.12 - 1	2-8	<0.12 - 0.25	<0.12 - 1

^a Range of MIC (minimum inhibitory concentration) for E. coli and Staph., including MRSA which are selected from those E. coli and Staph., presented in Tables I-XIII.

Table 1 (Cont)

Ex Number	Minimum inhibitory concentration MIC ^a (μg/ml)			
	E.coli (Mouse Serum)	E.coli (Water)	Staph (Mouse Serum)	Staph (Water)
	<0.12 -			
69	0.5	8-64	<0.12 - 0.25	<0.12 - 1
70	4-8	>64	1-4	2-4
71	0.12-0.25	>64	0.5-1	32-64
72	0.5-1	>64	0.5-1	4-8
73	0.5-1	>64	1-4	4-8
74	0.25-1	>64	0.5-4	64->64
75	16->64	>64	8-16	16-32
76	16->64	>64	8-16	8-32
77	8->64	>64	2-4	4-32
78	16-64	>64	8	8-32
79	16->64	>64	4	4-8
80	16->64	64->64	4-8	4-16
81	0.5-1	8-16	0.5-2	4-8
82	64->64	>64	4-16	4-8
83	64->64	>64	8-32	2-16
84	2-4	>64	0.5-2	0.5-4
85	1-2	>64	1-2	4-16
86	8-16	>64	2-8	8
87	64->64	>64	32-64	>64
88	0.5-2	8-16	1-4	4-16
89	0.25-1	4-8	0.5-1	1-4
90	2-4	>64	0.25-2	1-16
91	0.5-2	>64	0.12-0.25	0.25-2
92	4-8	>64	4	8-32
93	1-4	64->64	1-2	32-64
94	32-64	>64	16-32	>64
95	>64	>64	16->64	>64
96	0.25-1	64->64	0.25-1	4-16
97	4-8	>64	1-4	4-8
98	1-4	>64	0.5-2	2-4
99	1-2	>64	0.5-2	2-4
100	2	64->64	0.5-1	2-4
101	1	16-32	0.5-2	4-16
102	0.5-1	>64	0.5-1	64->64
103	8-16	>64	8-16	64->64
104	8-16	>64	16-64	64->64
105	2	>64	1-2	16->64

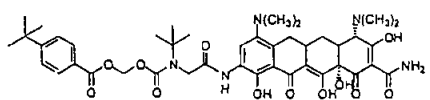
^a Range of MIC (minimum inhibitory concentration) for E. coli and Staph., including MRSA which are selected from those E. coli and Staph., presented in Tables I-XIII.

Table 1 (Cont)

Ex Number	Minimum inhibitory concentration MIC ^a (μg/ml)			
	E.coli (Mouse Serum)	E.coli (Water)	Staph (Mouse Serum)	Staph (Water)
106	>64	>64	>64	>64
107	>64	0.5-1	2-8	0.5-1
108	0.5-2	0.5-4	0.25-2	1-8
109	0.25-1	1-4	0.5-2	4-8
110	0.5-4	1-8	1-32	2->64
111	0.25-1	1-4	0.5-8	1-16
112	1-4	2-8	2-8	4-16
113	1-4	2-16	4-16	4-32

^a Range of MIC (minimum inhibitory concentration) for E. coli and Staph., including MRSA which are selected from those E. coli and Staph., presented in Tables I-XIII.

5 Table 2. In vitro activity (MIC) of Example 87.

Example 87			
			
	water	Mouse serum	Human serum
E. coli, tet(A-D), efflux	>64	0.25-0.5	>64
E. coli, tet (M,S,O) Tet (M)	>64	0.25-0.5	>64
E. coli (susceptible)	>64	0.5	>64
E. coli (IMP)	32	<0.06	16
S. aureus, tet (M)	64	0.5	16
S. aureus, tet (K), efflux	64	1	32
S. aureus (susceptible) ^a	32	1	16
Enterococcus spp.	0.25-32	0.12-0.5	0.25-8
Streptococcus spp.	0.5-2	<0.06	1-2
C. albicans	>64	>64	>64

^a Strain used for the in vivo testing

Representative examples of compounds of Formula I were further evaluated for oral efficacy, stability in physiological pH in mouse serum and human plasma.

5

Table 3. In vitro activity (MIC)^a of representative examples of compounds of Formula I

Minimum inhibitory concentration (MIC), μ g/mL				
Ex. No.	E. coli (mouse serum)	E. coli (water)	Staph. (mouse serum)	Staph. (water)
1	0.5-1	16-64	1-4	1-8
2	1-4	32-64	1-8	2-8
3	1-2	>64	1-4	4-32
4	0.5-2	64->64	0.5-2	2-16
12	0.5-2	16-64	0.5-4	1-16
13	1-4	8-16	1-4	2-8
17	0.5-2	32-64	1-4	2-32
18	0.5-2	4-8	1-4	1-4
20	0.5-2	>64	1-4	64->64
21	0.5-8	>64	1-4	32->64
22	1-8	>64	0.5-4	2->64
23	1-8	>64	0.25-4	0.5-8
29	0.5-1	>64	0.25-2	1-4
30	0.5-1	32->64	0.25-2	1-8
34	0.5-1	4-16	0.25-4	0.25-4
36	2-8	8-32	2-4	4-16
38	0.5-4	64->64	0.5-2	1-8
39	1-4	16-32	1-4	2-16

10 ^a Range of MIC (minimum inhibitory concentration) for E. coli and Staph., including MRSA which are selected from those E. coli and Staph., presented in Tables I-XIII.

15

164

Table 4. In vitro activity (MIC)^a of representative examples of compounds of Formula

5 I

Minimum inhibitory concentration (MIC), µg/mL				
Ex. No.	E. coli (mouse serum)	E. coli (water)	Staph. (mouse serum)	Staph. (water)
5	1-2	16-64	0.25-2	0.5-4
6	1-2	8-64	0.5-2	1-4
7	0.25-2	2-16	0.5-4	0.5-4
8	1-2	16->54	0.5-4	1-8
9	0.5-2	4-64	0.06-1	0.12-2
10	0.25-2	4-32	0.25-2	0.12-2
11	0.25-2	4->64	0.25-4	0.25-4
19	0.5-2	32->64	0.5-4	1-8
24	0.5-2	>64	0.25-4	0.5->64
25	1-2	32->64	0.25-2	0.5-4
26	1-4	64->64	0.25-1	0.25-4
27	0.5-1	32->64	0.12-2	0.12-2
28	0.25-1	>64	0.5-4	4-64
31	0.5-1	16->64	0.25-2	0.5-4
33	0.5-2	32->64	0.12-2	0.12-2
35	4-8	8-64	2-4	2-4
40	1-2	16->64	0.25-2	0.25-2
41	0.5-4	16-64	0.5-4	1-8

^a Range of MIC (minimum inhibitory concentration) for E. coli and Staph.including MRSA which are selected from those E. coli and Staph., presented in Tables I-XIII.

10

Table 5. In vitro activity (MIC) of Example 27

Example 27

	water	Mouse serum	Human serum
E. coli, tet(A-D), efflux	64->64	0.5-1	4-16
E. coli, tet (M,S,O) Tet (M)	0.5	0.5	4-8
E. coli (susceptible)	0.5	0.5	16
E. coli (IMP)	0.25	0.25	0.5
S. aureus, tet (M)	0.12	0.12	0.25
S. aureus, tet (K), efflux	1	1	1
S. aureus (susceptible) ^a	0.12	0.12	0.5
Enterococcus spp.	0.12-1	0.12-1	0.5-2
Streptococcus spp.	<0.06-0.12	<0.06-0.12	0.12-2
C. albicans	>64	>64	>64

^a Strain used for in vivo testing

- 5 Representative examples of compounds of Formula I
were tested for the oral efficacy using *S. aureus* Smith in mice. The summary of in
vivo and in vitro activities of selected compounds are listed in Table 6.

106

Table 6. In vitro and in vivo activity of representative examples of compounds of Formula I against Staph. aureus Smith in mice.

ED ₅₀ mg/kg (Staph aureus Smith)		μg/mL (Staph aureus Smith)	
Ex. No.	SOD ^b	SIV ^c	MIC ^a
42	5.68	1.43	8
44	4	0.75	4
45	5.9	0.66	1
47	14	1.2	4
48	10.1	1.1	0.25
49	16	0.92	0.25
50	16.88	1.65	0.5
52	10.69	1.29	2
53	5.08	0.73	1
54	8.4	0.83	0.5
87	12.82	0.83	32

5 ^a MIC (minimum inhibitory concentration)

^b SOD (Single oral dose)

^c SIV (Single intravenous dose)

10 Representative examples of compounds of Formula I were tested in vivo against gram-negative bacteria (E. coli) in mice. Results of the tests (MIC, oral and IV) are list in Table 7.

Table 7. In vivo (oral, iv) and in vitro (MIC)^a activity of representative examples of compounds of Formula I against E. coli in mice .

Ex. No.	ED ₅₀ mg/kg (E. coli)		μg/mL (E. coli)
	SOD ^b	SIV ^c	MIC
5	>64	3.17	>64
42	30.3	3.1	>64
44	42.8	2.85	>64
45	64	1.8	64
48	29.8	1.7	>64
49	49	2.2	64
50	29.8	1.7	>64
52	43.7	3.78	8
53	46.88	2.25	32
54	29.2	2.16	>64
87	60.4	3.6	>64

5 ^a MIC (minimum inhibitory concentration)
 ^b SOD (Single oral dose)
 ^c SIV (Single intravenous dose)

Test results of in vivo activity are shown in Table 8 for representative examples of compounds of Formula I.

5 Table 8. In vivo (oral, iv) and in vitro (MIC)^a activity of representative examples of compounds of Formula I, against Staph aureus Smith in mice.

Ex. No.	ED ₅₀ mg/kg (Staph aureus Smith)		μg/mL (Staph aureus Smith)
	SOD ^b	SIV ^c	MIC
1	4.7	0.6	4
5	8.51	0.5	1
19	8.05	0.31	1
26	8.79	0.43	0.5
27	3.9	0.44	0.12
28	6.61	0.6	32
33	4.91	0.48	0.12
35	3.5	0.43	4
36	5.15	0.84	8
38	5.3	0.6	2
40	4.65	0.39	0.5

^a MIC (minimum inhibitory concentration)

^b SOD (Single oral dose)

10 ^c SIV (Single intravenous dose)

Table 9
Minimum inhibitory concentration (MIC), $\mu\text{g/mL}$

Ex No.	E.coli (Human Serum)	E.coli (Water)	Staph (Human Serum)	Staph (Water)
4	8-32	32->64	0.5-4	2-8
19	8-32	16->64	0.12-1	0.25-4
27	4-16	64->64	0.25-2	0.5-4
42	>64	>64	2-4	4-8
43	>64	>64	4-64	32->64
44	>64	>64	2-4	2-4
45	4-16	16->64	0.12-1	0.5-2
46	4-16	64->64	0.25-1	0.25-2
47	16->64	>64	1-4	2-4
48	8->64	32->64	0.12-2	0.12-2
49	4-32	8->64	0.12-1	0.12-2
50	4-16	32-64	0.25-2	0.25-4
51	32-64	>64	0.25-2	1-4
52	4-16	4-16	0.5-4	2-4
53	8-16	16-64	0.5-2	0.5-2
54	16-32	>64	0.5-2	1-4
55	32->64	64->64	1-4	2-8
56	4-32	8->64	0.25-2	1-4
57	>64	>64	1-8	4-16
58	>64	>64	4	4-8
59	>64	>64	2-4	4-8
60	32->64	64->64	2-8	4-16
61	4-32	8->64	0.5-1	0.5-2
62	2-8	4->64	0.5	0.25-1
63	64->64	>64	1-4	2-16
102	64->64		>64	
105	64->64		8->64	

110

Table 10

Ex. No.	ED ₅₀ (mg/kg) Staph Smith		ED ₅₀ mg/kg E. coli #311		IV - RAT 2 mg/kg		PO - RAT 20 mg/kg					
	SOD	SIV	SOD	SIV	SOD	SIV	Cmax	AUC	T1/2	Cmax	AUC	%BA
1												
2	13.27	0.71										
3	16.05	0.59										
4	11.6	0.39	>32	>2								
5	8.51	0.5										
6	20.05	0.87										
7	16.1	0.52										
8	16.63	0.48										
9	11.27	0.32										
10	13.62	0.36										
11	30.27	0.59										
12	15.02	1										
13	10.98	0.82										
14	>32	>2										
16	>32	>2										
17	59.9	1.07										
18	29.02	0.6										
19	8.05	0.31	>32	>2								
20	19.4	0.6										
21	>32	0.77										
22	18.77	0.43										

Table 10 (cont)

Ex. No.	SOD	SIV	SOD	SIV	Cmax	AUC	T1/2	Cmax	AUC	%BA
23	19.01	0.47								
24	27	0.59								
25	15.71	0.56								
26	8.79	0.43								
27	3.9	0.44	>32	>2						
28	6.61	0.6	>32	>2						
29	13.67	0.43								
30	15.1	0.41								
31	11.11	0.31								
32	7.7	0.56								
33	4.91	0.45								
34	12.86	0.71								
35	3.5	0.43								
36	5.15	0.84								
37	4.1	0.55								
38	5.3	0.6								
39	13.3	0.6								
40	4.65	0.39								
41	11.3	0.83								
42	5.68	1.43	30.3	3.1	4.1	1.6	5.1	0.22	0.64	8.1
43	12.82	0.83	60.4	3.6	6.5	2.4	3.5	0.05	0.27	2.3
44	4	0.75	42.8	2.85						
45	5.9	0.66	64	1.8						

11/11

Table 10 (cont)

Ex. No.	Staph. Smith		E. coli #311		IV - RAT 2 mg/kg		PO - RAT 20 mg/kg			
	SOD	SIV	SOD	SIV	Cmax	AUC	T1/2	Cmax	AUC	%BA
46 -	8.4	0.83	29.2	2.16						
47	14	1.2	>64	3.17						
48	10.1	1.1	29.8	1.7						
49	16.6	0.92	49	2.2						

Table 10 (cont)

Ex. No.	ED ₅₀ (mg/kg) Staph Smith		ED ₅₀ mg/kg E. coli #311		IV - RAT 2 mg/kg			PO - RAT 20 mg/kg		
	SOD	SIV	SOD	SIV	Cmax	AUC	T1/2	Cmax	AUC	%BA
50	16.88	1.65	>64	2.59						
52	10.69	1.29	43.7	3.78						
53	5.08	0.73	46.88	2.25						
54	>16	1.17	>32	3.72						
55	>16	1.81	32	4.69						
56	>16	0.79								
57	6.36	1.17								
58			>32	>8						
59			>32	>8						
60			>32	>8						
61			>32	2-4						
62			>32	4-8						
63			>32	4-8						
71	>32	1	>32	>4						
74	>32	1.08	>32	>4						
81	16-32	>4								
82	21.97	0.52								
90	16-32	0.5-1								
91	11.73	1.21								
93	>32	0.5-1								
96	16-32	1-2	>32	2-4						
102	19.81	1.59	>32	2-4						

114

Table 10 (cont)

Ex No	ED ₅₀ (mg/kg) Staph Smith		ED ₅₀ mg/kg E. coli #311		IV - RAT 2 mg/kg		PO - RAT 20 mg/kg		%BA
	SOD	SIV	SOD	SIV	Cmax	AUC	Cmax	AUC	
108	>32	>2							
109	19.94	0.76							
110	31.94	0.6							
112	6.12	0.48							
113	7.01	0.4							

115

Table 10 (cont)

Ex No	IV - DOG				Oral - DOG				IV - MONKEY				Oral - MONKEY			
	2 mg/kg				10 mg/kg				2 mg/kg				10 mg/kg			
	Cmax	AUC	T1/2	Cmax	AUC	%BA	Cmax	AUC	T1/2	AUC	Cmax	T1/2	Cmax	AUC	%BA	%BA
1	10.8	8.3	14.9	0.11	0.67	1.6%	9.1	3.3	17.6	no levels detected						
27	1.9	9.8	10.7	0.018	0.22	0.5%	20	9.3	7.3	0.04	0.21	0.5%				
28	0.55	6	7.8	0.09	0.74	2.5%	0.77	3.6	13.2	0.05	0.23	1.3%				

When the compounds of the invention are employed as antibacterials, they can be combined with one or more pharmaceutically acceptable carriers, for example,
5 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
10 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 2.0 mg/kg of body weight to 100.0 mg/kg of
15 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,
20 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
25 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
30 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. The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred. 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 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 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 polyethylene glycol), suitable mixtures thereof, and vegetable oil.

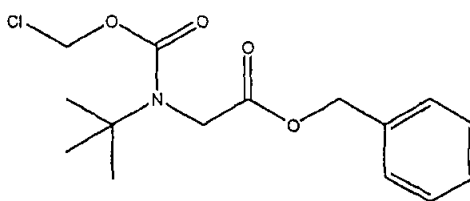
The present invention further provides a method of treating bacterial infections in warm-blooded animals including man, which comprises providing to the afflicted warm-blooded animals an antibacterially effective amount of a compound or a pharmaceutical composition of a compound of the invention.

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

Reference Compound 1

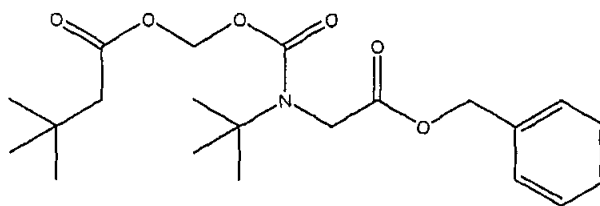
(Tert-butyl-chloromethoxycarbonyl-amino)-acidic acid benzyl ester.



- 10 To a solution of tert-butylamino-acetic acid benzyl ester in dichloromethane is added two equivalents of [1,8-bis(dimethylamino)naphthalene, N,N,N',N'-tetramethyl-1,8-naphthalenediamine]. The reaction mixture is then cooled in an ice bath and one equivalent of chloromethyl chloroformate is added. The reaction is then warm to room temperature and continue to stir for 24 hr. It is then washed with water and then
15 brine.

Reference Compound 2

3,3-Dimethyl-butyric acid (benzyloxycarbonylmethyl-tert-butyl-carbamoyloxy)-methyl
20 ester



- 25 Tert-butylacetic acid and 1.0 M tetrabutylammonium hydroxide in methanol is stirred for an hour, methanol is removed and THF is added. To this solution is then added benzyl N-(tert-butyl)-N-[(chloromethoxy)carbonyl]glycinate and stirred at room temperature for 24 hr. Solvent is removed and residue is diluted with ether, then

washed with water, then brine. It is dried over magnesium sulfate, filtered and solvent removed. MS (ESI) m/z 394.25

5

Reference Compounds 3-55 (Table A)

Substantially following the method described in detail hereinabove in Reference Compound 2 using (tert-butyl-chloromethoxycarbonyl-amino)-acidic acid benzyl ester from Reference Compound 1 and the appropriate carboxylic acid, the reference compounds 3-55 of this invention listed below in Table A are prepared.

Table A

15

Ref. Cpd. No.	Name	Spectra
3	([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 4-tert-butylbenzoate	MS (ESI) m/z 456.23
4	([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 2,2-dimethylbutanoate	MS m/z 01-400386LMS;
5	([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 2-methylpropanoate	MS (ESI) m/z 366.24; HRMS: calcd for C19H27NO6 + Na+, 388.17306; found (ESI+, [M+NA]1+), 388.17295;
6	([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl cyclopentanecarboxylate	MS (ESI) m/z 392.23;
7	([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 4-methylbenzoate	MS (ESI) m/z 414.24; MS (ESI) m/z 436.23; HRMS: calcd for C23H27NO6 + Na+, 436.17306; found (ESI+, [M+NA]1+), 436.17291;

Ref. Cpd. No.	Name	Spectra
8	(([[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl heptanoate	MS (ESI) m/z 408.24;
9	(([[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl propionate	MS (ESI) m/z 352.17; HRMS: calcd for C ₁₈ H ₂₅ NO ₆ + H ⁺ , 352.17546; found (ESI ⁺ , [M+H] ⁺), 352.17551;
10	(([[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl cyclohexanecarboxylate	MS (ESI) m/z 406.26;
11	(([[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 3,5-dimethylbenzoate MS (ESI) m/z 428.25; MS (ESI) m/z 87.54;	MS (ESI) m/z 428.25; MS (ESI) m/z 87.54;
12	(([[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 4-fluorobenzoate	MS (ESI) m/z 418.2; MS (ESI) m/z 440.2;
13	(([[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 3-methylbutanoate	MS (ESI) m/z 380.27; HRMS: calcd for C ₂₀ H ₂₉ NO ₆ + Na ⁺ , 402.18871; found (ESI ⁺ , [M+NA] ¹⁺), 402.18882;
14	benzyl N-(tert-butyl)-N-(((cyclopentylacetyl)oxy)methoxy)carbonyl)glycinate	MS (ESI) m/z 406.2;
15	(([[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 4-(trifluoromethyl)benzoate	MS (CI(ISOBUTANE)) m/z 468.13;
16	(([[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl cyclopropanecarboxylate	MS (ESI) m/z 364.26;
17	(([[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl adamantane-1-carboxylate	MS (ESI) m/z 458.3;
18	(([[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl pentanoate	MS (ESI) m/z 380.2;

Ref. Cpd. No.	Name	Spectra
19	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl cyclobutanecarboxylate	MS (ESI) m/z 378.2; MS (ESI) m/z 400.2;
20	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 3-cyclohexylpropanoate	MS (ESI) m/z 434.3; MS (ESI) m/z 451.3; HRMS: calcd for C ₂₄ H ₃₅ NO ₆ + Na ⁺ , 456.23566; found (ESI ⁺ , [M+NA] ¹⁺), 456.23661;
21	benzyl N-(tert-butyl)-N-([[(4-fluorophenoxy)acetyl]oxy]methoxy)carbonyl]glycinate	
22	benzyl N-(tert-butyl)-N-([[(cyclohexylacetyl)oxy]methoxy]carbonyl]glycinate	MS (ESI) m/z 420.2; MS (ESI) m/z 442.2;
23	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 2,6-dimethylbenzoate	MS (ESI) m/z 428.2;
24	benzyl N-(tert-butyl)-N-([[(phenylacetyl)oxy]methoxy]carbonyl]glycinate	MS (ESI) m/z 414.2; MS (ESI) m/z 436.2; HRMS: calcd for C ₂₃ H ₂₇ NO ₆ + H ⁺ , 414.19112; found (ESI ⁺ , [M+H] ¹⁺), 414.19143;
25	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl pivalate	MS (ESI) m/z 380.1; MS (ESI) m/z 781.3; HRMS: calcd for C ₂₀ H ₂₉ NO ₆ + H ⁺ , 380.20677; found (ESI ⁺ , [M+H] ¹⁺), 380.20649;

Ref. Cpd. No.	Name	Spectra
26	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 1-benzofuran-2-carboxylate	MS (ESI) m/z 440; MS (ESI) m/z 901.1; HRMS: calcd for C ₂₄ H ₂₅ NO ₇ + H ⁺ , 440.17038; found (ESI ⁺ , [M+H] ¹⁺), 440.17005;
27	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 1-methyl-1H-pyrrole-2-carboxylate	MS (ESI) m/z 403.3; MS (ESI) m/z 827.7;
28	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 1,1'-biphenyl-4-carboxylate	MS (ESI) m/z 476.2; HRMS: calcd for C ₂₈ H ₂₉ NO ₆ + Na ⁺ , 498.18871; found (ESI ⁺ , [M+NA] ¹⁺), 498.18857;
29	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 4-methoxybenzoate	MS (ESI) m/z 430.3; MS (ESI) m/z 452.3;
30	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 1H-indole-2-carboxylate	MS (ESI) m/z 439.1; HRMS: calcd for C ₂₄ H ₂₆ N ₂ O ₆ + Na ⁺ , 461.16831; found (ESI ⁺ , [M+NA] ¹⁺), 461.168;
31	benzyl N-(tert-butyl)-N-(((diphenylacetyl)oxy)methoxy)carbonyl)glycinate	MS (ESI) m/z 490.2;
32	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 1-naphthoate	MS (ESI) m/z 450.1;
33	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 2-naphthoate	MS (ESI) m/z 450.1;

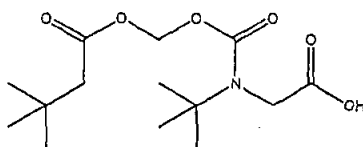
Ref. Cpd. No.	Name	Spectra
34	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 1-methyl-1H-indole-3-carboxylate	MS (ESI) m/z 453.3; MS (ESI) m/z 905.6; MS (ESI) m/z 927.5;
35	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl quinoline-2-carboxylate	MS (ESI) m/z 451.2; MS (ESI) m/z 901.4;
36	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl nicotinate	MS (ESI) m/z 401.1;
37	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl isonicotinate	MS (ESI) m/z 401;
38	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 2,6-difluorobenzoate	MS (ESI) m/z 436.2; MS (ESI) m/z 893.4; MS (ESI) m/z 453.2;
39	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 2-fluorobenzoate	MS (ESI) m/z 418.2; MS (ESI) m/z 857.5; MS (ESI) m/z 440.2;
40	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 2-(trifluoromethyl)benzoate	MS (ESI) m/z 468.1; MS (ESI) m/z 490.2;
41	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 4-(1H-pyrrol-1-yl)benzoate	MS (ESI) m/z 465.1; MS (ESI) m/z 482.1;
42	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 1,1'-biphenyl-2-carboxylate	MS (ESI) m/z 476.3; MS (ESI) m/z 493.3; MS (ESI) m/z 951.6;

Ref. Cpd. No.	Name	Spectra
43	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 2,4,6-trimethylbenzoate	MS (ESI) m/z 442.3; MS (ESI) m/z 459.3;
44	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 4-isopropoxybenzoate	MS (ESI) m/z 458.3;
45	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 3,4,5-trimethoxybenzoate	MS (ESI) m/z 490.3; MS (ESI) m/z 996.5; MS (ESI) m/z 979.5;
46	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 3,5-dimethoxybenzoate	MS (ESI) m/z 460.3; MS (ESI) m/z 936.5; MS (ESI) m/z 919.5;
47	3-phenyl-acrylic acid (benzyloxycarbonylmethyl-tert-butyl-carbamoyloxy)-methyl ester	PE added cpd
48	(([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 3-methyl-1-benzofuran-2-carboxylate	MS (ESI) m/z 454.2; MS (ESI) m/z 907.5; HRMS: calcd for C ₂₅ H ₂₇ NO ₇ + Na ⁺ , 476.16797; found (ESI, [M+NA] ¹⁺), 476.16858;

Ref. Cpd. No.	Name	Spectra
49	benzyl N-([3,5-bis(trifluoromethyl)phenyl]acetyl)oxy)methoxy]carbonyl)-N-(tert-butyl)glycinate	MS m/z 01-305267LMS; HRMS: calcd for C ₂₅ H ₂₅ F ₆ NO ₆ + Na ⁺ , 572.14783; found (ESI ⁺ , [M+NA] ¹⁺), 572.14702;
50	([2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl)oxy)methyl 4-(heptyloxy)benzoate	MS (ESI) m/z 514.3; HRMS: calcd for C ₂₉ H ₃₉ NO ₇ + H ⁺ , 514.27993; found (ESI ⁺ , [M+H] ¹⁺), 514.28023;
51	([2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl)oxy)methyl 2-(2-phenylethyl)benzoate	MS (ESI) m/z 526.2;
52	([2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl)oxy)methyl 4-(dodecyloxy)benzoate	MS (ESI) m/z 584.3; HRMS: calcd for C ₃₄ H ₄₉ NO ₇ + H ⁺ , 584.35818; found (ESI ⁺ , [M+H] ¹⁺), 584.3574;
53	([2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl)oxy)methyl 4-(acetylamino)benzoate	MS (ESI) m/z 457.2; MS (ESI) m/z 913.4; HRMS: calcd for C ₂₄ H ₂₈ N ₂ O ₇ + Na ⁺ , 479.17887; found (ESI ⁺ , [M+NA] ¹⁺), 479.17909;
54	([2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl)oxy)methyl anthracene-9-carboxylate	MS (ESI) m/z 500.2; MS (ESI) m/z 999.5;
55	([2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl)oxy)methyl 4-benzoylbenzoate	MS (ESI) m/z 504.2;

Reference Compound 56

3,3-Dimethyl-butyril (tert-butyl-carboxymethyl-carbamoyloxy)-methyl ester.



5

The product from Reference Compound 2, 10% palladium on carbon in ethyl acetate is hydrogenated in a Parr shaker at ca. 40 psi for about an hour. The catalyst is
10 filtered and solvent removed to give the corresponding carboxylic acid product of the example MS(ESI) m/z 394.25.

15

Reference Examples 57-108 (Table B)

Substantially following the method described in detail hereinabove in Reference Compound 56 the reference compounds 57-108 of this invention listed below in Table B are prepared using the appropriate benzyl esters of Reference Compounds
20 3-55.

25

Table B

Ref. Cpd. No.	Name	Spectra
57	N-(tert-butyl)-N-({[(4-tert-butylbenzoyl)oxy]methoxy}carbonyl)glycine	MS (ESI) m/z 366.18
58	N-(tert-butyl)-N-({[(isobutyryloxy)methoxy]carbonyl)glycine	MS (ESI) m/z 274.05; MS (ESI) m/z 549.13; HRMS: calcd for C ₁₂ H ₂₁ NO ₆ + H ⁺ , 276.14416; found (ESI ⁺ , [M+H] ¹⁺), 276.14314;
59	N-(tert-butyl)-N- (({[(cyclopentylcarbonyl)oxy]methoxy}carbonyl)glycine	MS (ESI) m/z 300.04; MS (ESI) m/z 601.1; HRMS: calcd for 2 C ₁₄ H ₂₃ NO ₆ - H ⁺ , 601.29780; found (ESI ⁻ , [2M-H] ¹⁻), 601.29741;
60	N-(tert-butyl)-N-({[(4-methylbenzoyl)oxy]methoxy}carbonyl)glycine	MS (ESI) m/z 324.19; HRMS: calcd for C ₁₆ H ₂₁ NO ₆ + Na ⁺ , 346.12611; found (ESI ⁺ , [M+NA] ¹⁺), 346.12625;
61	N-(tert-butyl)-N-({[(heptanoyloxy)methoxy]carbonyl)glycine	MS (ESI) m/z 316.25; MS (ESI) m/z 633.54;

Ref. Cpd. No.	Name	Spectra
62	N-(tert-butyl)-N-(((propionyloxy)methoxy)carbonyl)glycine	MS (ESI) m/z 260.05; MS (ESI) m/z 521.13; HRMS: calcd for C ₁₁ H ₁₉ NO ₆ + Na ⁺ , 284.11046; found (ESI, [M+NA] ⁺), 284.11017;
63	N-(tert-butyl)-N-(((cyclohexylcarbonyl)oxy)methoxy)carbonyl)glycine	MS (ESI) m/z 314.06; MS (ESI) m/z 629.14; HRMS: calcd for 2 C ₁₅ H ₂₅ NO ₆ - H ⁺ , 629.32910; found (ESI- [2M-H] ¹⁻), 629.32842;
64	N-(tert-butyl)-N-(((3,5-dimethylbenzoyl)oxy)methoxy)carbonyl)glycine	MS (ESI) m/z 338.16;
65	N-(tert-butyl)-N-(((4-fluorobenzoyl)oxy)methoxy)carbonyl)glycine	MS (ESI) m/z 326; MS (ESI) m/z 653; HRMS: calcd for C ₁₅ H ₁₈ FNO ₆ + Na ⁺ , 350.10103; found (ESI+ [M+NA] ¹⁺), 350.10131;

Ref. Cpd. No.	Name	Spectra
66	N-(tert-butyl)-N-({[(3-methylbutanoyl)oxy]methoxy}carbonyl)glycine	HRMS: calcd for C ₁₃ H ₂₃ NO ₆ + Na ⁺ , 312.14176; found (ESI ⁺ , [M+NA] ¹⁺), 312.14197;
67	N-(tert-butyl)-N-({[(cyclopentylacetyl)oxy]methoxy}carbonyl)glycine	MS (ESI) m/z 314; MS (ESI) m/z 629.1; HRMS: calcd for C ₁₅ H ₂₅ NO ₆ + H ⁺ , 316.17546; found (ESI ⁺ , [M+H] ¹⁺), 316.17503;
68	N-(tert-butyl)-N-({[(4-(trifluoromethyl)benzoyl)oxy]methoxy}carbonyl)glycine	MS (ESI) m/z 376; MS (ESI) m/z 752.9;
69	N-(tert-butyl)-N-({[(cyclopropylcarbonyl)oxy]methoxy}carbonyl)glycine	HRMS: calcd for C ₁₂ H ₁₉ NO ₆ + Na ⁺ , 296.11046; found (ESI ⁺ , [M+NA] ¹⁺), 296.11061;
70	N-({[(1-adamantylcarbonyl)oxy]methoxy}carbonyl)-N-(tert-butyl)glycine	MS (ESI) m/z 368.21; MS (ESI) m/z 757.37;

Ref. Cpd. No.	Name	Spectra
71	N-(tert-butyl)-N-[[pentanoyloxy]methoxy]carbonyl]glycine	MS (ESI) m/z 288; MS (ESI) m/z 577.1; HRMS: calcd for C ₁₃ H ₂₃ NO ₆ + H ⁺ , 290.15982; found (ESI ⁺ , [M+H] ¹⁺), 290.15951;
72	N-(tert-butyl)-N-([[(cyclobutylcarbonyl)oxy]methoxy]carbonyl]glycine	MS (ESI) m/z 288.1; MS (ESI) m/z 310.1; HRMS: calcd for C ₁₃ H ₂₁ NO ₆ + H ⁺ , 288.14416; found (ESI ⁺ , [M+H] ¹⁺), 288.14435;
73	N-(tert-butyl)-N-([[(3-cyclohexylpropanoyl)oxy]methoxy]carbonyl]glycine	MS (ESI) m/z 344.2; MS (ESI) m/z 709.4; HRMS: calcd for C ₁₇ H ₂₉ NO ₆ + Na ⁺ , 366.18871; found (ESI ⁺ , [M+NA] ¹⁺), 366.18863;
74	N-(tert-butyl)-N-([[(4-fluorophenoxy)acetyl]oxy]methoxy]carbonyl]glycine	MS (ESI) m/z 356.1;
75	N-(tert-butyl)-N-([[(cyclohexylacetyl)oxy]methoxy]carbonyl]glycine	MS (ESI) m/z 328; MS (ESI) m/z 657.1;

Ref. Cpd. No.	Name	Spectra
76	N-(tert-butyl)-N-({[(2,6-dimethylbenzoyl)oxy]methoxy}carbonyl)glycine	MS (ESI) m/z 338.2;
77	N-(tert-butyl)-N-({[(phenylacetyl)oxy]methoxy}carbonyl)glycine	MS (ESI) m/z 322.1; MS (ESI) m/z 645.2; HRMS: calcd for C ₁₆ H ₂₁ NO ₆ + H ⁺ , 324.14416; found (ESI ⁺ , [M+H] ¹⁺), 324.14351;
78	N-(tert-butyl)-N-({[(2,2-dimethylpropanoyl)oxy]methoxy}carbonyl)glycine	MS (ESI) m/z 288.1; MS (ESI) m/z 577.1; HRMS: calcd for C ₁₃ H ₂₃ NO ₆ + H ⁺ , 290.15982; found (ESI ⁺ , [M+H] ¹⁺), 290.15965;
79	N-({[(1-benzofuran-2-ylcarbonyl)oxy]methoxy}carbonyl)-N-(tert-butyl)glycine	MS (ESI) m/z 350; MS (ESI) m/z 721; HRMS: calcd for C ₁₇ H ₁₉ NO ₇ + H ⁺ , 350.12343; found (ESI ⁺ , [M+H] ¹⁺), 350.12327;
80	N-(tert-butyl)-N-({[(1-methyl-1H-pyrrol-2-yl)carbonyl]oxy}methoxy)carbonyl)glycine	MS (ESI) m/z 313; MS (ESI) m/z 647.1;

Ref. Cpd. No.	Name	Spectra
81	N-({[(1,1'-biphenyl-4-ylcarbonyl)oxy]methoxy}carbonyl)-N-(tert-butyl)glycine	MS (ESI) m/z 386.2; HRMS: calcd for C ₂₁ H ₂₃ NO ₆ + Na ⁺ , 408.14176; found (ESI ⁺ , [M+NA]1+), 408.14195;
82	N-(tert-butyl)-N-({[(4-methoxybenzoyl)oxy]methoxy}carbonyl)glycine	MS (ESI) m/z 338.1; MS (ESI) m/z 677.3; HRMS: calcd for C ₁₆ H ₂₁ NO ₇ + Na ⁺ , 362.12102; found (ESI ⁺ , [M+NA]1+), 362.12095;
83	N-(tert-butyl)-N-({[(1H-indol-2-ylcarbonyl)oxy]methoxy}carbonyl)glycine	MS (ESI) m/z 349.2; HRMS: calcd for C ₁₇ H ₂₀ N ₂ O ₆ + Na ⁺ , 371.12136; found (ESI ⁺ , [M+NA]1+), 371.12148;
84	N-(tert-butyl)-N-({[(diphenylacetyl)oxy]methoxy}carbonyl)glycine	MS (ESI) m/z 298.2;
85	N-(tert-butyl)-N-({[(1-naphthoyloxy)methoxy]carbonyl)glycine	MS (ESI) m/z 358.2; MS (ESI) m/z 717.4; MS (ESI) m/z 1076.6;

Ref. Cpd. No.	Name	Spectra
86	N-(tert-butyl)-N-[[[2-naphthoyloxy)methoxy]carbonyl]glycine	MS (ESI) m/z 360.1; MS (ESI) m/z 472.1;
87	N-(tert-butyl)-N-[[[[(1-methyl-1H-indol-3-yl)carbonyl]oxy)methoxy]carbonyl]glycine	MS (ESI) m/z 361.2; MS (ESI) m/z 1085.7; MS (ESI) m/z 723.5; HRMS: calcd for C ₁₈ H ₂₂ N ₂ O ₆ + H ⁺ , 363.15506; found (ESI ⁺ , [M+H] ⁺), 363.15556;
88	N-(tert-butyl)-N-[[[(quinolin-2-ylcarbonyl)oxy)methoxy]carbonyl]glycine	MS (ESI) m/z 359.2; MS (ESI) m/z 1079.7; MS (ESI) m/z 719.4;
89	N-(tert-butyl)-N-[[[(pyridin-3-ylcarbonyl)oxy)methoxy]carbonyl]glycine	MS (ESI) m/z 309.2; MS (ESI) m/z 929.5; MS (ESI) m/z 619.3;
90	N-(tert-butyl)-N-[[[isonicotinoyloxy)methoxy]carbonyl]glycine	MS (ESI) m/z 311.1; MS (ESI) m/z 333.1;
91	N-(tert-butyl)-N-[[[(2,6-difluorobenzoyl)oxy)methoxy]carbonyl]glycine	MS (ESI) m/z 390.2; MS (ESI) m/z 689.3;

Ref. Cpd. No.	Name	Spectra
92	N-(tert-butyl)-N-({[2-fluorobenzoyl]oxy}methoxy)carbonyl)glycine	MS (ESI) m/z 326.2; MS (ESI) m/z 980.6; MS (ESI) m/z 653.3;
93	N-(tert-butyl)-N-([2-(trifluoromethyl)benzoyl]oxy)methoxy)carbonyl)glycine	MS (ESI) m/z 422.1; MS (ESI) m/z 753;
94	N-(tert-butyl)-N-({[4-pyrrolidin-1-ylbenzoyl]oxy}methoxy)carbonyl)glycine	MS (ESI) m/z 379.2;
95	N-({[1,1'-biphenyl-2-ylcarbonyl]oxy}methoxy)carbonyl)-N-(tert-butyl)glycine	MS (ESI) m/z 384.3; MS (ESI) m/z 1154.7; MS (ESI) m/z 769.5;
96	N-(tert-butyl)-N-({[mesitylcarbonyl]oxy}methoxy)carbonyl)glycine	MS (ESI) m/z 701.5; MS (ESI) m/z 386.2; MS (ESI) m/z 1052.8;
97	N-(tert-butyl)-N-({[4-isopropoxybenzoyl]oxy}methoxy)carbonyl)glycine	MS (ESI) m/z 733.3; MS (ESI) m/z 1100.3; MS (ESI) m/z 412.2; HRMS: calcd for C ₁₈ H ₂₅ NO ₇ + H ⁺ , 368.17038; found (ESI ⁺ , [M+H] ¹⁺), 368.17069;

Ref. Cpd. No.	Name	Spectra
98	N-(tert-butyl)-N-({[(3,4,5-trimethoxybenzoyl)oxy]methoxy}carbonyl)glycine	MS (ESI) m/z 398; MS (ESI) m/z 797.2; MS (ESI) m/z 1195.9; HRMS: calcd for C ₁₈ H ₂₅ NO ₉ + H ⁺ , 400.16021; found (ESI ⁺ , [M+H] ¹⁺), 400.1610
99	N-(tert-butyl)-N-({[(3,5-dimethoxybenzoyl)oxy]methoxy}carbonyl)glycine	MS (ESI) m/z 368.1; MS (ESI) m/z 737.1; MS (ESI) m/z 414; HRMS: calcd for C ₁₇ H ₂₃ NO ₈ + H ⁺ , 370.14965; found (ESI ⁺ , [M+H] ¹⁺), 370.15016;
100	N-(tert-butyl)-N-({[(2E)-3-phenylprop-2-enoyl]oxy}methoxy)carbonyl)glycine	MS (ESI) m/z 334.2; MS (ESI) m/z 669.4; MS (ESI) m/z 1004.6; HRMS: calcd for C ₁₇ H ₂₁ NO ₆ + Na ⁺ , 358.12611; found (ESI ⁺ , [M+NA] ¹⁺), 358.12763;

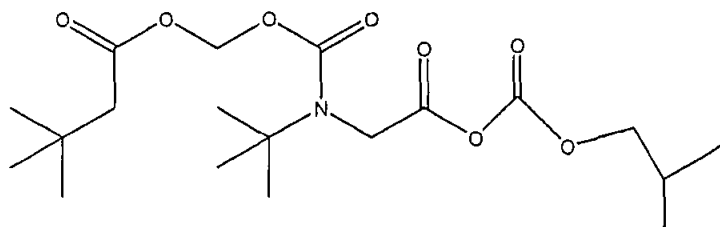
Ref. Cpd. No.	Name	Spectra
101	N-(tert-butyl)-N-[[[(3-methyl-1-benzofuran-2-yl)carbonyl]oxy}methoxy)carbonyl]glycine	MS (ESI) m/z 725.4; MS (ESI) m/z 1088.6; MS (ESI) m/z 398.2; HRMS: calcd for C ₁₈ H ₂₁ NO ₇ + H ⁺ , 364.13908; found (ESI, [M+H] ¹⁺), 364.13956;
102	N-[[[3,5-bis(trifluoromethyl)phenyl]acetyl]oxy}methoxy]carbonyl}-N-(tert-butyl)glycine	MS (ESI) m/z 458.1; MS (ESI) m/z 917.1; HRMS: calcd for C ₁₈ H ₁₉ F ₆ NO ₆ + H ⁺ , 460.11893; found (ESI+, [M+H] ¹⁺), 460.11854;
103	N-(tert-butyl)-N-[[[4-(heptyloxy)benzoyl]oxy}methoxy)carbonyl]glycine	MS (ESI) m/z 422.2; MS (ESI) m/z 468.3; MS (ESI) m/z 845.3; HRMS: calcd for C ₂₂ H ₃₃ NO ₇ + H ⁺ , 424.23298; found (ESI+, [M+H] ¹⁺), 424.23295;

Ref. Cpd. No.	Name	Spectra
104	N-(tert-butyl)-N-([2-(2-phenylethyl)benzoyl]oxy)methoxy)carbonyl]glycine	MS (ESI+) m/z 414.19088; MS (ESI+) m/z 414.19112; HRMS: calcd for C ₂₃ H ₂₇ NO ₆ + H ⁺ , 414.19112; found (ESI+, [M+H] ¹⁺), 414.19088;
105	N-(tert-butyl)-N-([4-(dodecyloxy)benzoyl]oxy)methoxy)carbonyl]glycine	MS (ESI+) m/z 494.31095; MS (ESI+) m/z 494.31123; HRMS: calcd for C ₂₇ H ₄₃ NO ₇ + H ⁺ , 494.31123; found (ESI+, [M+H] ¹⁺), 494.31095;
106	N-([4-(acetylamino)benzoyl]oxy)methoxy)carbonyl]-N-(tert-butyl)glycine	MS (ESI) m/z 367.1; MS (ESI) m/z 733.1;
107	N-([9-anthrylcarbonyl]oxy)methoxy)carbonyl]-N-(tert-butyl)glycine	MS (ESI) m/z 408.3; MS (ESI) m/z 1226.7; MS (ESI) m/z 817.5;
108	N-([4-benzoylbenzoyl]oxy)methoxy)carbonyl]-N-(tert-butyl)glycine	MS (ESI) m/z 414.2;

Reference Compound 109

3,3-Dimethyl-butylric acid [tert-butyl-(2-isobutoxycarbonyloxy-2-oxo-ethyl)-
carbamoyloxy)-methyl ester.

5

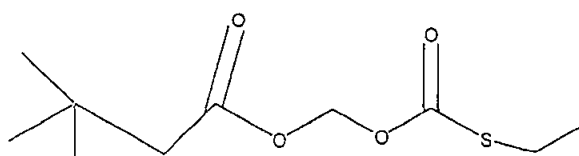


To a solution of Reference Compound 56 in dichloromethane at room temperature is added 1.2 equivalent of [1,8-bis(dimethylamino)naphthalene, N,N,N',N'-tetramethyl-
10 1,8-naphthalenediamine] and 0.95 equivalent of iso-butylchloroformate. The reaction is stirred for 24 hour, diluted with dichloromethane, washed with dilute HCl, brine, then water. It is dried with sodium sulfate. Solvent removed and the product is used in the next step without further purification.

15

Reference Compound 110

3,3-Dimethylbutyric acid ethylsulfanylcabonyloxymethyl ester

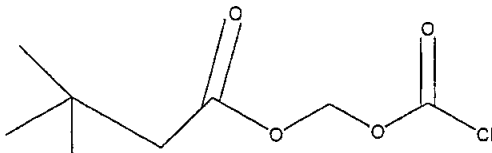


To a solution of t-butylacetic acid (0.025 mol, 3 g) in methanol is added
20 tetrabutylammonium hydroxide (1M/methanol, 25 ml). The mixture is stirred for 1 h and the solvent removed to a residue. The residue is dissolved in 150 ml of methylene chloride and 150 ml of water and a solution of O-chloromethyl S-ethyl carbonothioate (0.025 mol, 3.85 f) in 50 ml of methylene chloride added. The mixture
25 is stirred at room temperature for 24 h. The methylene chloride layer is separated, washed with water, brine and dried over sodium sulfate. The solvent is removed under vacuo and the residue stirred in 300 ml of ether for 24 h. The resulting white

solid is filtered, the solid discarded and the solvent removed from the filtrate to give 6 g of a crude oil.

Reference Compound 111

5



To a stirred solution of 3,3-dimethylbutyric acid ethylsulfanyloxymethyl ester (Reference Compound 110) (0.025 ml, 6 g) in methylene chloride at -20°C (dry ice/carbon tetrachloride) is added sulfuryl chloride (0.025 mol, 3.5 g). After 10 min, 0.1 ml of boron trifluoride etherate is added. The mixture is stirred at 0°C for 1 h, at room temperature for 30 min. The volatiles are removed by distillation to yield 4.9 g of the desired acid chloride.

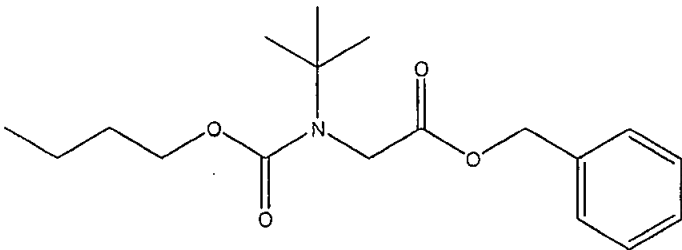
15

Following the procedure of Reference Compound 111 the corresponding acid chloride used in Examples 112 to 120 was prepared.

Reference Compound 112

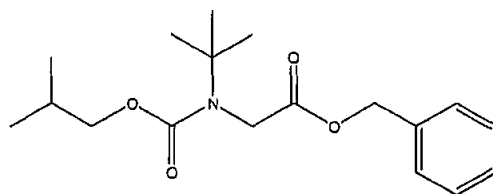
20

benzyl N-(butoxycarbonyl)-N-(tert-butyl)glycinate



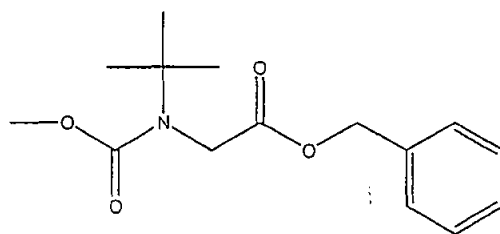
Reference Compound 113
benzyl N-(tert-butyl)-N-(isobutoxycarbonyl)glycinate

5



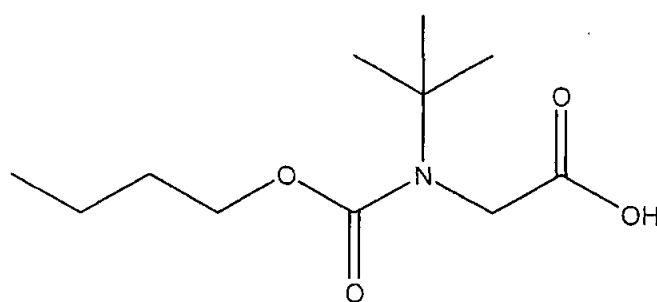
Reference Compound 114
benzyl N-(tert-butyl)-N-(methoxycarbonyl)glycinate

10



Reference Compound 115
N-(butoxycarbonyl)-N-(tert-butyl)glycine

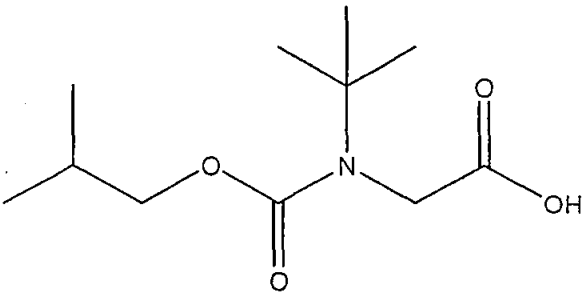
15



20

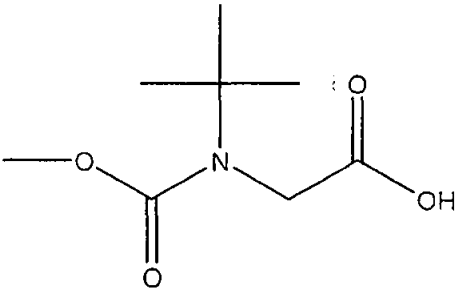
5

Reference Compound 116
N-(tert-butyl)-N-(isobutoxycarbonyl)glycine



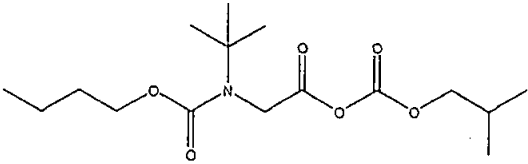
10

Reference Compound 117
N-(tert-butyl)-N-(methoxycarbonyl)glycine



15

Reference Compound 118
isobutoxycarbonyl N-(butoxycarbonyl)-N-(tert-butyl)glycinate

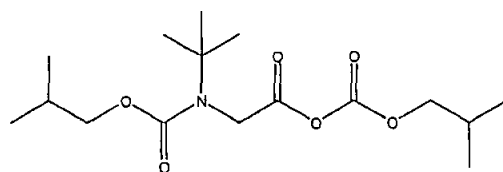


20

Reference Compound 119

isobutoxycarbonyl N-(tert-butyl)-N-(isobutoxycarbonyl)glycinate

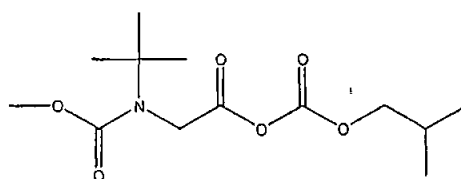
5



Reference compound 120

isobutoxycarbonyl N-(tert-butyl)-N-(methoxycarbonyl)glycinate

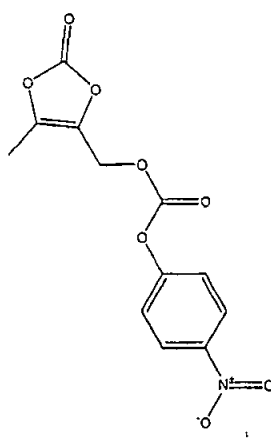
10



15

Reference Compound 121

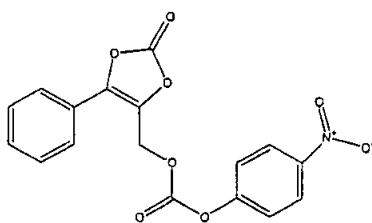
(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-nitrophenyl carbonate



The product of the Reference Example was prepared using the conditions described by R. Sakamoto et al, Chem. Pharm. Bull. 32(6), 2241-2248(1984).

Reference Compound 122

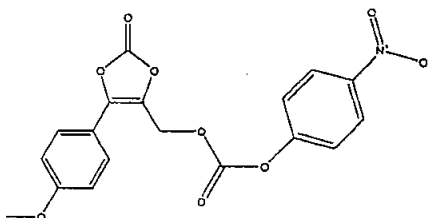
5 4-nitrophenyl (2-oxo-5-phenyl-1,3-dioxol-4-yl)methyl carbonate



10 The product of the Reference Example was prepared using the conditions described by R. Sakamoto et al, Chem. Pharm. Bull. 32(6), 2241-2248(1984).

Reference Compound 123

15 [5-(4-methoxyphenyl)-2-oxo-1,3-dioxol-4-yl]methyl 4-nitrophenyl carbonate



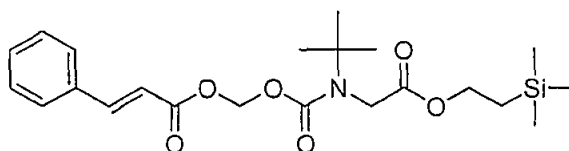
20 The product of the Reference Example was prepared using the conditions described by R. Sakamoto et al, Chem. Pharm. Bull. 32(6), 2241-2248(1984).

25

144

Reference Compound 124

4-tert-butyl-10,10-dimethyl-3,6-dioxo-2,7-dioxa-4-aza-10-silaundec-1-yl (2E)-3-phenylacrylate



5

Trans-cinnamic acid (23.1 mmol) and 1.0 M tetrabutylammonium hydroxide (22.2 mmol) in methanol are stirred for one hour, and the methanol is removed. THF is added. To this solution is added 2-(trimethylsilyl)ethyl 2-(tert-butyl((chloromethoxy)carbonyl)amino)-acetate (18.5 mmol) and the mixture is stirred at room temperature for 24 hr. The solvent is removed and the residue is diluted with ether. The resulting solution is washed with water and brine. The organic layer is dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield 5.01 g (61%) MS (ESI) m/z 436.3.

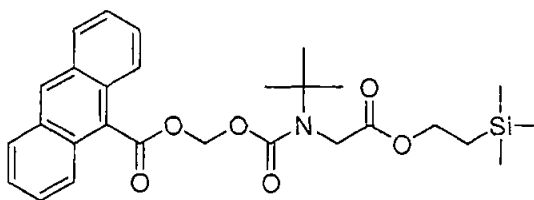
10

Using substantially the same procedure as described above for Reference Compound 124 the following reference compounds were prepared from the appropriate carboxylic acids:

15

Reference Compound 125

4-tert-butyl-10,10-dimethyl-3,6-dioxo-2,7-dioxa-4-aza-10-silaundec-1-yl anthracene-9-carboxylate



MS (ESI) m/z 510.3

25

Reference Compound 126

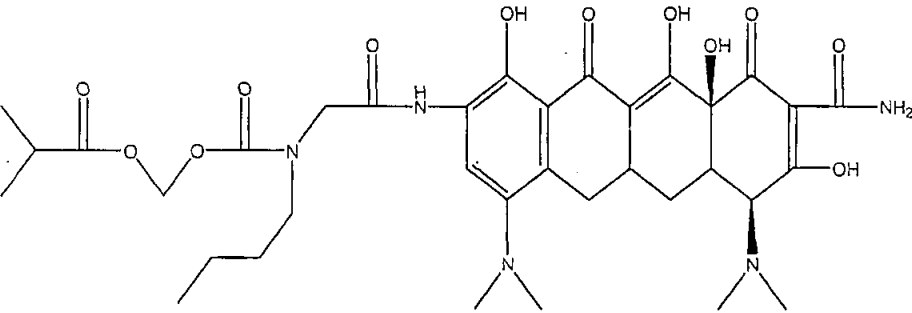
4-tert-butyl-10,10-dimethyl-3,6-dioxo-2,7-dioxa-4-aza-10-silaundecyl 4-benzoylbenzoate

5

MS (ESI) m/z 536.2

Example 1

10 {{{(2-(((7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(butyl)amino]carbonyl)oxy)methyl 2-methylpropanoate



15

To a solution of n-Butylglycylcycline in acetonitrile/DMPA (1:5), sodium carbonate is added. The reaction mixture is stirred for 5 min and propanoic acid, 2-methyl-
 20 [(chlorocarbonyl)oxy]methyl ester prepared according to the methods described in M. Folkmann and F.J. Lund, Synthesis, December 1990, 1159-1166, is added. Stirring is continued for about 30 to 45 minute (or monitored by MS (ES)). Upon completion of the reaction, 0.5 mL of methanol is added and the mixture poured slowly into a mixture of isopropanol and ether. 1.0M HCl in ether is added and the solid is filtered. The solid is dissolved in water and is extracted with methylene chloride to give the
 25 product of the Example. MS (ESI) m/z 730.28 (M+H);

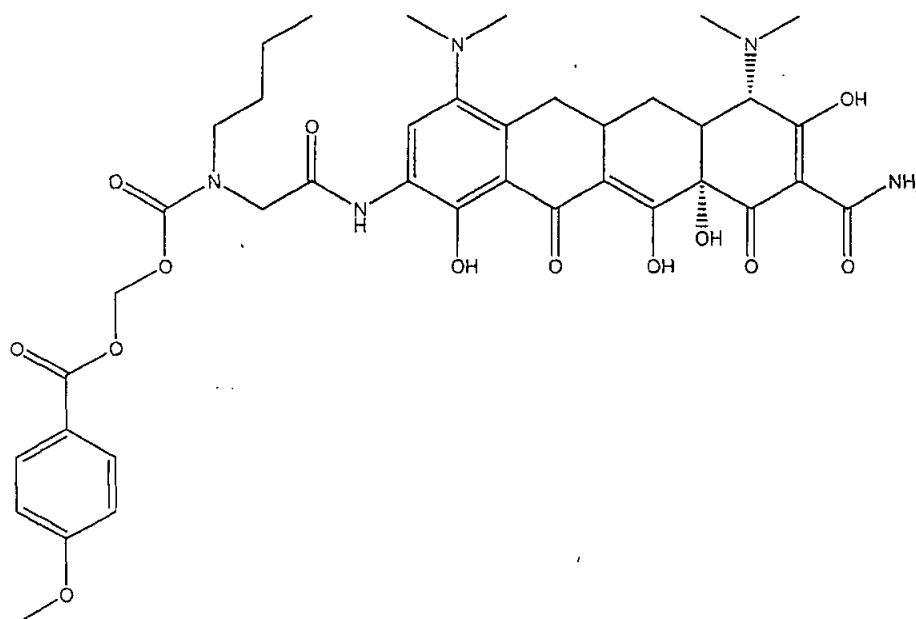
Following the procedure of Example 1, and the corresponding acid chloride prepared by methods described in M. Folkmann and F.J. Lund, Synthesis, December 1990, 1159-1166 and N-butylglycylcycline or N-propylglycylcycline the following Examples 2-41 are prepared.

5

Example 2

({[(2-[[[(7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl 4-methoxybenzoate

10



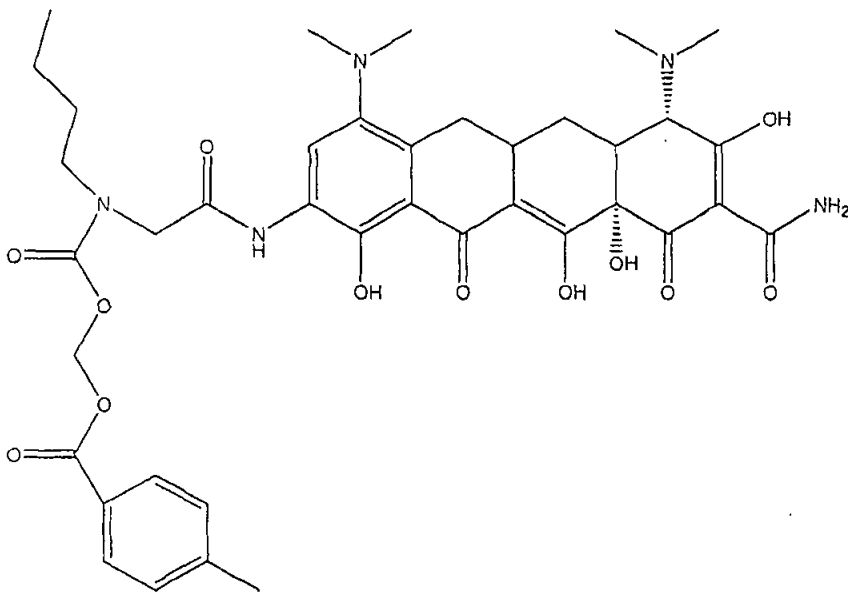
The title compound is prepared by the procedure of Example 1, using

[(chlorocarbonyl)oxy]methyl 4-methoxybenzoate and N-butylglycylcycline to give the product of the Example.

15

Example 3

5 (((2-(((7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl 4-methylbenzoate

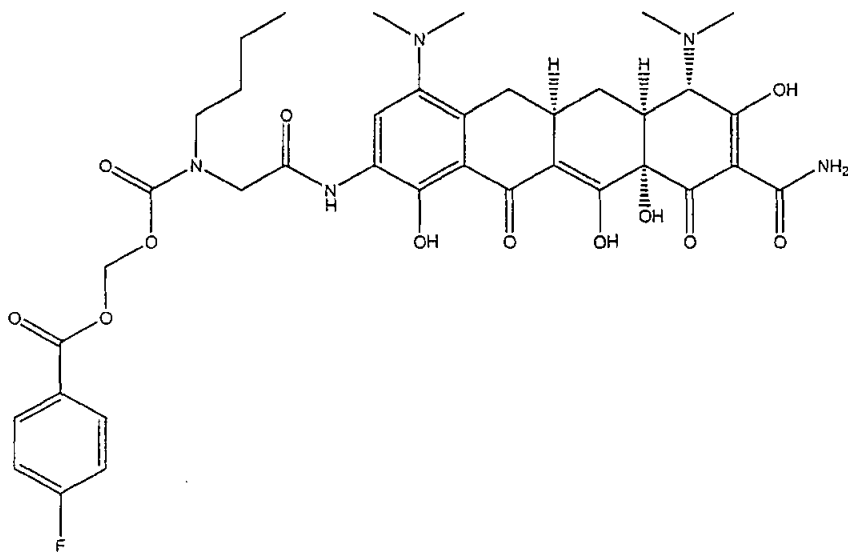


10 The title compound is prepared by the procedure of Example 1, using [(chlorocarbonyl)oxy]methyl 4-methylbenzoate and N-butylglycylcyclocline to give the product of the Example.

15 MS (ESI) m/z 778.3 ((M+H)+);

Example 4

5 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(butyl)amino]carbonyl)oxy)methyl 4-fluorobenzoate



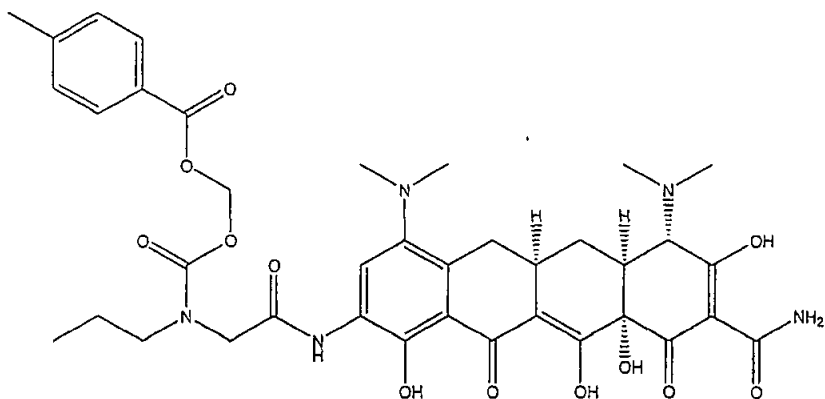
10 The title compound is prepared by the procedure of Example 1, using [(chlorocarbonyl)oxy]methyl 4-fluorobenzoate and N-butylglycylcycline to give the product of the Example.

MS (ESI) m/z 782.3 ((M+H)+);

15

Example 5

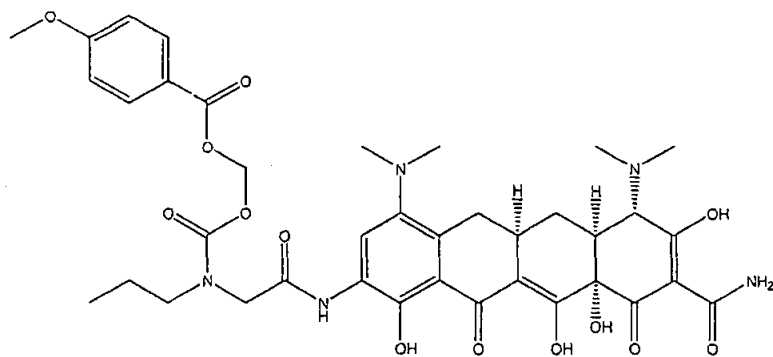
20 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(propyl)amino]carbonyl)oxy)methyl 4-methylbenzoate



The title compound is prepared by the procedure of Example 1, using
 5 [(chlorocarbonyl)oxy]methyl 4-methylbenzoate and N-propylglycylcycline to give the product of the Example.
 MS (ESI) m/z 764.3 ((M+H)+);

Example 6

10 ({[(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](propyl)amino]carbonyl}oxy)methyl 4-methoxybenzoate

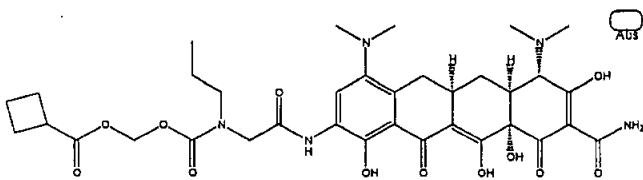


15 The title compound is prepared by the procedure of Example 1, using
 [(chlorocarbonyl)oxy]methyl 4-methoxybenzoate and N-propylglycylcycline to give the product of the Example.

20 MS (ESI) m/z 780.3 ((M+H)+);

Example 7

5 {{{2-{{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl}amino}-2-oxoethyl}(propyl)amino]carbonyl}oxy)methyl cyclobutanecarboxylate



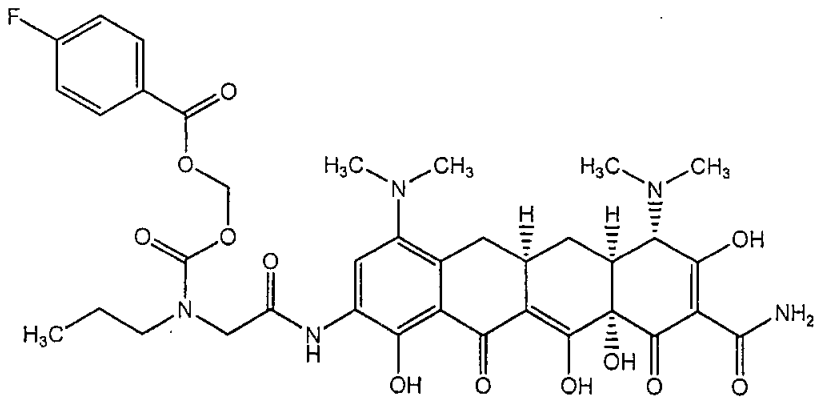
10

The title compound is prepared by the procedure of Example 1, using [(chlorocarbonyl)oxy]methyl cyclobutanecarboxylate and N-propylglycylcycline to give the product of the Example.

15 MS (ESI) m/z 728.3 ((M+H)+);

Example 8

20 {{{2-{{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl}amino}-2-oxoethyl}(propyl)amino]carbonyl}oxy)methyl 4-fluorobenzoate

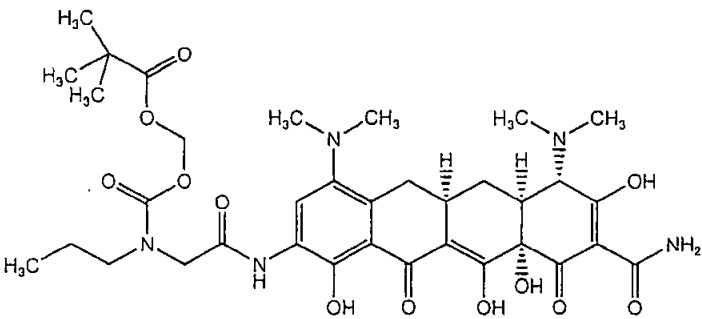


The title compound is prepared by the procedure of Example 1, using [(chlorocarbonyl)oxy]methyl 4-fluorobenzoate and N-propylglycylcycline to give the product of the Example.

MS (ESI) m/z 768.3 ((M+H)+);

Example 9

((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(propyl)amino]carbonyl)oxy)methyl pivalate

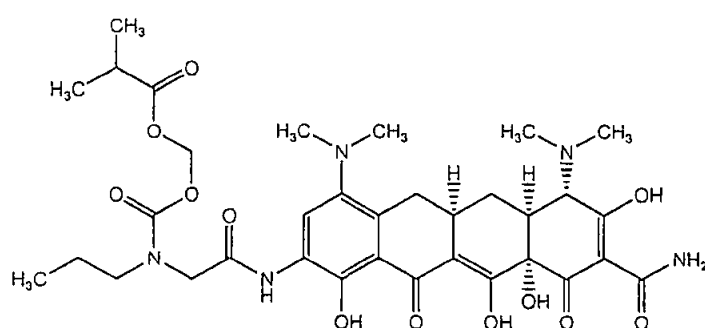


The title compound is prepared by the procedure of Example 1, using Propanoic acid, 2,2-dimethyl-, [(chlorocarbonyl)oxy]methyl ester and N-propylglycylcycline to give the product of the Example.

MS (ESI) m/z 730.3 ((M+H)+);

Example 10

- 5 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(propyl)amino]carbonyl)oxy)methyl 2-methylpropanoate



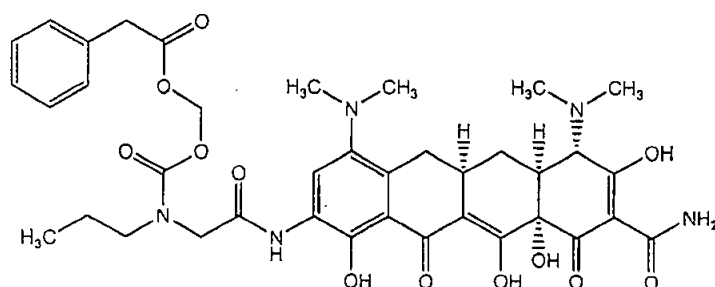
10

The title compound is prepared by the procedure of Example 1, using propanoic acid, 2-methyl-,[(chlorocarbonyl)oxy]methyl ester and N-propylglycylcycline to give the product of the Example.

- 15 MS (ESI) m/z 716.3 ((M+H)+);

Example 11

- 20 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(propyl)amino]carbonyl)oxy)methyl phenylacetate



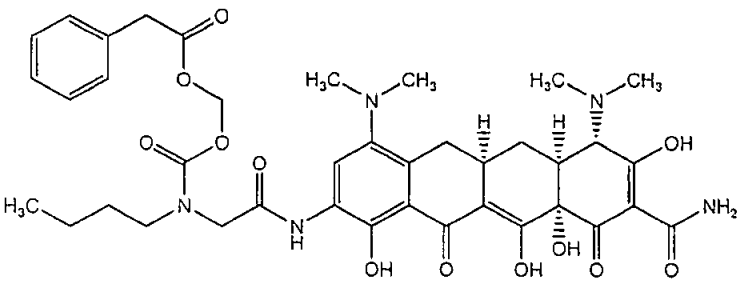
The title compound is prepared by the procedure of Example 1, using benzeneacetic acid, [(chlorocarbonyl)oxy]methyl ester and N-propylglycylcyclycline to give the product of the Example.

5

MS (ESI) m/z 764.3 ((M+H)+

Example 12

10 {{{2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl}(butyl)amino]carbonyl}oxy)methyl phenylacetate



15

The title compound is prepared by the procedure of Example 1, using using benzeneacetic acid, [(chlorocarbonyl)oxy]methyl ester and N-butylglycylcyclycline to give the product of the Example.

20

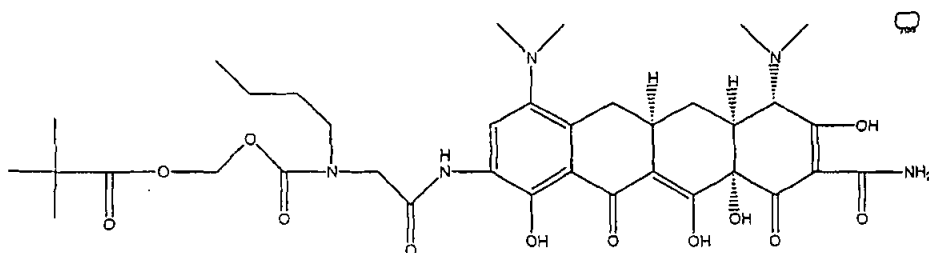
MS (ESI) m/z 778.3 ((M+H)+);

Example 13

5

<{[(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl pivalate

10



The title compound is prepared by the procedure of Example 1, using propanoic acid, 2,2-dimethyl-, [(chlorocarbonyl)oxy]methyl ester and N-butylglycylcycline to give the product of the Example.

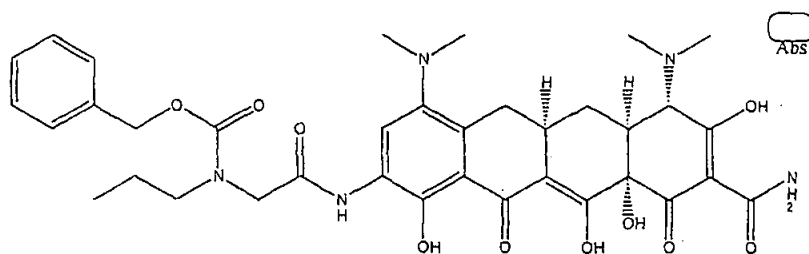
15

MS (ESI) m/z 744.3 ((M+H)+);

Example 14

20 benzyl 2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl(propyl)carbamate

25



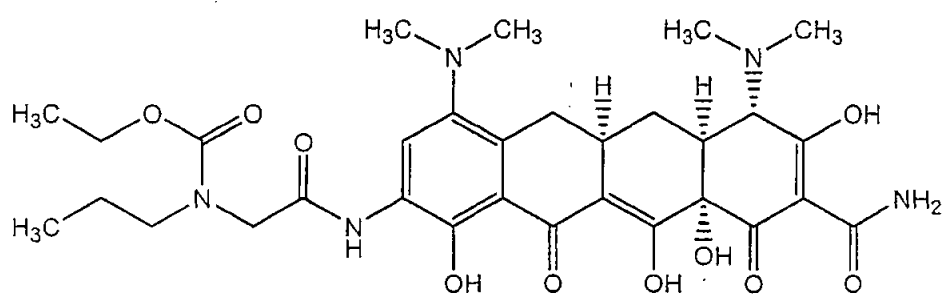
The title compound is prepared by the procedure of Example 1, using benzyl chloroformate and N-propylglycylcycline in the presence of sodium carbonate and DMPU in acetonitrile to give the product of the Example.

- 5 MS (ESI) m/z 706.3 ((M+H)⁺);
HRMS: calcd for $C_{35}H_{43}N_5O_{10} \cdot HCl$, 741.2777; found (ESI), 706.31133;

Example 15

10

ethyl 2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl(propyl)carbamate



The title compound is prepared by the procedure of Example 1, using ethyl chloroformate and N-propylglycylcycline in the presence of sodium carbonate and DMPU in acetonitrile to give the product of the Example.

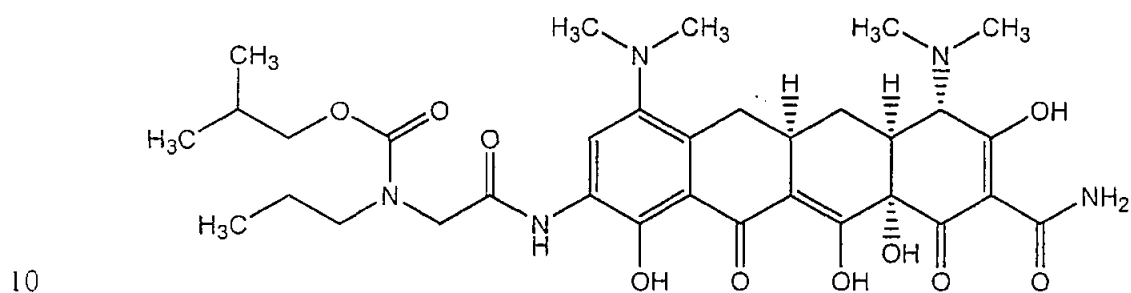
20

- MS (ESI) m/z 644.3 ((M+H)⁺);
HRMS: calcd for $C_{31}H_{41}N_5O_{10} \cdot HCl$, 679.2620; found (ESI⁺), 644.29398;

152

Example 16

- 5 isobutyl 2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl(propyl)carbamate



The title compound is prepared by the procedure of Example 1, using isobutyl chloroformate and N-propylglycylcycline in the presence of sodium carbonate and DMPU in acetonitrile to give the product of the Example.

15

MS (ESI) m/z 672.3 ((M+H)+);

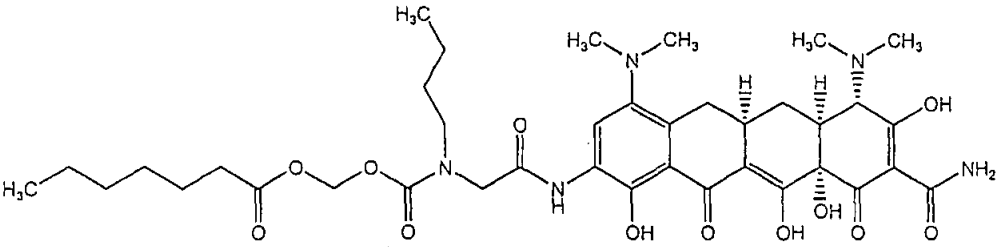
MS (ESI) m/z 336.9 ((M+2H)2+);

HRMS: calcd for $C_{33}H_{45}N_5O_{10} \cdot HCl$, 707.2933; found (ESI+), 672.32618

20

Example 17

- 25 (((2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl)(butyl)amino]carbonyl)oxy)methyl heptanoate

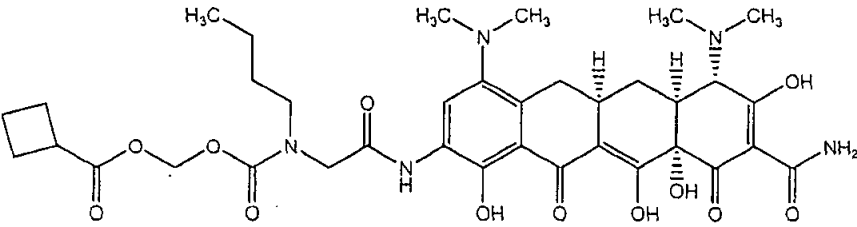


The title compound is prepared by the procedure of Example 1, using heptanoic acid, [(chlorocarbonyl)oxy]methyl ester and N-butylglycylcyclohexanecarboxamide to give the product of the Example.

MS (ESI+) m/z 772.2 (M+H);
 HRMS: calcd for C₃₈H₅₃N₅O₁₂ · 2.00 HCl, 843.3224; found (ESI+), 772.37696;

Example 18

(((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(butyl)amino]carbonyl)oxy)methyl cyclobutanecarboxylate

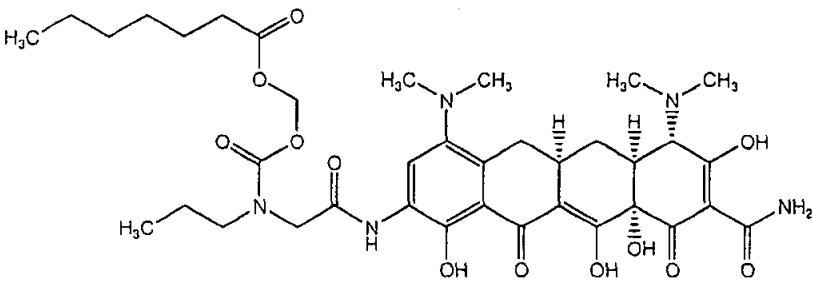


The title compound is prepared by the procedure of Example 1, using [(chlorocarbonyl)oxy]methyl cyclobutanecarboxylate and N-butylglycylcyclohexanecarboxamide to give the product of the Example.

MS (ESI) m/z 742.3 ((M+H)+);
 HRMS: calcd for C₃₆H₄₇N₅O₁₂ · 2.00 HCl, 813.2755; found (ESI+), 742.32898;

Example 19

- 5 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl heptanoate



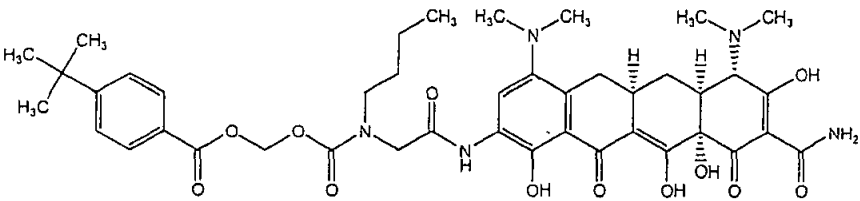
10

The title compound is prepared by the procedure of Example 1, using Heptanoic acid, [(chlorocarbonyl)oxy]methyl ester and N-propylglycylcycline to give the product of the Example.

- 15 MS (ESI) m/z 758.4 ((M+H)+);
 HRMS: calcd for C₃₇H₅₁N₅O₁₂ · HCl, 793.3301; found (ESI+), 758.36175;

Example 20

- 20 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl 4-tert-butylbenzoate



25

The title compound is prepared by the procedure of Example 1, using [(chlorocarbonyl)oxy]methyl 4-tert-butylbenzoate and N-butylglycylcycline to give the product of the Example.

5

MS (ESI+) m/z 820.2 (M+H);

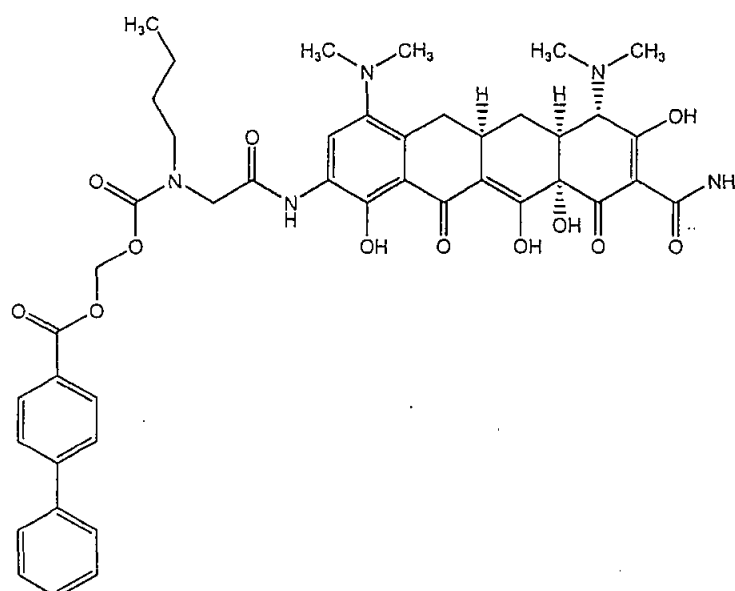
HRMS: calcd for C₄₂H₅₃N₅O₁₂ · HCl, 855.3458; found (ESI+), 820.37684;

10

Example 21

(([(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(butyl)amino]carbonyl)oxy)methyl 1,1'-biphenyl-4-carboxylate

15



The title compound is prepared by the procedure of Example 1, using [(chlorocarbonyl)oxy]methyl biphenyl-4-carboxylate and N-butylglycylcycline to give the product of the Example.

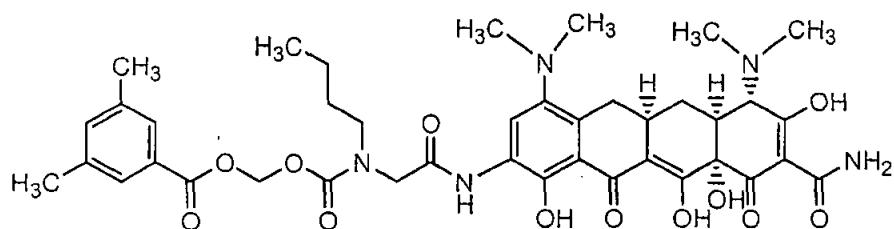
20

MS (ESI) m/z 840.3 ((M+H)⁺);

HRMS: calcd for $C_{44}H_{49}N_5O_{12} \cdot HCl$, 875.3145; found (ESI+), 840.34337;

Example 22

([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](butyl)amino]carbonyl)oxy)methyl 3,5-dimethylbenzoate



The title compound is prepared by the procedure of Example 1, using

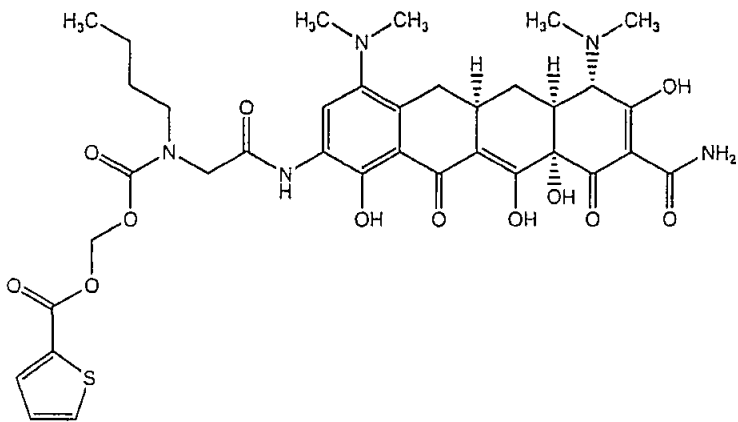
[(chlorocarbonyl)oxy]methyl 3,5-dimethylbenzoate and N-butylglycylcycline to give the product of the Example.

MS (ESI) m/z 792.3 ((M+H)⁺);

HRMS: calcd for $C_{40}H_{49}N_5O_{12} \cdot 2.00 \text{ HCl}$, 863.2911; found (ESI+), 792.34378;

Example 23

([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](butyl)amino]carbonyl)oxy)methyl thiophene-2-carboxylate



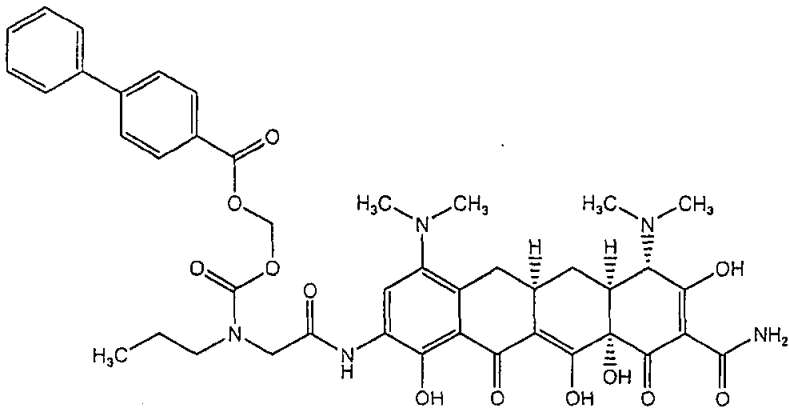
The title compound is prepared by the procedure of Example 1, using
 [(chlorocarbonyl)oxy]methyl thiophene-2-carboxylate and N-butylglycylcycline to give
 5 the product of the Example.

MS (ESI) m/z 770.1 ((M+H)+);
 HRMS: calcd for C₃₆H₄₃N₅O₁₂S · HCl, 805.2396; found (ESI+), 770.27084;

10

Example 24

15 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(propyl)amino]carbonyl)oxy)methyl 1,1'-biphenyl-4-carboxylate



The title compound is prepared by the procedure of Example 1, using [(chlorocarbonyl)oxy]methyl biphenyl-4-carboxylate and N-propylglycylcycline to give the product of the Example.

5

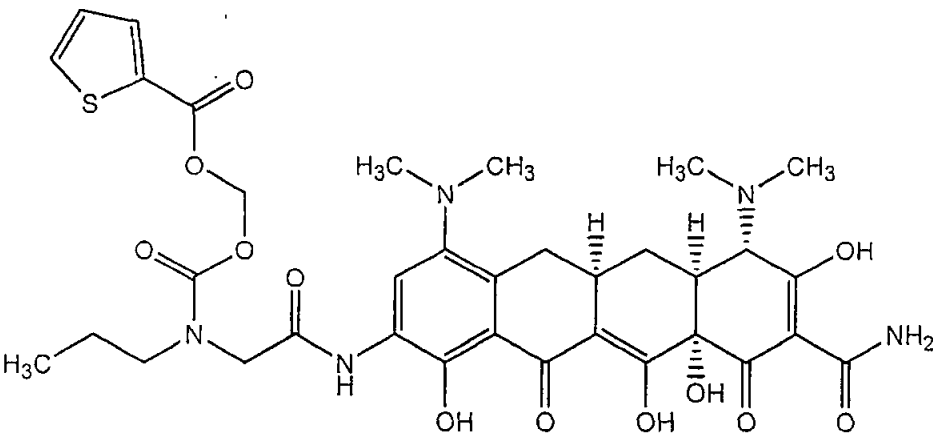
MS (ESI) m/z 826.4 ((M+H)+);
 MS (ESI) m/z 414 ((M+2H)2+);
 HRMS: calcd for C₄₃H₄₇N₅O₁₂ · HCl, 861.2988; found (ESI+), 826.32782;

10

Example 25

({[(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl thiophene-2-carboxylate

15



20

The title compound is prepared by the procedure of Example 1, using [(chlorocarbonyl)oxy]methyl thiophene-2-carboxylate and N-propylglycylcycline to give the product of the Example.

25

MS (ESI) m/z 756.3 ((M+H)+);

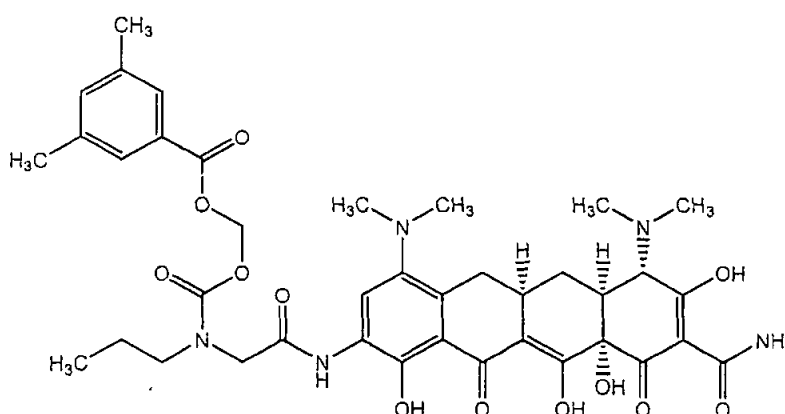
MS (ESI) m/z 378.9 ((M+2H)2+);

HRMS: calcd for C₃₅H₄₁N₅O₁₂S · HCl, 791.2239; found (ESI+), 756.2532;

5

Example 26

10 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(propyl)amino]carbonyl)oxy)methyl 3,5-dimethylbenzoate



15 The title compound is prepared by the procedure of Example 1, using [(chlorocarbonyl)oxy]methyl 3,5-dimethylbenzoate and N-propylglycylcycline to give the product of the Example.

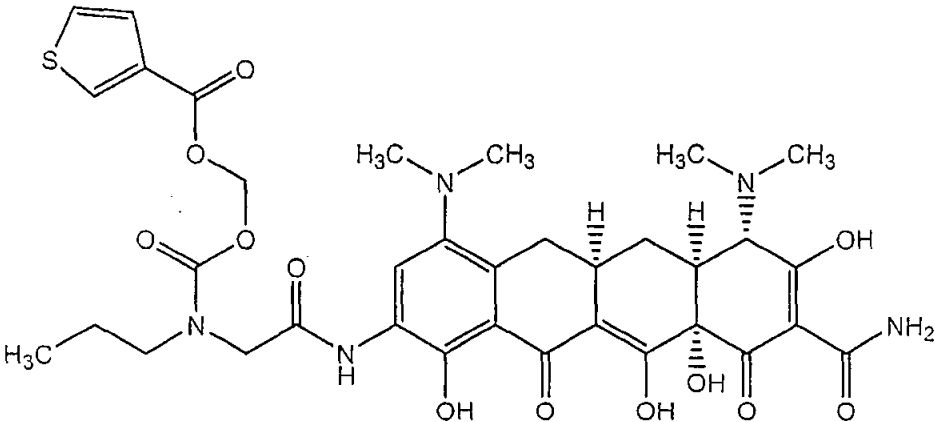
20 MS (ESI) m/z 778.3 ((M+H)+);

HRMS: calcd for C₃₉H₄₇N₅O₁₂ · HCl, 813.2988; found (ESI+), 778.32984;

Example 27

25 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(propyl)amino]carbonyl)oxy)methyl thiophene-3-carboxylate

164



5

10 The title compound is prepared by the procedure of Example 1, using [(chlorocarbonyl)oxy]methyl thiophene-3-carboxylate and N-propylglycylcycline to give the product of the Example.

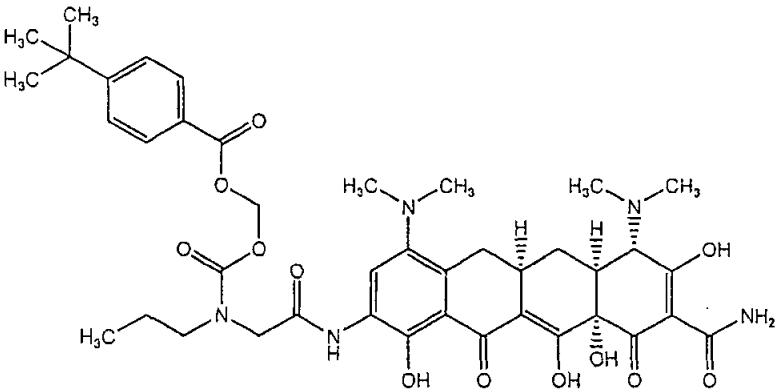
15 MS (ESI) m/z 756.3 ((M+H)+);
HRMS: calcd for C₃₅H₄₁N₅O₁₂S · HCl, 791.2239; found (ESI+), 756.2547;

Example 28

20

(([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](propyl)amino]carbonyl)oxy)methyl 4-tert-butylbenzoate

25

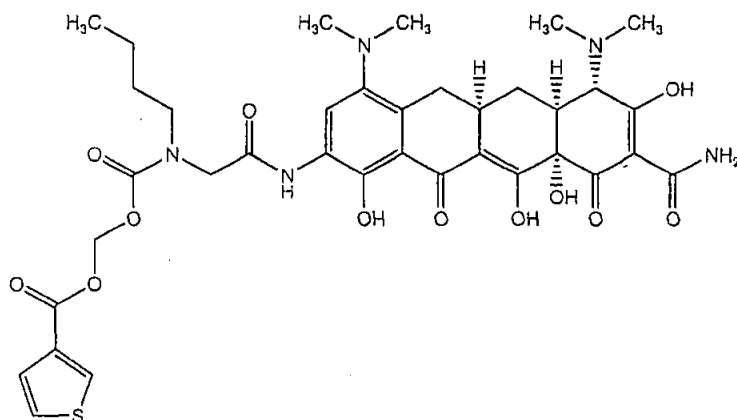


The title compound is prepared by the procedure of Example 1, using
 5 [(chlorocarbonyl)oxy]methyl 4-tert-butylbenzoate and N-propylglycylcycline to give
 the product of the Example.

MS (ESI) m/z 806.4 ((M+H)+);
 MS (ESI) m/z 403.9 ((M+2H)2+);
 10 HRMS: calcd for C₄₁H₅₁N₅O₁₂ · HCl, 841.3301; found (ESI+), 806.36024;

Example 29

5 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(butyl)amino]carbonyl)oxy)methyl thiophene-3-carboxylate



10

The title compound is prepared by the procedure of Example 1, using [(chlorocarbonyl)oxy)methyl thiophene-3-carboxylate and N-butylglycylcycline to give the product of the Example.

15

MS (ESI) m/z 770.3 ((M+H)⁺);

HRMS: calcd for $C_{36}H_{43}N_5O_{12}S \cdot HCl$, 805.2396; found (ESI⁺), 770.27028;

20

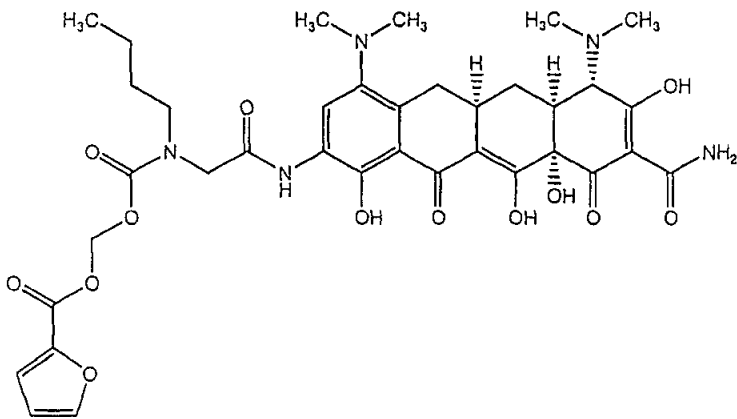
Example 30

(((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(butyl)amino]carbonyl)oxy)methyl 2-furoate

25

162

5



10

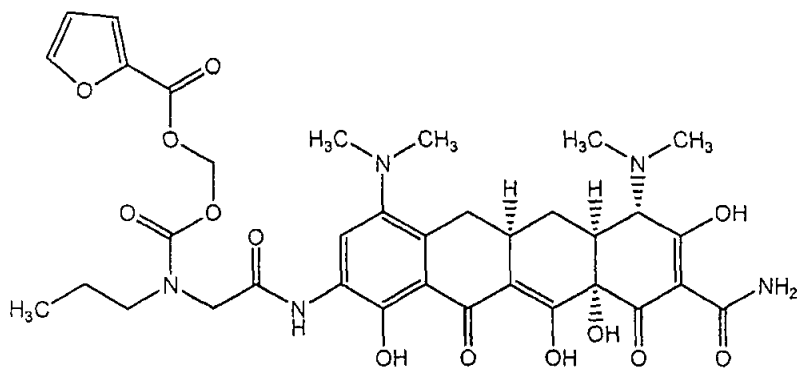
The title compound is prepared by the procedure of Example 1, using [(chlorocarbonyl)oxy]methyl 2-furoate and N-butylglycylcycline to give the product of the Example.

MS (ESI) m/z 752.2 ((M-H)-);
HRMS: calcd for C₃₆H₄₃N₅O₁₃ · HCl, 789.2624; found (ESI+), 754.29242;

Example 31

15

(([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl 2-furoate



The title compound is prepared by the procedure of Example 1, using [(chlorocarbonyl)oxy]methyl 2-furoate and N-propylglycylcycline to give the product of the Example.

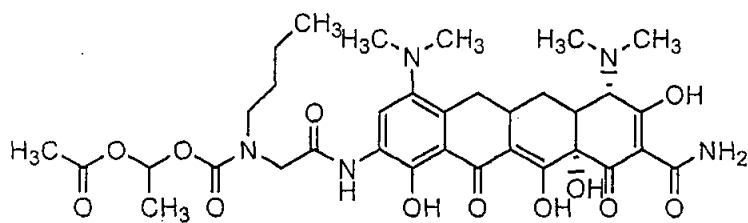
MS (ESI) m/z 740.19 (M+H);

10

Example 32

1-([[(2-[[[(7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](butyl)amino]carbonyl]oxy)ethyl acetate

15



The title compound is prepared by the procedure of Example 1, using 1-[(chlorocarbonyl)oxy]ethyl acetate and N-butylglycylcycline to give the product of the Example.

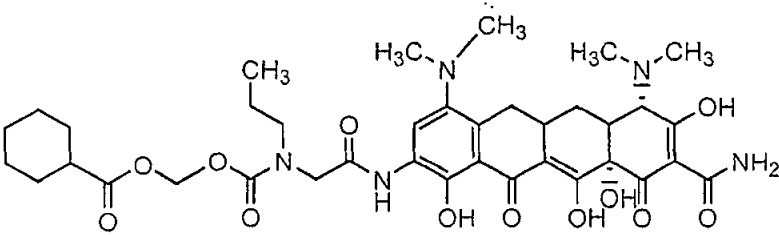
MS (ESI) m/z 716.14 (M+H);
HRMS: calcd for C₃₄H₄₅N₅O₁₂, 715.3065; found (ESI+), 716.31469;

Example 33

5

((2-(((7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(propyl)amino]carbonyl)oxy)methyl cyclohexanecarboxylate

10



The title compound is prepared by the procedure of Example 1, using cyclohexanecarboxylic acid, [(chlorocarbonyl)oxy]methyl ester and N-propylglycylcyclycline to give the product of the Example.

15

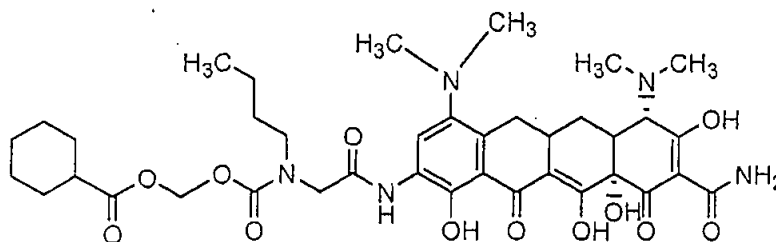
MS (ESI) m/z 756.08 (M+H);
HRMS: calcd for C₃₇H₄₉N₅O₁₂, 755.3378; found (ESI+), 756.34507;

20

Example 34

((2-(((7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(butyl)amino]carbonyl)oxy)methyl cyclohexanecarboxylate

25



The title compound is prepared by the procedure of Example 1, using
 5 cyclohexanecarboxylic acid, [(chlorocarbonyl)oxy]methyl ester and N-
 butylglycylcyclocline to give the product of the Example.

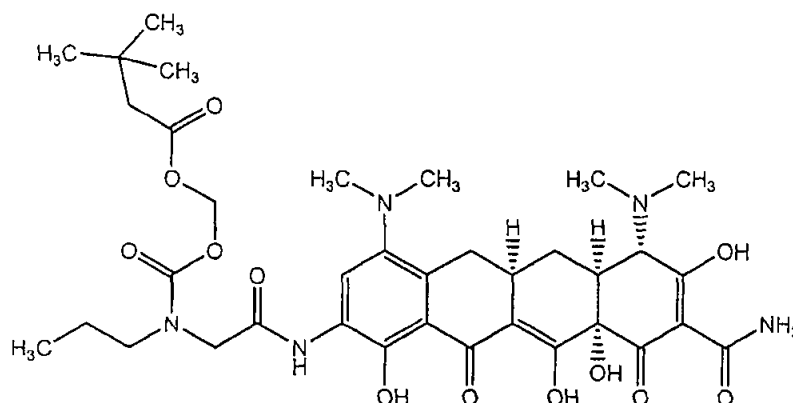
MS (ESI) m/z 70.64 (M+H);

HRMS: calcd for $C_{38}H_{51}N_5O_{12} \cdot HCl$, 805.3301; found (ESI+), 770.36093;

10

Example 35

([[(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-
 15 tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-
 oxoethyl)(propyl)amino]carbonyl]oxy)methyl 3,3-dimethylbutanoate



The title compound is prepared by the procedure of Example 1, using butanoic acid,
 3,3-dimethyl-, [(chlorocarbonyl)oxy]methyl ester and N-propylglycylcyclocline to give
 20 the product of the Example.

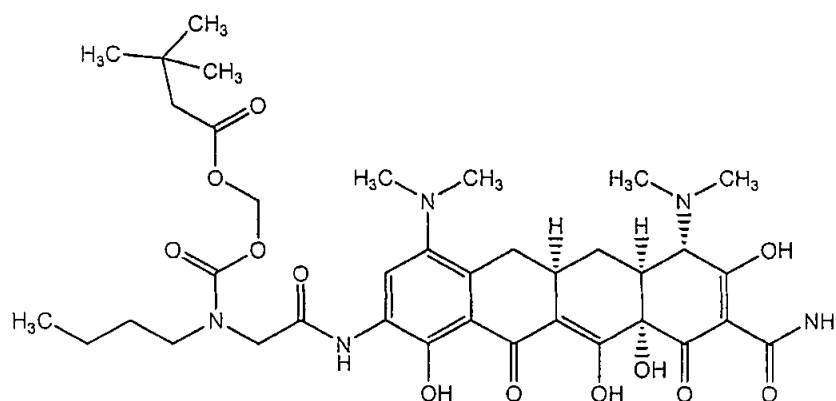
MS m/z 00-304761LMS;

HRMS: calcd for $C_{36}H_{49}N_5O_{12} \cdot HCl$, 779.3145; found (ESI+), 744.34539;

Example 36

5

(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(butyl)amino]carbonyl]oxy)methyl 3,3-dimethylbutanoate



The title compound is prepared by the procedure of Example 1, using Butanoic acid, 3,3-dimethyl-, [(chlorocarbonyl)oxy]methyl ester and N-butylglycylcycline to give the product of the Example.

15

MS m/z 00-304762LMS;

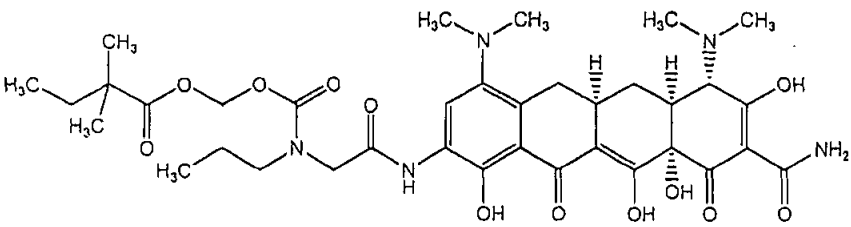
HRMS: calcd for $C_{37}H_{51}N_5O_{12} \cdot HCl$, 793.3301; found (ESI+), 758.36071;

Example 37

20

(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(propyl)amino]carbonyl]oxy)methyl 2,2-dimethylbutanoate

25



The title compound is prepared by the procedure of Example 1, using
[(chlorocarbonyl)oxy]methyl 2,2-dimethylbutanoate and N-propylglycylcycline to give
5 the product of the Example.

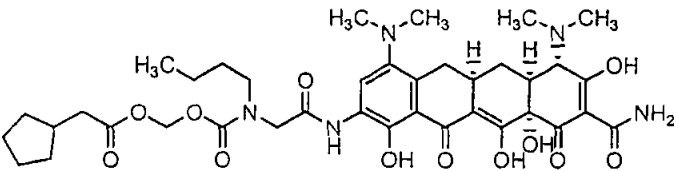
MS m/z 00-304763LMS;

HRMS: calcd for C₃₆H₄₉N₅O₁₂ · HCl, 779.3145; found (ESI+), 744.3452;

10 Example 38

(([(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-
tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-
oxoethyl)(butyl)amino]carbonyl)oxy)methyl cyclopentylacetate

15



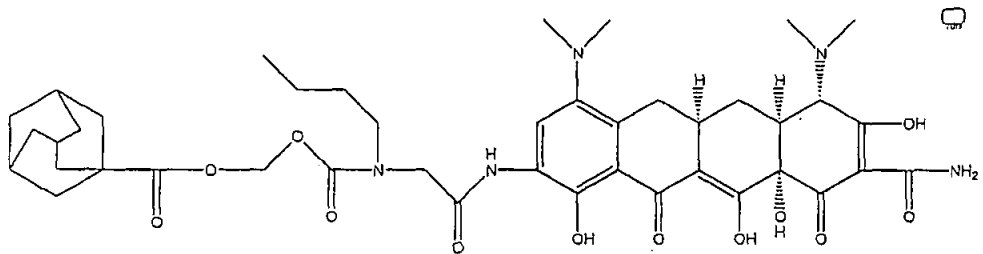
20 The title compound is prepared by the procedure of Example 1, using
[(chlorocarbonyl)oxy]methyl cyclopentylacetate and N-butylglycylcycline to give the
product of the Example.

25 MS (ESI) m/z 770.7 (M+H);

HRMS: calcd for C₃₈H₅₁N₅O₁₂ · HCl, 805.3301; found (ESI+), 770.36062;

Example 39

5 {{{(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl adamantane-1-carboxylate

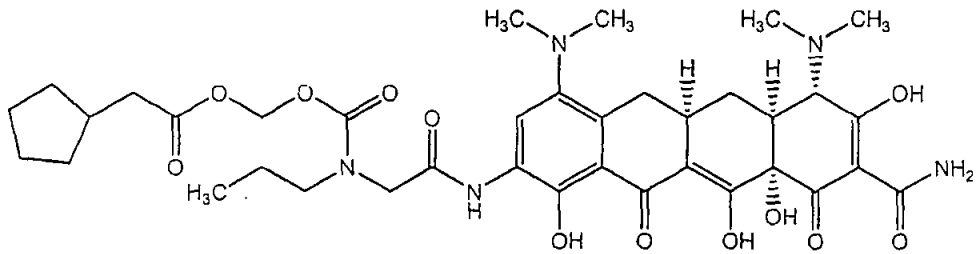


10 The title compound is prepared by the procedure of Example 1, using [(chlorocarbonyl)oxy]methyl adamantane-1-carboxylate and N-butylglycylcycline to give the product of the Example.

MS (ESI) m/z 822.9 (M+H);
 HRMS: calcd for C₄₂H₅₅N₅O₁₂ · HCl, 857.3614; found (ESI+), 822.39184;
 15

Example 40

20 {{{(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl cyclopentylacetate

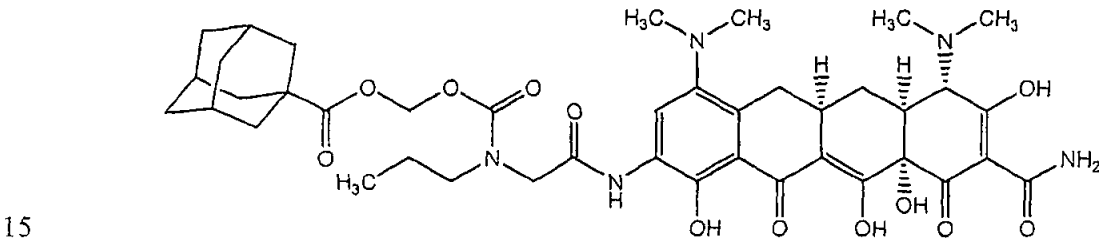


The title compound is prepared by the procedure of Example 1, using [(chlorocarbonyl)oxy]methyl cyclopentylacetate and N-propylglycylcyclycline to give the product of the Example.

5 MS (ESI) m/z 754.2 ((M-H)-);
HRMS: calcd for C₃₇H₄₉N₅O₁₂ · HCl, 791.3145; found (ESI+), 756.34433;

Example 41

10 {{{(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl adamantane-1-carboxylate

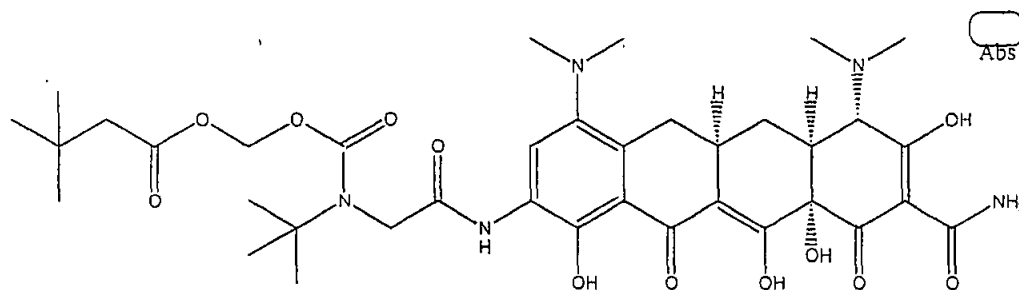


The title compound is prepared by the procedure of Example 1, using [(chlorocarbonyl)oxy]methyl adamantane-1-carboxylate and N-propylglycylcyclycline to give the product of the Example.

MS (ESI) m/z 808.8 (M+H);
HRMS: calcd for C₄₁H₅₃N₅O₁₂ · HCl, 843.3458; found (ESI+), 808.37604;

Example 42

25 {{{(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 3,3-dimethylbutanoate



5

To a solution of 9-amino-minocycline monosulfate (0.0055 mol, 3.135g, 1 equivalent)
 10 in a mixture of 12 ml of acetonitrile and 50 ml of DMPU is added 1.66 g (3
 equivalents) of triethylamine and Reference Compound 109 (0.012 mole, 4.88g),
 3,3-Dimethyl-butyric acid [tert-butyl-(2-isobutoxycarbonyloxy-2-oxo-ethyl)-
 carbamoyloxy]-methyl ester. The reaction is stirred at room temperature for 2 hour, 1
 mL methanol is added, stirred for 5 min. and the mixture is poured onto a mixture of
 15 500 ml of ether and 100 ml of isopropanol. Solid is collected and purified by
 extraction to give 1.5 g of the product of the Example.

MS (ESI) m/z 758.55 ($M+H$);

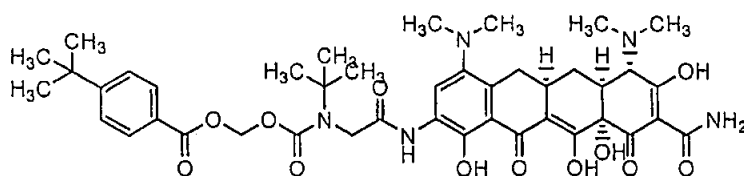
HRMS: calcd for $C_{37}H_{51}N_5O_{12} \cdot HCl$, 793.3301; found (ESI+), 758.36201;

20

Example 43

Prepared according to Scheme II

25 {{{(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-
 tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-
 oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 4-tert-butylbenzoate



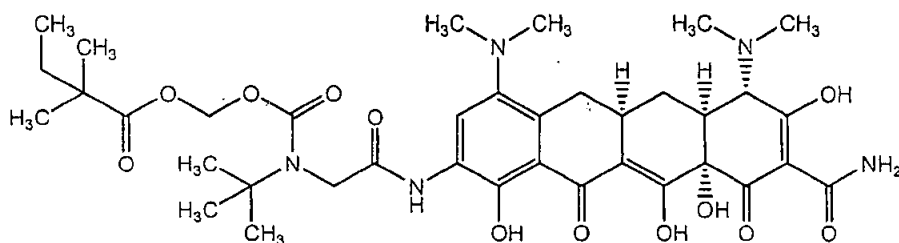
Reference Compound 57 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomincycline 5 using the conditions of Example 42 to give the product of the Example.

MS (ESI) m/z 820.37 (M+H);

HRMS: calcd for $C_{42}H_{53}N_5O_{12} \cdot HCl$, 855.3458; found (ESI+), 820.37574;

10 Example 44

([[(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 2,2-dimethylbutanoate



The title compound is prepared by reacting the product of the reaction of N-(tert-butyl)-N-([[(2,2-dimethylbutanoyl)oxy]methoxy]carbonyl)glycine using the conditions of Reference Compound 109 with 9-aminomincycline using the conditions of Example 42 to give the product of the Example.

MS (ESI) m/z 758.63 (M+H);

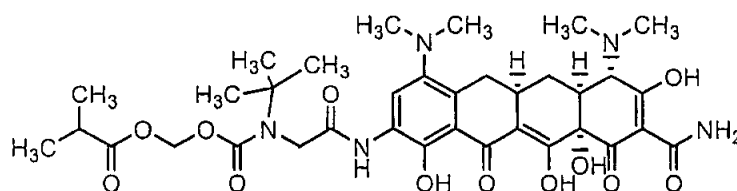
25 HRMS: calcd for $C_{37}H_{51}N_5O_{12} \cdot HCl$, 793.3301; found (ESI+), 758.36119;

Example 45

Prepared according to Scheme 2

- 5 CC(C)C(=O)OCCOC(=O)N(C(C)(C)C)CC(=O)Nc1c(O)c2c(c1)c(=O)c3c2c(O)c(O)c(=O)c3N
 tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 2-methylpropanoate

10



Reference Compound 58 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomincycline using the conditions of Example 42 to give the product of the Example.

15

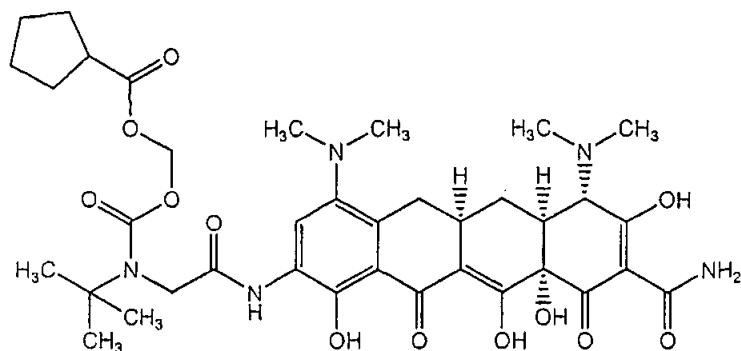
MS (ESI) m/z 730.38 ($M+H$);HRMS: calcd for $C_{35}H_{47}N_5O_{12} \cdot HCl$, 765.2988; found (ESI+), 730.33002;

20

Example 46

25

CC(C)C(=O)OCCOC(=O)N(C(C)(C)C)CC(=O)Nc1c(O)c2c(c1)c(=O)c3c2c(O)c(O)c(=O)c3N
 tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl cyclopentanecarboxylate



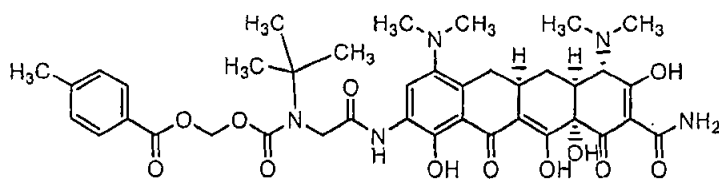
Reference Compound 59 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomincycline using the conditions of Example 42 to give the product of the Example.

MS (ESI) m/z 754.09 ((M-H)-);

HRMS: calcd for $C_{37}H_{49}N_5O_{12} \cdot HCl$, 791.3145; found (ESI+), 378.67644;

Example 47

(([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](tert-butyl)amino]carbonyl)oxy)methyl 4-methylbenzoate



Reference Compound 60 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomincycline using the conditions of Example 42 to give the product of the Example.

MS (ESI) m/z 778.34 ($M+H$);

HRMS: calcd for $C_{39}H_{47}N_5O_{12}$, 777.3221; found (ESI+), 778.33065;

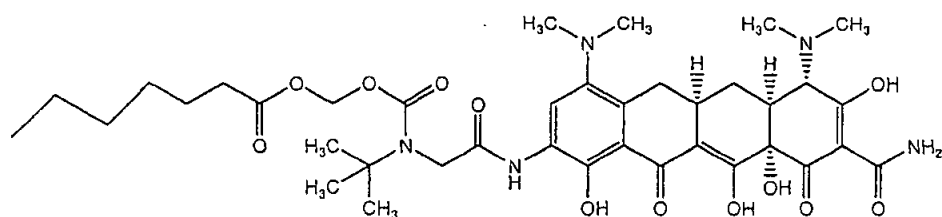
Example 48

5

Prepared according to Scheme II

(([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl](tert-butyl)amino]carbonyl)oxy)methyl heptanoate

10



Reference Compound 61 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-amininocycline using the conditions of Example 42 to give the product of the Example.

15

MS (ESI) m/z 772.45 ($M+H$);

HRMS: calcd for $C_{38}H_{53}N_5O_{12} \cdot HCl$, 807.3458; found (ESI+), 772.37695;

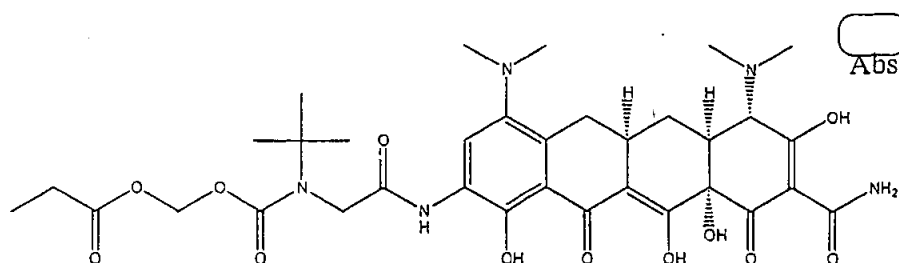
20

Example 49

Prepared according to Scheme II

(([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl](tert-butyl)amino]carbonyl)oxy)methyl propionate

25



Reference Compound 62 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomincycline
5 using the conditions of Example 42 to give the product of the Example.

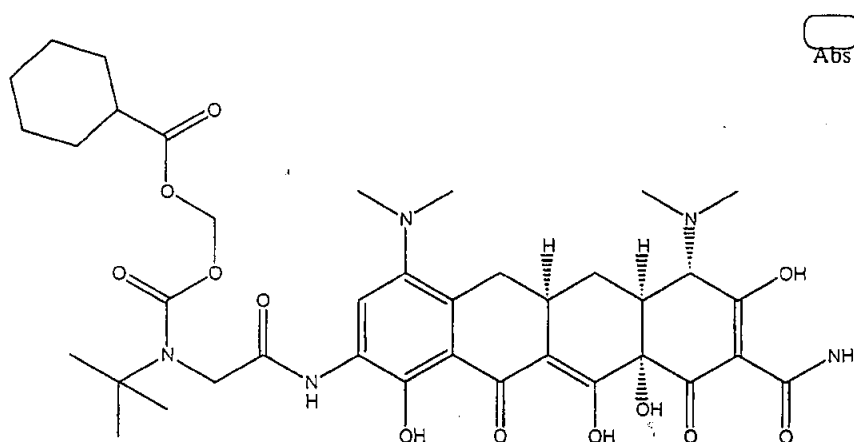
MS (ESI) m/z 716.3 (M+H);

HRMS: calcd for $C_{34}H_{45}N_5O_{12} \cdot HCl$, 751.2832; found (ESI+), 716.31461;

10

Example 50

(((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl cyclohexanecarboxylate
15



Reference Compound 63 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomincycline
20 using the conditions of Example 42 to give the product of the Example.

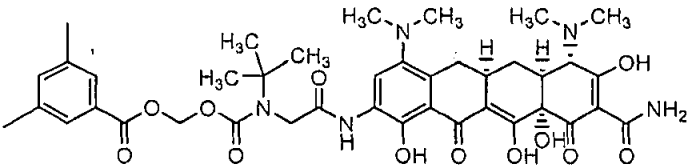
MS (ESI) m/z 770.36 (M+H);
 HRMS: calcd for C₃₈H₅₁N₅O₁₂ · HCl, 805.3301; found (ESI-), 768.34546;

5

Example 51

Prepared according to Scheme 2

10 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 3,5-dimethylbenzoate



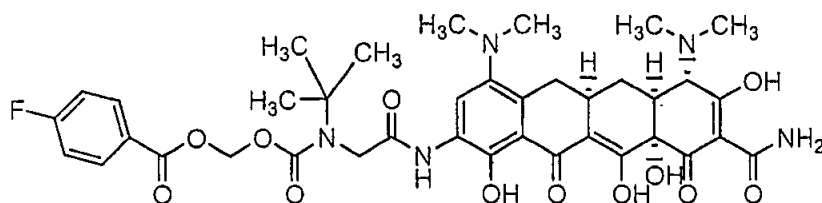
15

Reference Compound 64 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminocycline using the conditions of Example 42 to give the product of the Example.

20 MS (ESI) m/z 792.32 (M+H);
 HRMS: calcd for C₄₀H₄₉N₅O₁₂ · HCl, 827.3145; found (ESI+), 792.34613;

Example 52

25 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 4-fluorobenzoate



- 5 Reference Compound 65 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminocycline using the conditions of Example 42 to give the product of the Example.

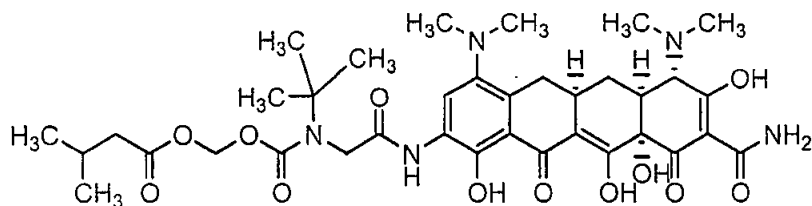
MS (ESI) m/z 782.3 (M+H);

- 10 HRMS: calcd for $C_{38}H_{44}FN_5O_{12} \cdot HCl$, 817.2737; found (ESI+), 782.30406

Example 53

Prepared according to Scheme 2

- 15 {{{(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 3-methylbutanoate



20

- Reference Compound 66 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminocycline using the conditions of Example 42 to give the product of the Example.
- 25

MS (ESI) m/z 744.37 (M+H);

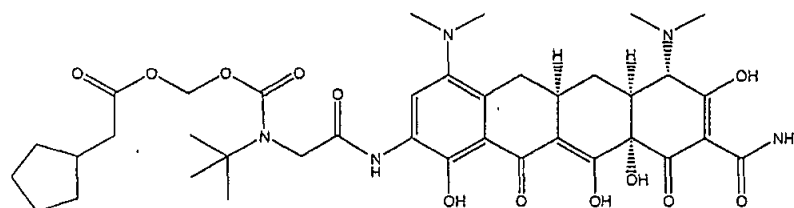
HRMS: calcd for $C_{36}H_{49}N_5O_{12} \cdot HCl$, 779.3145; found (ESI+), 744.34481;

Example 54

5

(([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](tert-butyl)amino]carbonyl)oxy)methyl cyclopentylacetate

10



Reference Compound 67 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomincycline using the conditions of Example 42 to give the product of the Example.

15

MS (ESI) m/z 770.4 (M+H);

HRMS: calcd for $C_{38}H_{51}N_5O_{12} \cdot HCl$, 805.3301; found (ESI+), 770.35888;

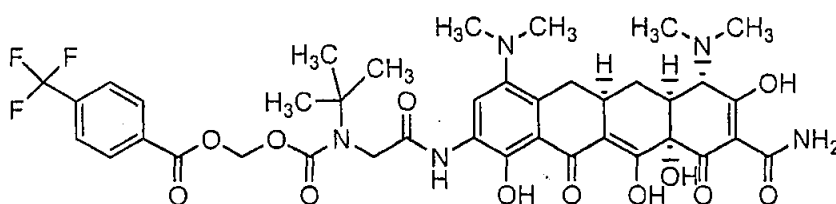
20

Example 55

Prepared according to Scheme 2

(([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](tert-butyl)amino]carbonyl)oxy)methyl 4-(trifluoromethyl)benzoate

25



Reference Compound 68 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminocycline
5 using the conditions of Example 42 to give the product of the Example.

MS (ESI) m/z 832.2 (M+H);

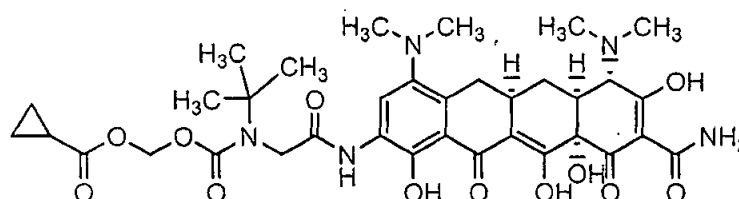
MS (ESI) m/z 416.6 (M+2H);

HRMS: calcd for $C_{39}H_{44}F_3N_5O_{12} \cdot HCl$, 867.2705; found (ESI+), 832.30055;

10

Example 56

(([(2-((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl](tert-butyl)amino]carbonyl)oxy)methyl cyclopropanecarboxylate
15



Reference Compound 69 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminocycline
20 using the conditions of Example 42 to give the product of the Example.

MS (ESI) m/z 728.34 (M+H);

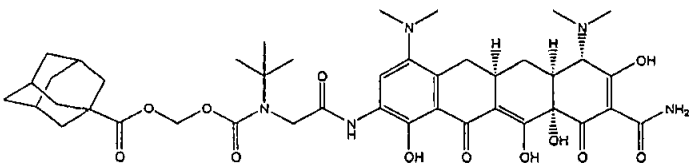
HRMS: calcd for $C_{35}H_{45}N_5O_{12} \cdot HCl$, 763.2832; found (ESI+), 728.31289;

25

Example 57

Prepared according to Scheme 2

5 {[2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl adamantane-1-carboxylate



10

Reference Compound 70 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomincycline
15 using the conditions of Example 42 to give the product of the Example.

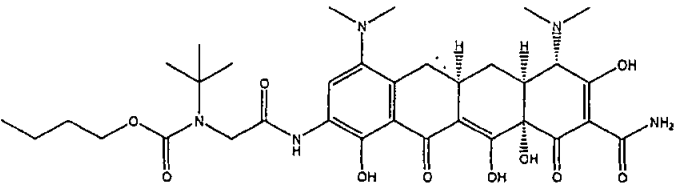
MS (ESI) m/z 822.5 (M+H);
HRMS: calcd for C₄₂H₅₅N₅O₁₂ · HCl, 857.3614; found (ESI+), 822.39237

20

Example 58

butyl 2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl](tert-butyl)carbamate

25



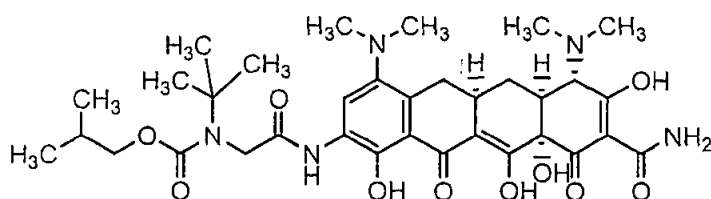
The title compound is prepared by the procedure of Example 42, using 1 equivalent of 9-amino-minocycline and 2 equivalents of isobutoxycarbonyl N-(butoxycarbonyl)-N-(tert-butyl)glycinate Reference Example 118 to give the product of the example.

5 MS (ESI) m/z 686.4 (M+H);

HRMS: calcd for $C_{34}H_{47}N_5O_{10} \cdot HCl$, 721.3090; found (ESI+), 686.34079;

Example 59

10 isobutyl 2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl(tert-butyl)carbamate



15

The title compound is prepared by the procedure of Example 42, using 1 equivalent of 9-amino-minocycline and 2 equivalents of isobutoxycarbonyl N-(tert-butyl)-N-(isobutoxycarbonyl)glycinate, Reference Example 119 to give the product of the example.

20

MS (ESI) m/z 686.3 (M+H);

MS (ESI) m/z 1371.7 (2M+H);

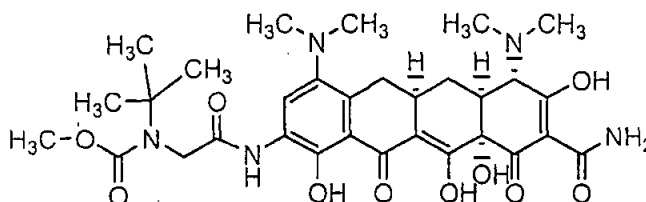
HRMS: calcd for $C_{34}H_{47}N_5O_{10} \cdot HCl$, 721.3090; found (ESI-), 684.32433;

25

Example 60

methoxy 2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl(tert-butyl)carbamate

30



5 The title compound is prepared by the procedure of Example 42, using 1 equivalent of 9-amino-minocycline and 2 equivalents of isobutoxycarbonyl N-(tert-butyl)-N-(methoxycarbonyl)glycinate Reference Example 120 to give the product of the example.

10 MS (ESI) m/z 644.3 (M+H);

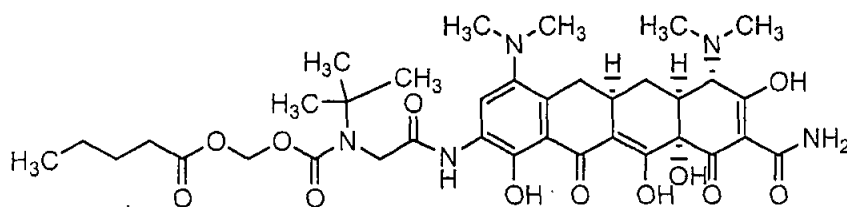
MS (ESI) m/z 322.6 (M+2H);

HRMS: calcd for $C_{31}H_{41}N_5O_{10} \cdot HCl$, 679.2620; found (ESI-), 642.27736;

Example 61

15

{{[(2-{{[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl pentanoate



20

Reference Compound 71 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminominocycline using the conditions of Example 42 to give the product of the Example.

25

MS (ESI) m/z 742 (M-H);

HRMS: calcd for $C_{36}H_{49}N_5O_{12} \cdot HCl$, 779.3145; found (ESI+), 744.34613;

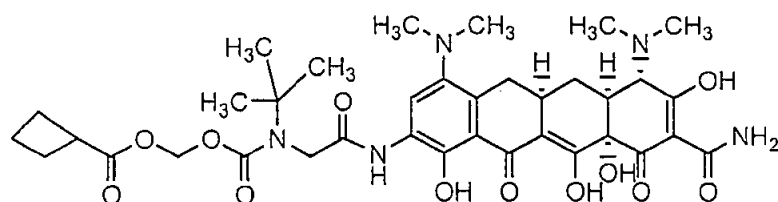
Example 62

5

Prepared according to Scheme II

((((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl]oxy)methyl cyclobutanecarboxylate

10



Reference Compound 72 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomycinocycline using the conditions of Example 42 to give the product of the Example.

15

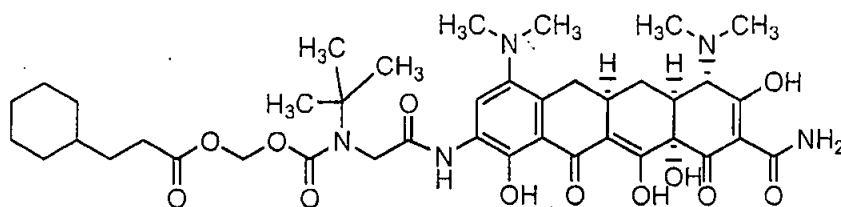
MS (ESI) m/z 742.4 (M+H);

Example 63

20

((((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl]oxy)methyl 3-cyclohexylpropanoate

25



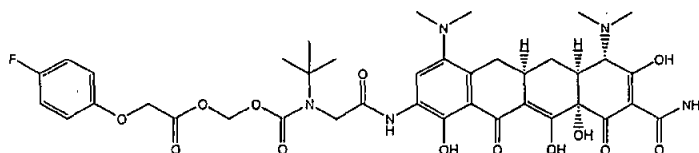
Reference Compound 73 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomycinocycline using the conditions of Example 42 to give the product of the Example.

5

MS (ESI) m/z 796.4 (M-H);

Example 64

- 10 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl (4-fluorophenoxy)acetate



15

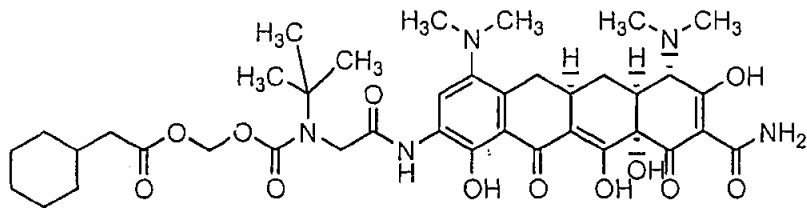
Reference Compound 74 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomycinocycline using the conditions of Example 42 to give the product of the Example.

- 20 MS (ESI) m/z 812.4 (M+H);
 MS (ESI) m/z 406.7 (M+2H);
 HRMS: calcd for $C_{39}H_{46}FN_5O_{13} \cdot HCl$, 847.2843; found (ESI+), 812.31518;

Example 65

25

((((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl cyclohexylacetate

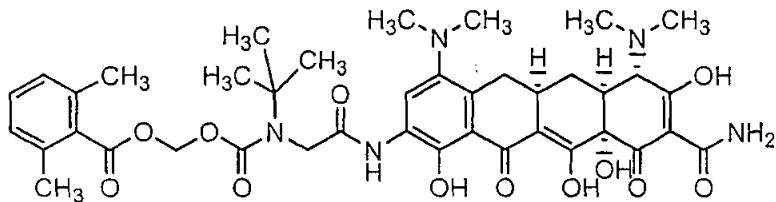


Reference Compound 75 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminocycline using the conditions of Example 42 to give the product of the Example.

MS (ESI) m/z 782.2 (M-H);
 HRMS: calcd for C₃₉H₅₃N₅O₁₂ · HCl, 819.3458; found (ESI+), 784.37621;

Example 66

(([(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 2,6-dimethylbenzoate

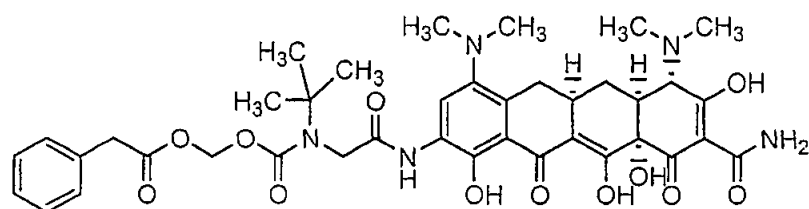


Reference Compound 76 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminocycline using the conditions of Example 42 to give the product of the Example.

MS (ESI) m/z 790.4 (M-H);
 HRMS: calcd for C₄₀H₄₉N₅O₁₂ · HCl, 827.3145; found (ESI+), 792.34423;

Example 67

5 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl phenylacetate



10 Reference Compound 77 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomycinocycline using the conditions of Example 42 to give the product of the Example.

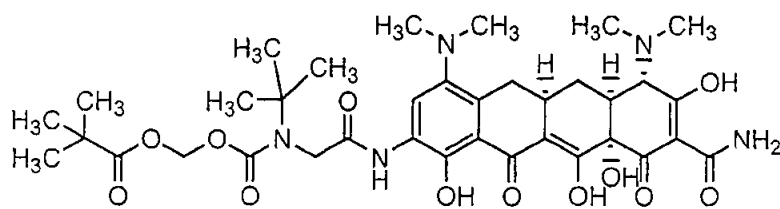
MS (ESI) m/z 778.3 (M+H);

HRMS: calcd for $C_{39}H_{47}N_5O_{12} \cdot HCl$, 813.2988; found (ESI+), 778.3299;

15

Example 68

20 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl pivalate



25 Reference Compound 78 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomycinocycline using the conditions of Example 42 to give the product of the Example.

MS (ESI) m/z 744.5 (M+H);

HRMS: calcd for $C_{36}H_{49}N_5O_{12} \cdot HCl$, 779.3145; found (ESI+), 744.34434;

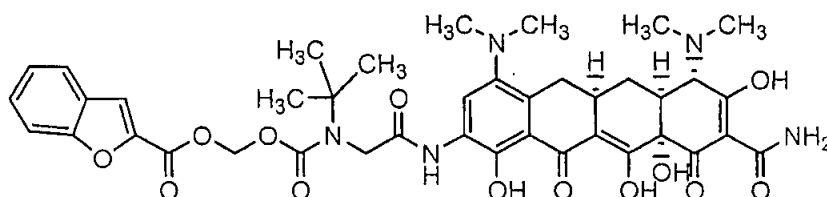
Example 69

5

Prepared according to Scheme II

(([(2-([(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 1-benzofuran-2-carboxylate

10



Reference Compound 79 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomincycline using the conditions of Example 42 to give the product of the Example.

15

MS (ESI) m/z 804.4 (M+H);

MS (ESI) m/z 402.7 (M+2H);

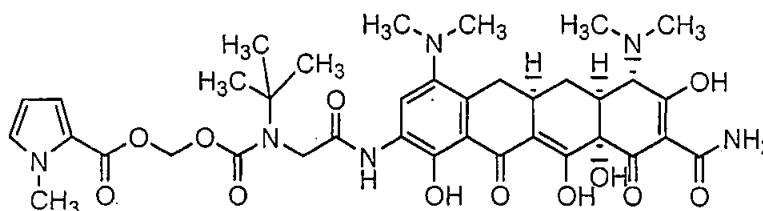
HRMS: calcd for $C_{40}H_{45}N_5O_{13} \cdot HCl$, 839.2781; found (ESI+), 804.30779;

20

Example 70

(([(2-([(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 1-benzofuran-2-carboxylate

25



Reference Compound 80 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomycinocycline
5 using the conditions of Example 42 to give the product of the Example.

MS (ESI) m/z 767.4 (M+H);

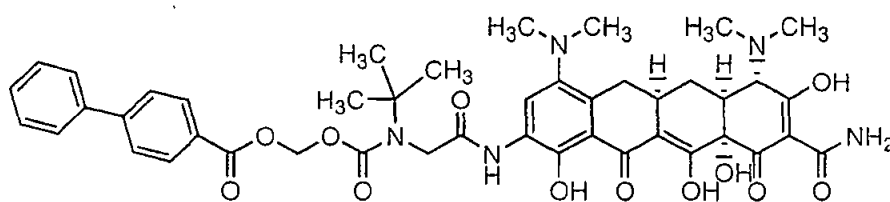
HRMS: calcd for $C_{37}H_{46}N_6O_{12}$, 766.3174; found (ESI+), 767.32406;

10

Example 71

{{[2-{{[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl]}(tert-butyl)amino]carbonyl}oxy)methyl 1,1'-biphenyl-4-carboxylate

15



Reference Compound 81 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomycinocycline
20 using the conditions of Example 42 to give the product of the Example.

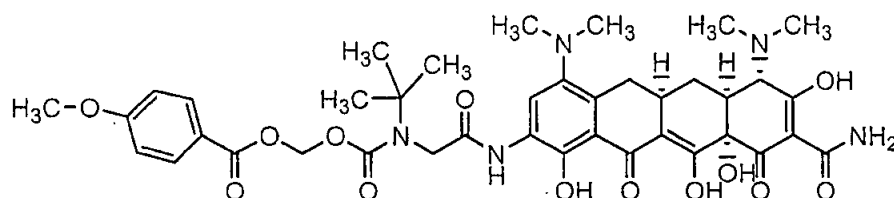
MS (ESI) m/z 838.2 (M-H);

MS (ESI) m/z 113 (TFA-H);

25 HRMS: calcd for $C_{44}H_{49}N_5O_{12} \cdot HCl$, 875.3145; found (ESI+), 840.34496;

Example 72

5 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 4-methoxybenzoate



10 Reference Compound 82 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminocycline using the conditions of Example 42 to give the product of the Example.

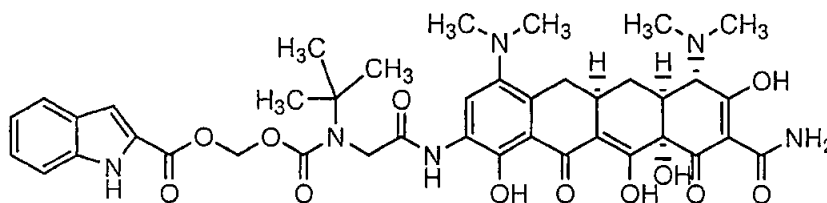
MS (ESI) m/z 792.3 (M-H);

15 HRMS: calcd for $C_{39}H_{47}N_5O_{13} \cdot HCl$, 829.2937; found (ESI+), 794.32511;

Example 73

Prepared according to Scheme II

20 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 1H-indole-2-carboxylate



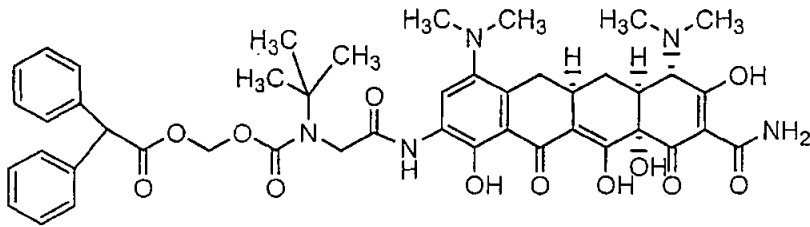
25

Reference Compound 83 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomycinocycline using the conditions of Example 42 to give the product of the Example.

- 5 MS (ESI) m/z 803.4 (M+H);
HRMS: calcd for C₄₀H₄₆N₆O₁₂ · HCl, 838.2941; found (ESI+), 803.32375;

Example 74

- 10 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl diphenylacetate

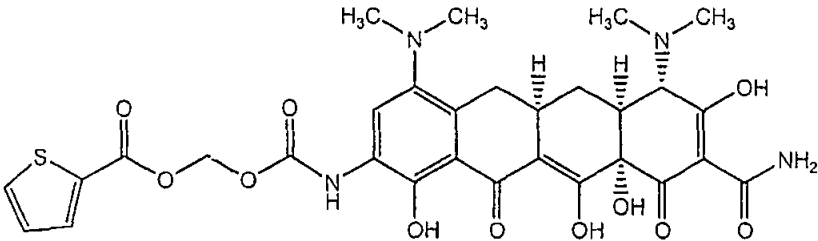


- 15 Reference Compound 84 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomycinocycline using the conditions of Example 42 to give the product of the Example.

- 20 MS (ESI) m/z 852.4 (M-H);
HRMS: calcd for C₄₅H₅₁N₅O₁₂ · HCl, 889.3301; found (ESI-), 852.3463;

Example 75

- 25 Prepared according to scheme 6
[(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)carbonyl)oxy]methyl thiophene-2-carboxylate



5 The title compound is prepared by the procedure of Example 42, using [(chlorocarbonyl)oxy]methyl thiophene-2-carboxylate in place of the Reference Compound 109 to give the product of the example.

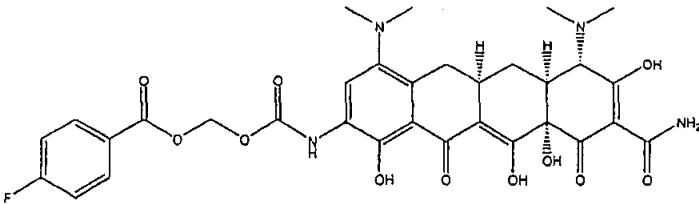
MS (ESI) m/z 655.2 (M-H);

10 HRMS: calcd for C₃₀H₃₂N₄O₁₁S · HCl, 692.1555; found (ESI+), 657.18613;

Example 76

Prepared according to scheme 6

15 [(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)carbonyl)oxy]methyl 4-fluorobenzoate



20

The title compound is prepared by the procedure of Example 42, using [(chlorocarbonyl)oxy]methyl 4-fluorobenzoate in place of the Reference Compound 109 to give the product of the example.

25

1a8

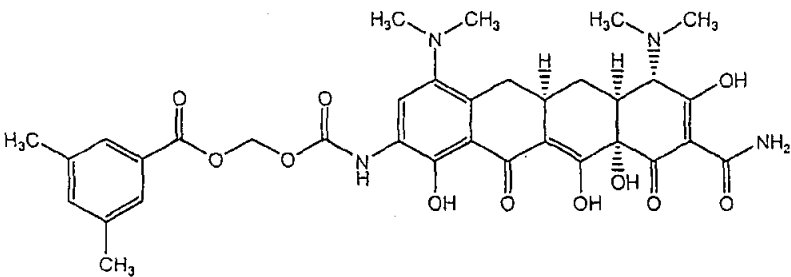
MS (ESI) m/z 667.2 (M-H);
 HRMS: calcd for C₃₂H₃₃FN₄O₁₁ · HCl, 704.1897; found (ESI+), 669.22024;

5

Example 77

Prepared according to scheme 6

10 [(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)carbonyl)oxy)methyl 3,5-dimethylbenzoate



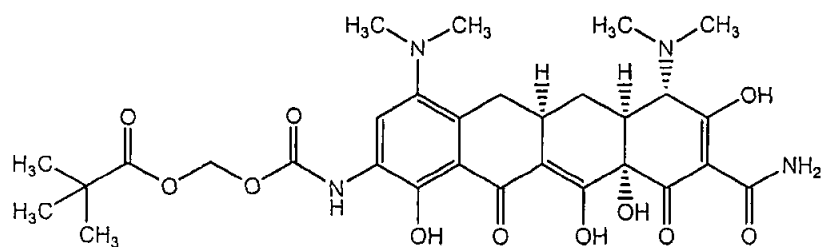
15 The title compound is prepared by the procedure of Example 42, using [(chlorocarbonyl)oxy)methyl 3,5-dimethylbenzoate in place of the Reference Compound 109 to give the product of the example.

MS (ESI) m/z 679.2 (M+H);
 20 HRMS: calcd for C₃₄H₃₈N₄O₁₁ · HCl, 714.2304; found (ESI+), 679.26076;

Example 78

Prepared according to scheme 6

25 [(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)carbonyl)oxy)methyl pivalate



The title compound is prepared by the procedure of Example 42, using [(chlorocarbonyl)oxy]methyl pivalate in place of the Reference Compound 109 to give the product of the example.

MS (ESI) m/z 631.2 (M+H);

HRMS: calcd for C₃₀H₃₈N₄O₁₁ · HCl, 666.2304; found (ESI+), 631.26094;

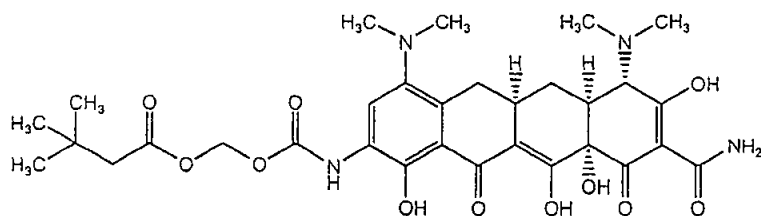
10

Example 79

Prepared according to scheme 6

[[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]carbonyl]oxy]methyl 3,3-dimethylbutanoate

15



The title compound is prepared by the procedure of Example 42, using [(chlorocarbonyl)oxy]methyl 3,3-dimethylbutanoate in place of the Reference Compound 109 to give the product of the example.

MS (ESI) m/z 643.3 (M-H);

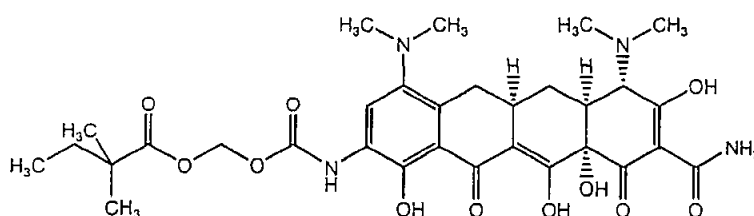
HRMS: calcd for C₃₁H₄₀N₄O₁₁ · HCl, 680.2460; found (ESI+), 645.27632;

25

Example 80

Prepared according to scheme 6

5 [({[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}carbonyl)oxy]methyl 2,2-dimethylbutanoate



10

The title compound is prepared by the procedure of Example 42, using [(chlorocarbonyl)oxy]methyl 2,2-dimethylbutanoate in place of the Reference Compound 109 to give the product of the example.

15

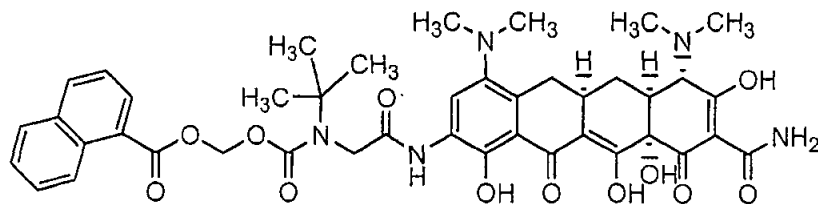
MS (ESI) m/z 645.2 (M+H);

HRMS: calcd for $C_{31}H_{40}N_4O_{11} \cdot HCl$, 680.2460; found (ESI+), 645.27637;

20

Example 81

25 ({{(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl}(tert-butyl)amino]carbonyl)oxy]methyl 1-naphthoate



Reference Compound 85 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomincycline using the conditions of Example 42 to give the product of the Example.

5

MS (ESI) m/z 812.5 (M-H);

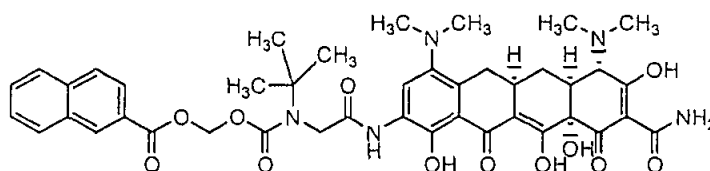
HRMS: calcd for $C_{42}H_{47}N_5O_{12} \cdot HCl$, 849.2988; found (ESI+), 814.33029;

Example 82

10

((((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 2-naphthoate

15



Reference Compound 86 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomincycline using the conditions of Example 42 to give the product of the Example.

20

MS (ESI) m/z 812.5 (M-H);

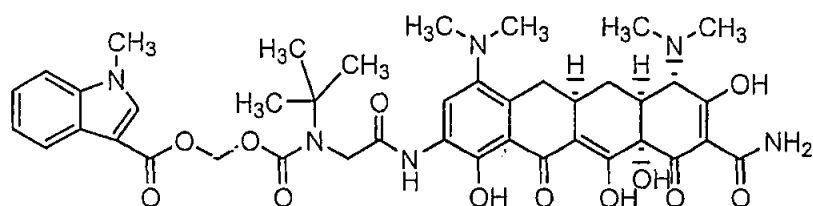
HRMS: calcd for $C_{42}H_{47}N_5O_{12} \cdot HCl$, 849.2988; found (ESI+), 814.33004;

25

Example 83

((((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 1-methyl-1H-indole-3-carboxylate

30



Reference Compound 87 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomycin
 5 using the conditions of Example 42 to give the product of the Example.

MS (ESI) m/z 815.5 (M-H);

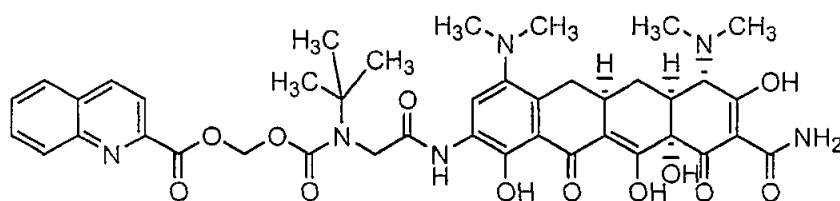
HRMS: calcd for $C_{41}H_{48}N_6O_{12} \cdot HCl$, 852.3097; found (ESI-), 815.32484;

10

Example 84

(([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](tert-butyl)amino]carbonyl)oxy)methyl quinoline-2-carboxylate

15



Reference Compound 88 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomycin
 20 using the conditions of Example 42 to give the product of the Example.

MS (ESI) m/z 813.5 (M-H);

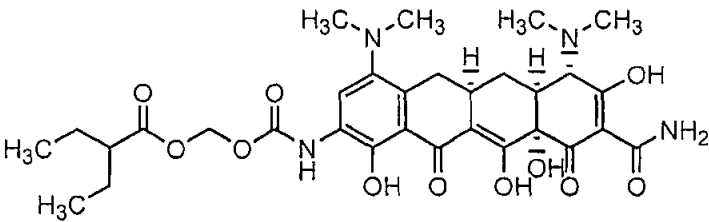
HRMS: calcd for $C_{41}H_{46}N_6O_{12} \cdot HCl$, 850.2941; found (ESI+), 815.32509;

25

Example 85
Prepared according to scheme 6

5 [(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}carbonyl)oxy]methyl 2-ethylbutanoate

10



15

The title compound is prepared by the procedure of Example 42, using [(chlorocarbonyl)oxy]methyl 2-ethylbutanoate in place of the Reference Compound 109 to give the product of the example.

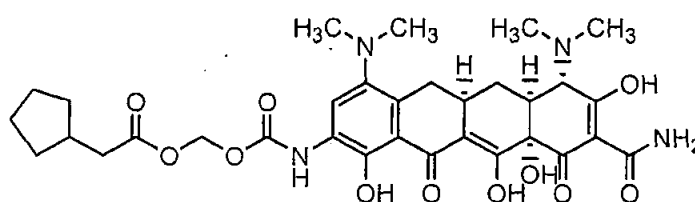
MS (ESI) m/z 643.4 (M-H);
MS (ESI) m/z 1287.7 (2M-H);
HRMS: calcd for C₃₁H₄₀N₄O₁₁ · HCl, 680.2460; found (ESI+), 645.27618;

20

Example 86

Prepared according to scheme 6

- 5 [(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}carbonyl)oxy]methyl cyclopentylacetate



10

The title compound is prepared by the procedure of Example 42, using [(chlorocarbonyl)oxy]methyl cyclopentylacetate in place of the Reference Compound 109 to give the product of the example.

15

MS (ESI) m/z 655.3 (M-H);

MS (ESI) m/z 1311.7 (2M-H);

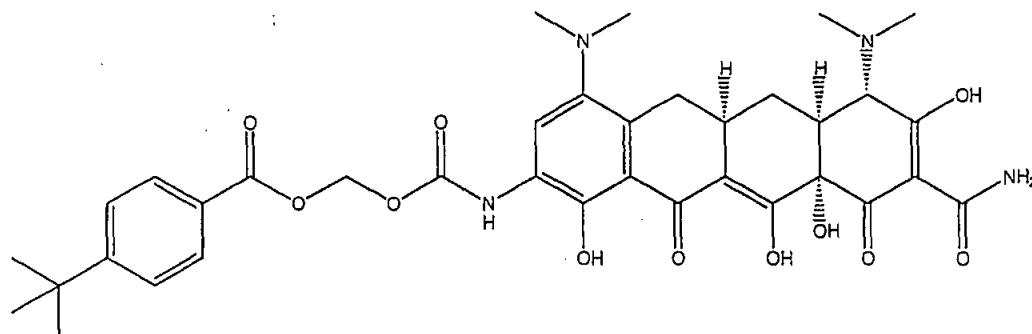
HRMS: calcd for $C_{32}H_{40}N_4O_{11} \cdot HCl$, 692.2460; found (ESI+), 657.27572;

20

Example 87

Prepared according to scheme 6

- 25 [(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}carbonyl)oxy]methyl 4-tert-butylbenzoate



The title compound is prepared by the procedure of Example 42, using
 [(chlorocarbonyl)oxy]methyl 4-tert-butylbenzoate in place of the Reference
 5 Compound 109 to give the product of the example.

MS (ESI) m/z 705.1 (M-H);

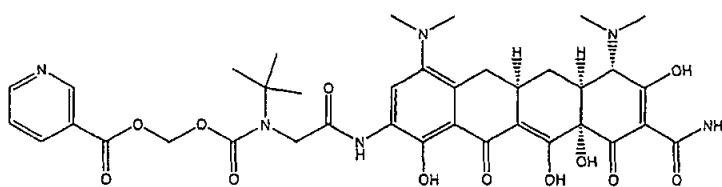
MS (ESI) m/z 1410.9 (2M-H);

HRMS: calcd for $C_{36}H_{42}N_4O_{11} \cdot HCl$, 742.2617; found (ESI+), 707.29336;

10

Example 88

(((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-
 tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-
 15 oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl nicotinate



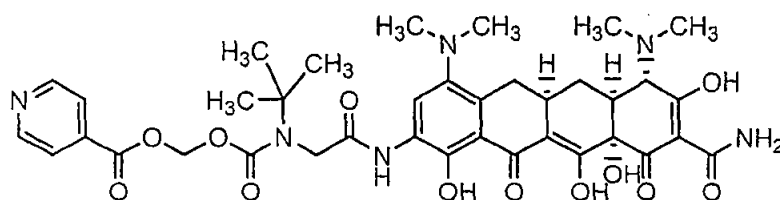
Reference Compound 89 is reacted under the conditions of Reference Compound
 109 and the product of said reaction is further contacted with 9-aminomincycline
 20 using the conditions of Example 42 to give the product of the Example.

MS (ESI) m/z 763.5 (M-H);

HRMS: calcd for $C_{37}H_{44}N_6O_{12} \cdot HCl$, 800.2784; found (ESI+), 765.30896;

Example 89

5 {{{(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl isonicotinate



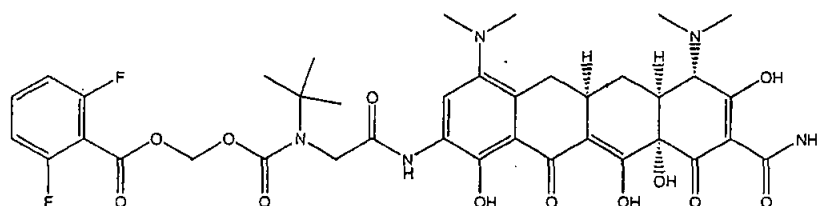
10 Reference Compound 90 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomycinocycline using the conditions of Example 42 to give the product of the Example.

HRMS: calcd for $C_{37}H_{44}N_6O_{12} \cdot HCl$, 800.2784; found (ESI+), 765.3117;

15

Example 90

20 {{{(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 2,6-difluorobenzoate



Reference Compound 91 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomycinocycline using the conditions of Example 42 to give the product of the Example.

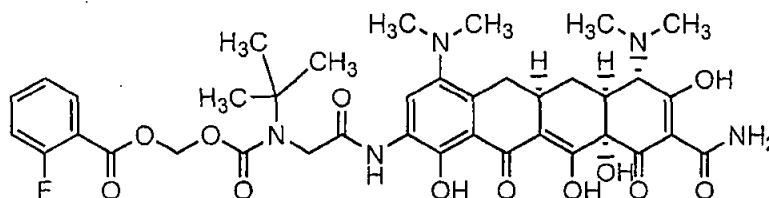
25

MS (ESI) m/z 798.2 (M-H);

HRMS: calcd for $C_{38}H_{43}F_2N_5O_{12} \cdot HCl$, 835.2643; found (ESI+), 800.29464;

Example 91

5 {{{(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 2-fluorobenzoate



10

Reference Compound 92 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminocycline using the conditions of Example 42 to give the product of the Example.

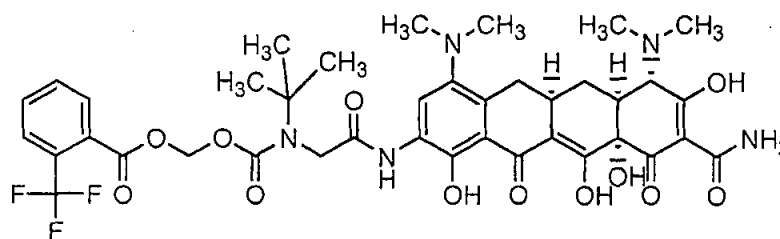
15

MS (ESI) m/z 780 (M-H);

HRMS: calcd for C₃₈H₄₄FN₅O₁₂ · HCl, 817.2737; found (ESI+), 782.30558;

Example 92

20 {{{(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 2-(trifluoromethyl)benzoate

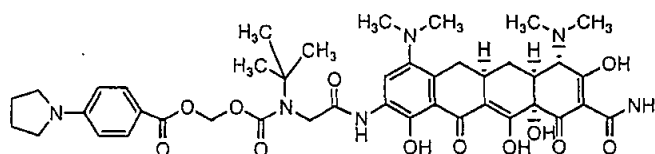


Reference Compound 93 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomincycline using the conditions of Example 42 to give the product of the Example.

- 5 HRMS: calcd for $C_{39}H_{44}F_3N_5O_{12} \cdot HCl$, 867.2705; found (ESI+), 832.30026;

Example 93

- 10 $\{[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](tert-butyl)amino]carbonyl\}oxy\}$ methyl 4-pyrrolidin-1-ylbenzoate



Reference Compound 94 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomincycline using the conditions of Example 42 to give the product of the Example.

20

MS (ESI) m/z 833.4 (M+H);

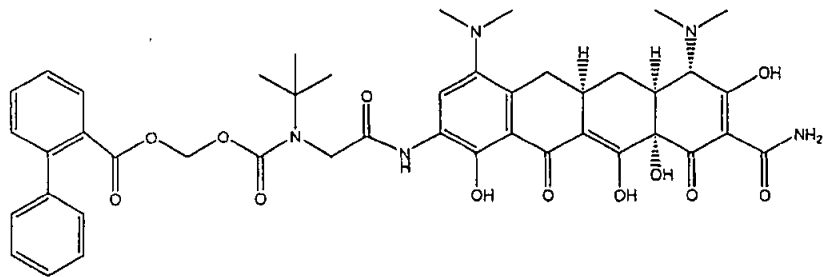
HRMS: calcd for $C_{42}H_{52}N_6O_{12} \cdot HCl$, 868.3410; found (ESI-), 831.3565;

Example 94

25

$\{[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](tert-butyl)amino]carbonyl\}oxy\}$ methyl 1,1'-biphenyl-2-carboxylate

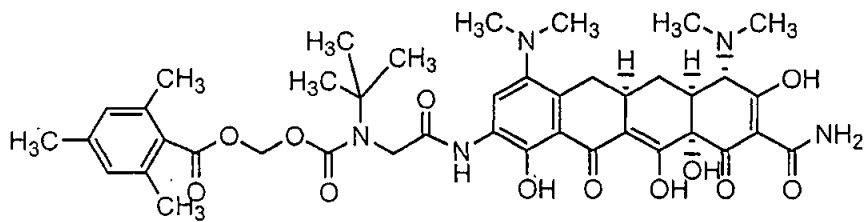
30



Reference Compound 95 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomino-9,10-dihydro-10H-phenanthrene-2,7,11-triol using the conditions of Example 42 to give the product of the Example.

MS (ESI) m/z 838.4 (M-H);
HRMS: calcd for C₄₄H₄₉N₅O₁₂ · HCl, 875.3145; found (ESI+), 840.34553;

Example 95
({[2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 2,4,6-trimethylbenzoate

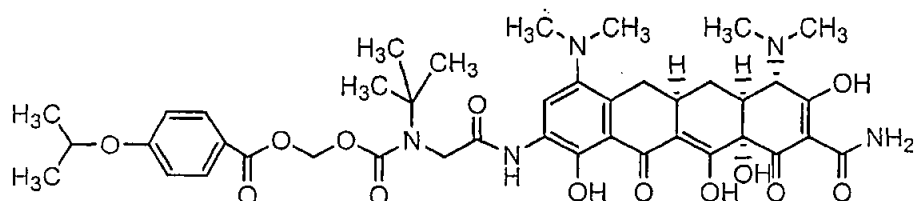


Reference Compound 96 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomino-9,10-dihydro-10H-phenanthrene-2,7,11-triol using the conditions of Example 42 to give the product of the Example.

MS (ESI) m/z 804.5 (M-H);
HRMS: calcd for C₄₁H₅₁N₅O₁₂ · HCl, 841.3301; found (ESI+), 806.36101;

Example 96

5 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 4-isopropoxybenzoate



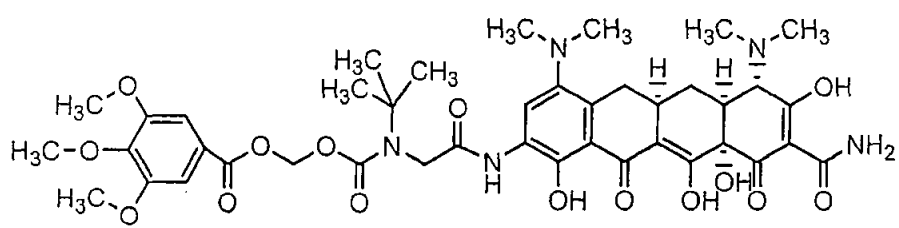
10

Reference Compound 97 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminominocycline using the conditions of Example 42 to give the product of the Example.

15 MS (ESI) m/z 820.2 (M-H);
HRMS: calcd for C₄₁H₅₁N₅O₁₃ · HCl, 857.3250; found (ESI-), 820.34117;

Example 97

20 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 3,4,5-trimethoxybenzoate



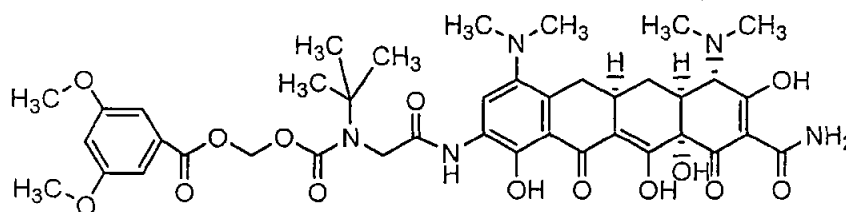
25

Reference Compound 98 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomincycline using the conditions of Example 42 to give the product of the Example.

- 5 MS (ESI) m/z 852.2 (M-H);
 HRMS: calcd for $C_{41}H_{51}N_5O_{15} \cdot HCl$, 889.3148; found (ESI+), 854.34728;

Example 98

- 10 {{{(2-{{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl}amino}-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 3,5-dimethoxybenzoate

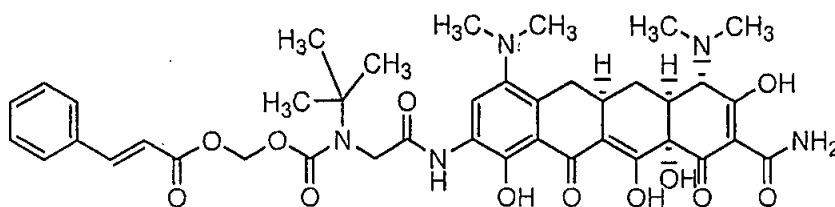


- 15 Reference Compound 99 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomincycline using the conditions of Example 42 to give the product of the Example.

- 20 MS (ESI) m/z 822.1 (M-H);
 HRMS: calcd for $C_{40}H_{49}N_5O_{14}$, 824.3349; found (ESI+), 824.3351;

Example 99

- 25 {{{(2-{{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl}amino}-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl (2E)-3-phenylprop-2-enoate



Reference Compound 100 is reacted under the conditions of Reference Compound
 5 109 and the product of said reaction is further contacted with 9-aminomincycline
 using the conditions of Example 42 to give the product of the Example.

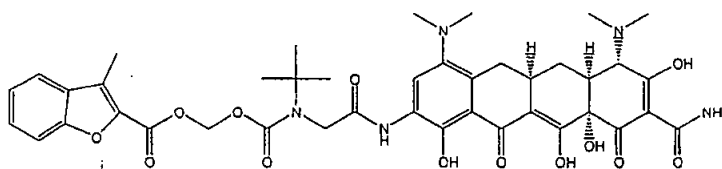
MS (ESI) m/z 788.3 (M-H);

HRMS: calcd for $C_{40}H_{47}N_5O_{12} \cdot HCl$, 825.2988; found (ESI+), 790.33068;

10

Example 100

{{(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-
 tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-
 15 oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 3-methyl-1-benzofuran-2-carboxylate



Reference Compound 101 is reacted under the conditions of Reference Compound
 20 109 and the product of said reaction is further contacted with 9-aminomincycline
 using the conditions of Example 42 to give the product of the Example.

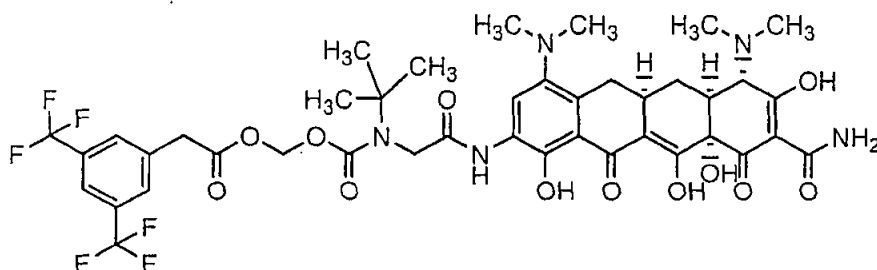
MS (ESI) m/z 816.5 (M-H);

HRMS: calcd for $C_{41}H_{47}N_5O_{13} \cdot HCl$, 853.2937; found (ESI+), 818.3234;

25

Example 101

5 {{{(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl [3,5-bis(trifluoromethyl)phenyl]acetate



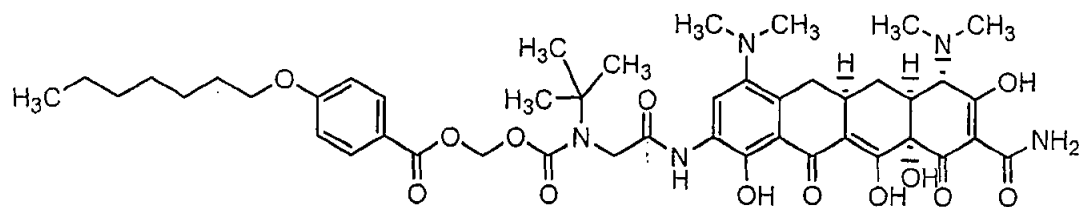
10 Reference Compound 102 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomincycline using the conditions of Example 42 to give the product of the Example.

MS (ESI) m/z 912 (M-H);

15 HRMS: calcd for $C_{41}H_{45}F_6N_5O_{12} \cdot HCl$, 949.2736; found (ESI+), 914.30367;

Example 102

20 {{{(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 4-(heptyloxy)benzoate



25

Reference Compound 103 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomycinocycline using the conditions of Example 42 to give the product of the Example.

5

MS (ESI) m/z 876.1 (M-H);

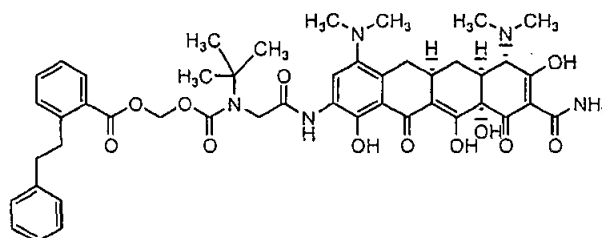
HRMS: calcd for $C_{45}H_{59}N_5O_{13} \cdot HCl$, 913.3876; found (ESI+), 878.41791;

10

Example 103

(2-(((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 2-(2-phenylethyl)benzoate

15



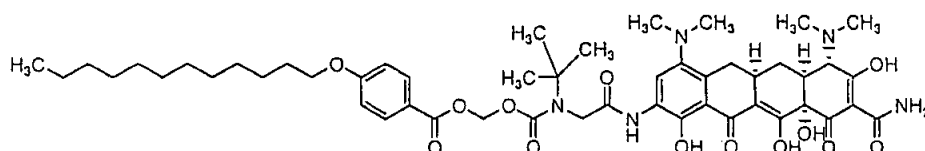
Reference Compound 104 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomycinocycline using the conditions of Example 42 to give the product of the Example.

MS (ESI) m/z 866.5 (M-H);

HRMS: calcd for $C_{46}H_{53}N_5O_{12} \cdot HCl$, 903.3458; found (ESI), 868.37357;

Example 104

(2-oxoethyl)(tert-butylamino]carbonyl]oxy)methyl 4-(dodecyloxy)benzoate
 5 tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-



10

Reference Compound 105 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomincycline using the conditions of Example 42 to give the product of the Example.

15

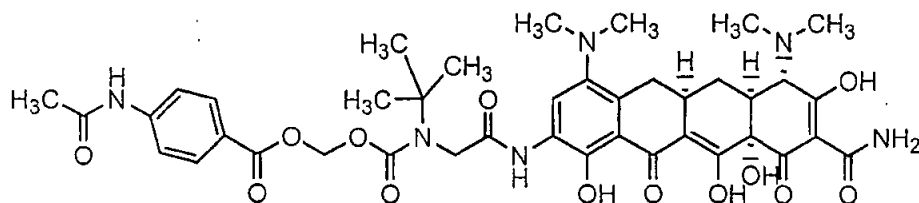
MS (ESI) m/z 946.7 (M-H);

HRMS: calcd for $C_{50}H_{69}N_5O_{13} \cdot HCl$, 983.4659; found (ESI-), 946.48106;

20

Example 105

(2-oxoethyl)(tert-butylamino]carbonyl]oxy)methyl 4-(acetylamino)benzoate
 25 tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-



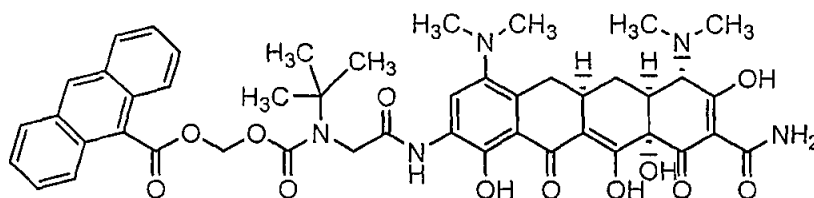
25

Reference Compound 106 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomincycline using the conditions of Example 42 to give the product of the Example.

- 5 MS (ESI) m/z 819.1 (M-H);
HRMS: calcd for $C_{40}H_{48}N_6O_{13} \cdot HCl$, 856.3046; found (ESI-), 819.32051;

Example 106

- 10 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl anthracene-9-carboxylate



15

Reference Compound 107 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomincycline using the conditions of Example 42 to give the product of the Example.

20

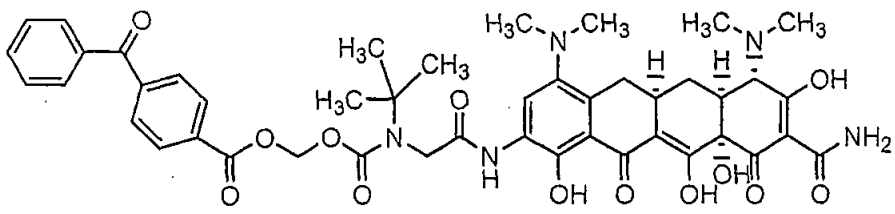
- MS (ESI) m/z 864.3 (M+H);
HRMS: calcd for $C_{46}H_{49}N_5O_{12} \cdot HCl$, 899.3145; found (ESI-), 862.32855;

25

Example 107

- (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 4-benzoylbenzoate

30

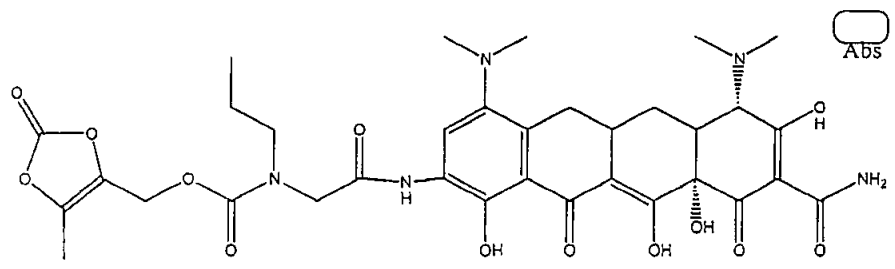


Reference Compound 108 is reacted under the conditions of Reference Compound 109 and the product of said reaction is further contacted with 9-aminomycinol using the conditions of Example 42 to give the product of the Example.

MS (ESI) m/z 866.3 (M-H);
 HRMS: calcd for C₄₅H₄₉N₅O₁₃ · HCl, 903.3094; found (ESI-), 866.32405;

Example 108

(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-[[[(7S,10aR)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl(propyl)carbamate



To a solution of 107 mg (0.166 mmol) of N-propyl-glycylcycline (N-prop-glycyl) in DMPU (2 ml) is added 5 equivalents of sodium carbonate (95 mg, 0.9 mmol) followed by 2 equivalents of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-nitrophenyl carbonate (95 mg, 0.33 mmol) Reference Compound 121 and stirring for 2 hr at room temperature. The reaction mixture is filtered through diatomaceous earth and the filtrate added to a mixture of (1:4)(20 ml) ether:isopropyl alcohol and HCl (1M in ether) is added and the formed solid filtered, redissolved in water, the pH adjusted to

about 2 and extracted with methylene chloride to give 15 mg of the product of the Example.

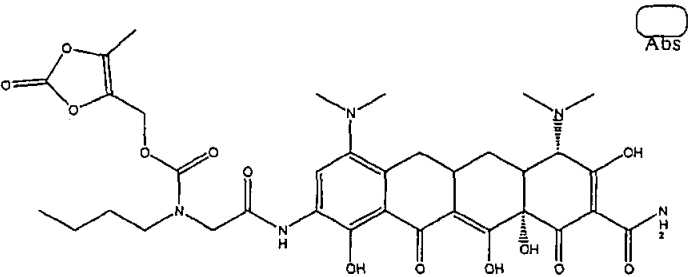
MS (ESI) m/z 728.5 (M+H);

MS (ESI) m/z 364.8 (M+2H);

5 HRMS: calcd for C₃₄H₄₁N₅O₁₃, 727.2701; found (ESI+), 728.27606;

Example 109

(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-[[[(7S,10aS)-9-(aminocarbonyl)-4,7-
10 bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-
octahydrotetracen-2-yl]amino]-2-oxoethyl(butyl)carbamate



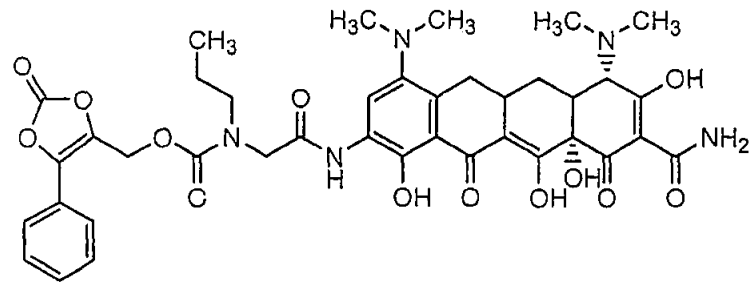
15 The title compound is prepared by the procedure of Example 108, using N-butyl-glycylcycline (N-bu-glycyl) and (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-nitrophenyl carbonate Reference Compound 121 to give the product of the Example.

MS (ESI) m/z 742.3 ((M+H)+);

20

Example 110

(2-oxo-5-phenyl-1,3-dioxol-4-yl)methyl 2-[[[(7R,10aS)-9-(aminocarbonyl)-4,7-
25 bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-
octahydrotetracen-2-yl]amino]-2-oxoethyl(propyl)carbamate



The title compound is prepared by the procedure of Example 108, using N-propylglycylcycline (N-prop-glycyl) and 4-nitrophenyl (2-oxo-5-phenyl-1,3-dioxol-4-yl)methyl carbonate Reference Compound 122 to give the product of the Example.

5

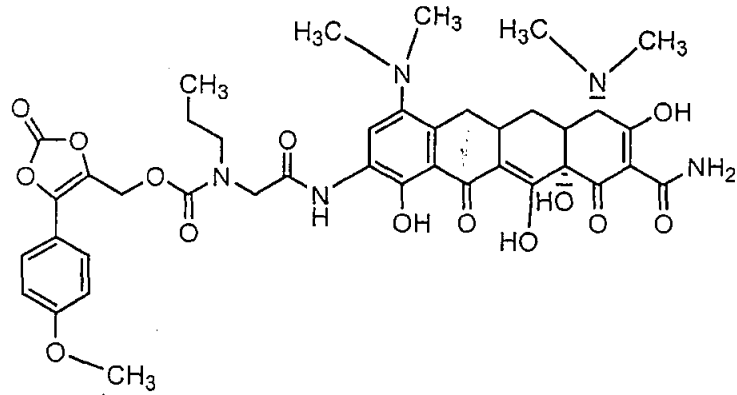
MS (ESI) m/z 790.3 ((M+H)+);
HRMS: calcd for C₃₉H₄₃N₅O₁₃, 789.2857; found (ESI+), 790.29243;

10

Example 111

[5-(4-methoxyphenyl)-2-oxo-1,3-dioxol-4-yl]methyl 2-[[[(7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl(propyl)carbamate

15



The title compound is prepared by the procedure of Example 108, using N-propylglycylcycline (N-prop-glycyl) and [5-(4-methoxyphenyl)-2-oxo-1,3-dioxol-4-yl]methyl

20

4-nitrophenyl carbonate Reference Compound 123 to give the product of the Example.

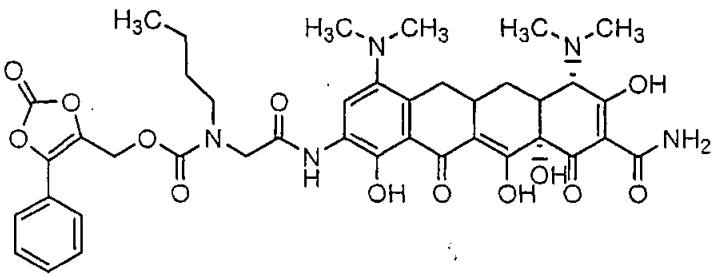
MS (ESI) m/z 820.3 ((M+H)+);

5

Example 112

(2-oxo-5-phenyl-1,3-dioxol-4-yl)methyl 2-[[[(7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl(butyl)carbamate

10



The title compound is prepared by the procedure of Example 108, using N-butyl-glycylcycline (N-bu-glycyl) and 4-nitrophenyl (2-oxo-5-phenyl-1,3-dioxol-4-yl)methyl carbonate Reference Compound 122 to give the product of the Example.

15

MS (ESI) m/z 804.12 (M+H);

MS (ESI) m/z 402.58 (M+2H);

20 HRMS: calcd for C₄₀H₄₅N₅O₁₃, 803.3014; found (ESI+), 804.30946;

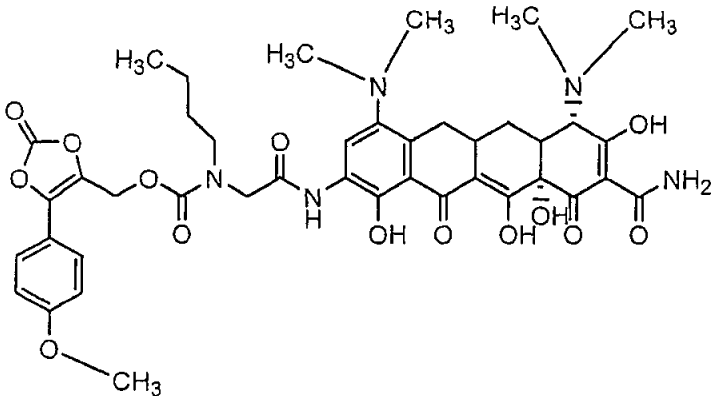
25

Example 113

5

[5-(4-methoxyphenyl)-2-oxo-1,3-dioxol-4-yl]methyl 2-[(7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino-2-oxoethyl(butyl)carbamate

10



15

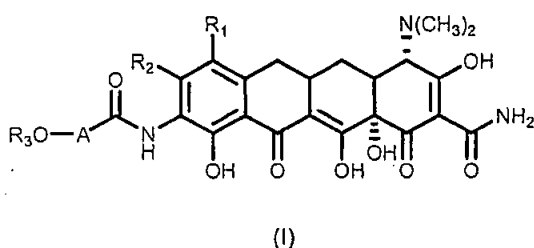
The title compound is prepared by the procedure of Example 108, using N-butylglycylcycline (N-bu-glycyl) and [5-(4-methoxyphenyl)-2-oxo-1,3-dioxol-4-yl]methyl 4-nitrophenyl carbonate Reference Compound 123 to give the product of the Example.

20

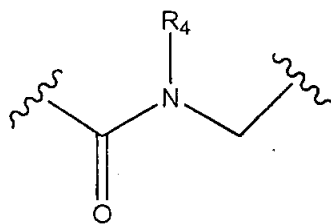
WHAT IS CLAIMED IS:

1. A compound represented by Formula (I);

5



10 wherein:



A is a moiety

or is absent;

- 15 R_1 is selected from hydrogen, -OH, amino, -NR₇R₈, halogen, alkyl of 1 to 12 carbon atoms, optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon atoms, phenyl, hydroxyl, alkoxy of 1 to 12 carbon atoms, N-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon atoms, heterocyclyl of 3 to 8 ring atoms, aryl, aryloxy and N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl, aryloxy and aryl of N-(alkyl of 1 to 12 carbon atoms)-aryl may optionally be substituted with 1 to 3 substituents independently selected from
- 20 halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, alkenyl of 2 to 12 carbon atoms optionally substituted with 1
- 25 to 3 substituents independently selected from the group phenyl, heteroaryl, halogen,

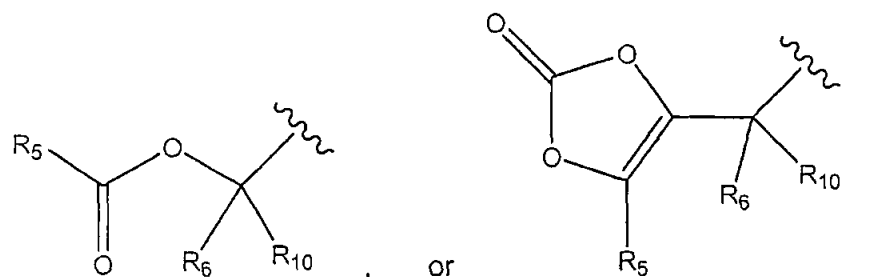
amino, cyano, alkyl, hydroxyl, alkoxy, aryl, alkynyl and N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl and aryl of

N-(alkyl of 1 to 12 carbon atoms)-aryl may optionally be substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aryloxy, heterocyclyl and phenyl, and alkynyl of 2 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, alkyl, hydroxyl, and alkoxy;

10 R₂ is selected from hydrogen, halogen, alkyl of 1 to 12 carbon atoms, optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon atoms, phenyl, hydroxyl, alkoxy of 1 to 12 carbon atoms, N-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon atoms, heterocyclyl of 3 to 8 ring atoms, aryl, aryloxy and
15 N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl, aryloxy and aryl of N-(alkyl of 1 to 12 carbon atoms)-aryl may optionally be substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, alkenyl of 2 to 12 carbon atoms
20 optionally substituted with 1 to 3 substituents independently selected from the group phenyl, heteroaryl, halogen, amino, cyano, alkyl, hydroxyl, alkoxy, aryl, alkynyl and N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl and aryl of N-(alkyl of 1 to 12 carbon atoms)-aryl may optionally be substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl,
25 alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, and alkynyl of 2 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, alkyl, hydroxyl, and alkoxy;

30

R₃ is the moiety R₉,



- R₄ is selected from hydrogen, alkyl of 1 to 12 carbon atoms, optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon atoms, phenyl, hydroxyl, alkoxy of 1 to 12 carbon atoms, N-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon atoms, heterocyclyl of 3 to 8 ring atoms, aryl, aryloxy and N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl, aryloxy and aryl of N-(alkyl of 1 to 12 carbon atoms)-aryl may optionally be substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, alkenyl of 2 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group phenyl, heteroaryl, halogen, amino, cyano, alkyl, hydroxyl, alkoxy, aryl, alkynyl and N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl and aryl of N-(alkyl of 1 to 12 carbon atoms)-aryl may optionally be substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, alkynyl of 2 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, alkyl, hydroxyl, and alkoxy, aryl of 6, 10 or 14 carbon atoms said aryl optionally substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, N-(alkyl of 1 to 12 carbon atoms)-aryl, said aryl optionally substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl,

alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, aralkyl of 7 to 16 carbon atoms optionally substituted, aroyl of 7 to 13 carbon atoms optionally substituted, SR³, heteroaryl optionally substituted and heteroarylcarbonyl optionally substituted;

R₅ is selected from alkyl of 1 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon atoms, phenyl, hydroxyl, alkoxy of 1 to 12 carbon atoms, N-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon atoms, heterocyclyl of 3 to 8 ring atoms, aryl of 6, 10 or 14 carbon atoms, aryloxy and N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl, aryloxy and aryl of N-(alkyl of 1 to 12 carbon atoms)-aryl, may be optionally substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, aralkyl of 7 to 16 carbon atoms optionally substituted, aroyl, -CH₂(CO)OCH₂aryl, said aryl optionally substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryloxy and phenyl, alkenyl of 2 to 12 carbon atoms optionally substituted, heteroaryl optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, alkynyl of 2 to 12 carbon atoms optionally substituted, cycloalkyl 3 to 6 ring atoms, aryl-CH=CH-, cycloalkyl-alkyl; and adamantly;

R₆ is selected from hydrogen, alkyl of 1 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon atoms, phenyl, hydroxyl, alkoxy of 1 to 12 carbon atoms, N-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon atoms, heterocyclyl of 3 to 8 ring atoms, aryl, aryloxy and N-(alkyl of 1 to 12 carbon atoms)-aryl, wherein said aryl, aryloxy and aryl of N-(alkyl of 1 to 12 carbon atoms)-aryl may optionally be substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl,

alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, and cycloalkyl of 3 to 6 carbon atoms;

- 5 R₇ and R₈ are each independently H or alkyl of 1 to 12 carbon atoms or R₇ and R₈ when optionally taken together with the nitrogen atom to which each is attached form a 3 to 8 membered heterocyclyl ring;

R₉ is aralkyl of 7 to 16 carbon atoms optionally substituted or alkyl of 1 to 12 carbon
10 atoms;

R₁₀ is H or alkyl of 1 to 12 carbon atoms;

or a pharmaceutically acceptable salt thereof.

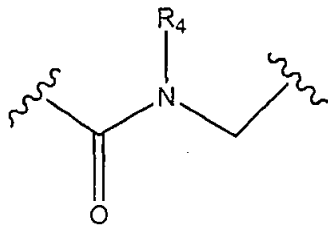
- 15 2. A compound according to claim 1, wherein R₁ is -NR₇R₈, R₇ is hydrogen, R₈ is methyl, ethyl, n-propyl, n-butyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1, wherein R₁ is -NR₇R₈, R₇ is methyl or ethyl, R₈
20 is methyl, ethyl, n-propyl, 1-methylethyl, n-propyl, 1-methylpropyl, or 2-methylpropyl or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 1, wherein R₁ is -NR₇R₈, R₇ and R₈ are taken
25 together with the nitrogen atom to which each is attached form a 3 to 8 membered heterocyclyl ring or a pharmaceutically acceptable salt thereof.

5. A compound according to any one of claims 1 to 5, wherein R₂ is H or a pharmaceutically acceptable salt thereof.

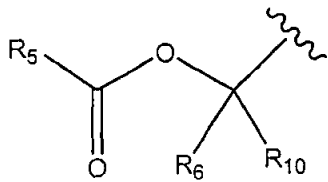
- 30 6. A compound according to any one of claims 1 to 5, wherein A is a moiety



or a pharmaceutically acceptable salt thereof.

7. A compound according to any one of claims 1 to 5, wherein A is absent or a
5 pharmaceutically acceptable salt thereof.

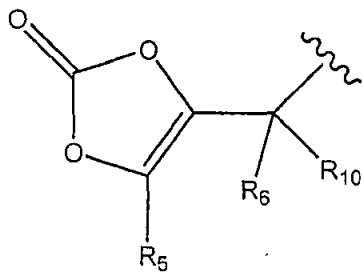
8. A compound according to any one of claims 1 to 7, wherein R₃ is a moiety



10

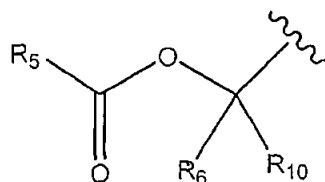
or a pharmaceutically acceptable salt thereof.

9. A compound according to any one of claims 1 to 7, wherein R₃ is a moiety
15



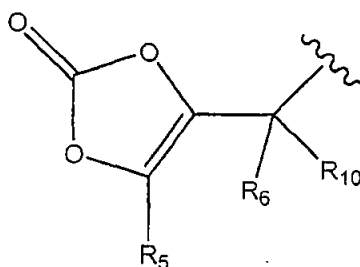
or a pharmaceutically acceptable salt thereof.

20 10. A compound according to any one of claims 1 to 7, wherein R₃ is a moiety



and R_6 and R_{10} are H or a pharmaceutically acceptable salt thereof.

- 5 11. A compound according to any one of claims 1 to 7, wherein R_3 is a moiety

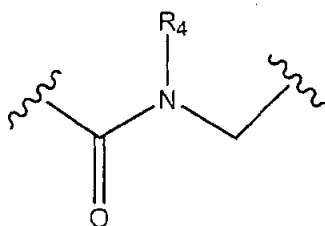


and R_6 and R_{10} are H or a pharmaceutically acceptable salt thereof.

10

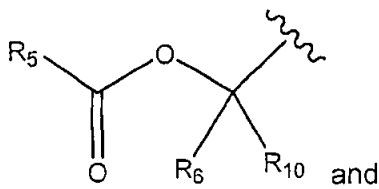
12. A compound according to any one of claims 1 to 7, wherein R_3 is R_9 or a pharmaceutically acceptable salt thereof.

- 15 13. A compound according to claim 1, wherein A is the moiety,



20

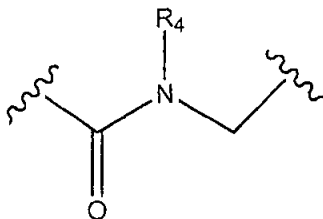
R_3 is the moiety



R₅ is aryl of 6 carbon atoms or a pharmaceutically acceptable salt thereof.

5

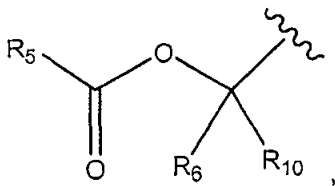
14. A compound according to claim 1, wherein A is the moiety



10

R₃ is the moiety ,

15



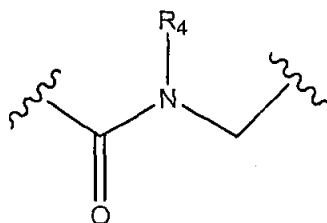
R₄ is 1,1-dimethylethyl and

20

R₅ is aryl of 6 carbon atoms or a pharmaceutically acceptable salt thereof.

15. A compound according to claim 1, wherein

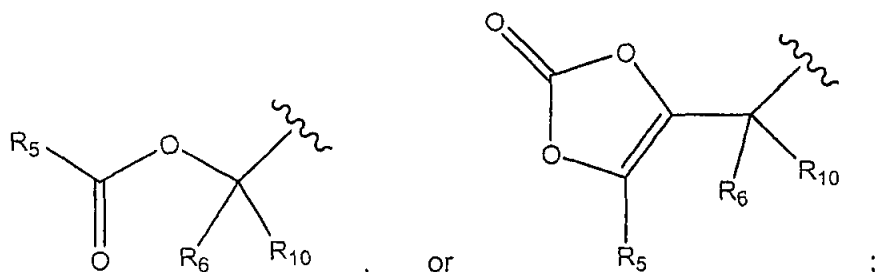
A is a moiety



R₁ is -NR₇R₈;

R₂ is hydrogen;

10 R₃ is the moiety



15 R₄ is selected from alkyl of 1 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, cycloalkyl of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon atoms, phenyl, hydroxyl, alkoxy of 1 to 12 carbon atoms, N-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon atoms, heterocyclyl of 3 to 8 ring atoms, aryl, and aryloxy wherein said aryl and aryloxy is optionally substituted with 1 to 3 substituents independently selected
20 from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryloxy and phenyl;

R₅ is selected from alkyl of 1 to 12 carbon atoms optionally substituted with 1 to 3 substituents independently selected from the group halogen, amino, cyano, cycloalkyl
25 of 3 to 6 carbon atoms, alkyl of 1 to 12 carbon atoms, phenyl, hydroxyl, alkoxy of 1 to

12 carbon atoms, N-alkyl of 1 to 12 carbon atoms, N-cycloalkyl of 3 to 6 carbon atoms, heterocyclyl of 3 to 8 ring atoms, aryl of 6, 10 or 14 carbon atoms, and aryloxy wherein said aryl, aryloxy and aryl of N-(alkyl of 1 to 12 carbon atoms)-aryl, may be optionally substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryl-C(O)-, CH₃-C(O)-NH-, aralkyl, aryloxy, heterocyclyl and phenyl, aralkyl of 7 to 16 carbon atoms optionally substituted, aroyl, -CH₂(CO)OCH₂aryl, said aryl optionally substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, alkenyl, hydroxyl, alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, carboxyl, alkoxycarbonyl, aryloxy and phenyl, heteroaryl optionally substituted, aryl of 6, 10 or 14 carbon atoms optionally substituted, cycloalkyl 3 to 6 ring atoms, aryl-CH=CH-, cycloalkyl-alkyl; and adamantyl;

15 R₈ is hydrogen;

R₇ and R₈ are each independently H or alkyl of 1 to 12 carbon atoms;

20 R₉ is aralkyl of 7 to 16 carbon atoms optionally substituted or alkyl of 1 to 12 carbon atoms;

R₁₀ is H;

or a pharmaceutically acceptable salt thereof.

25

16. A compound according to claim 1, selected from the group or pharmaceutically acceptable salts thereof

30 (((2-(((7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(butyl)amino]carbonyl)oxy)methyl 2-methylpropanoate,

231

- {{(2-{{(7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl 4-methoxybenzoate,
- 5 {{{(2-{{(7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl 4-methylbenzoate,
- 10 {{{(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl 4-fluorobenzoate,
- 15 {{{(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl 4-methylbenzoate,
- 20 {{{(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl 4-methoxybenzoate,
- 25 {{{(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl 4-fluorobenzoate,
- 30 {{{(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl pivalate,

- (([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](propyl)amino]carbonyl}oxy)methyl 2-methylpropanoate,
- 5 (([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](propyl)amino]carbonyl}oxy)methyl phenylacetate,
- 10 (([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](butyl)amino]carbonyl}oxy)methyl phenylacetate,
- 15 (([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](butyl)amino]carbonyl}oxy)methyl pivalate,
- 20 (([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](butyl)amino]carbonyl}oxy)methyl heptanoate,
- 25 (([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](butyl)amino]carbonyl}oxy)methyl cyclobutanecarboxylate,
- 30 (([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](propyl)amino]carbonyl}oxy)methyl heptanoate,
- (([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](butyl)amino]carbonyl}oxy)methyl 4-tert-butylbenzoate,

- (([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](butyl)amino]carbonyl)oxy)methyl 1,1'-biphenyl-4-carboxylate,
- 5 (([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](butyl)amino]carbonyl)oxy)methyl 3,5-dimethylbenzoate,
- 10 (([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](propyl)amino]carbonyl)oxy)methyl 1,1'-biphenyl-4-carboxylate,
- 15 (([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](propyl)amino]carbonyl)oxy)methyl 3,5-dimethylbenzoate,
- 20 (([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](propyl)amino]carbonyl)oxy)methyl 4-tert-butylbenzoate,
- 1-(((2-[(7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(butyl)amino]carbonyl)oxy)ethyl acetate,
- 25 (([(2-[(7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](propyl)amino]carbonyl)oxy)methyl cyclohexanecarboxylate,
- 30 (([(2-[(7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(butyl)amino]carbonyl)oxy)methyl cyclohexanecarboxylate,

{{(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl 3,3-dimethylbutanoate,

5 {{(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl 3,3-dimethylbutanoate,

10 {{(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl 2,2-dimethylbutanoate,

15 {{(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl cyclopentylacetate,

20 {{(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl adamantane-1-carboxylate,

25 {{(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl cyclopentylacetate,

30 {{(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl adamantane-1-carboxylate,

35 {{(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 3,3-dimethylbutanoate,

- (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 4-tert-butylbenzoate,
- 5 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 2,2-dimethylbutanoate,
- 10 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 2-methylpropanoate,
- 15 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl cyclopentanecarboxylate,
- 20 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 4-methylbenzoate,
- 25 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl heptanoate, and
- 30 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 4-methoxybenzoate.
17. A compound according to claim 1 selected from the group
- benzyl 2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl(propyl)carbamate,

ethyl 2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl(propyl)carbamate, and

isobutyl 2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl(propyl)carbamate,
or pharmaceutically acceptable salts thereof.

18. A compound according to claim 1 selected from the group

(([(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl thiophene-2-carboxylate,

(([(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl thiophene-2-carboxylate,

(([(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl)(propyl)amino]carbonyl}oxy)methyl thiophene-3-carboxylate,

(([(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl thiophene-3-carboxylate,

(([(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]-2-oxoethyl)(butyl)amino]carbonyl}oxy)methyl 2-furoate, and

(([(2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(propyl)amino]carbonyl)oxy)methyl 2-furoate,

5 or pharmaceutically acceptable salts thereof.

19. A compound according to claim 1 selected from the group

10 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl propionate,

15 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl cyclohexanecarboxylate,

20 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 3,5-dimethylbenzoate,

(((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 4-fluorobenzoate,

25 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 3-methylbutanoate,

30 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl cyclopentylacetate,

- (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 4-(trifluoromethyl)benzoate,
- 5 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl cyclopropanecarboxylate,
- 10 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl adamantane-1-carboxylate,
- butyl 2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)carbamate,
- 15 isobutyl 2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)carbamate,
- 20 methyl 2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)carbamate,
- 25 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl pentanoate,
- 30 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl cyclobutanecarboxylate,

- (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 3-cyclohexylpropanoate,
- 5 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl (4-fluorophenoxy)acetate,
- 10 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl cyclohexylacetate,
- 15 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 2,6-dimethylbenzoate,
- 20 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl phenylacetate,
- 25 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl pivalate,
- 30 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 1,1'-biphenyl-4-carboxylate,
- (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl}oxy)methyl 1-naphthoate,

- (([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](tert-butyl)amino]carbonyl)oxy)methyl 2-naphthoate,
- 5 (([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](tert-butyl)amino]carbonyl)oxy)methyl 2,6-difluorobenzoate,
- 10 (((2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 2-fluorobenzoate,
- 15 (((2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 2-(trifluoromethyl)benzoate,
- 20 (((2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 1,1'-biphenyl-2-carboxylate,
- 25 (((2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 2,4,6-trimethylbenzoate,
- 30 (((2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 4-isopropoxybenzoate,
- (((2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 3,4,5-trimethoxybenzoate,

- (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 3,5-dimethoxybenzoate,
- 5 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl (2E)-3-phenylprop-2-enoate,
- 10 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl [3,5-bis(trifluoromethyl)phenyl]acetate,
- 15 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 4-(heptyloxy)benzoate,
- 20 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 2-(2-phenylethyl)benzoate,
- 25 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl 4-(dodecyloxy)benzoate,
- 30 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl)amino)-2-oxoethyl)(tert-butyl)amino]carbonyl)oxy)methyl anthracene-9-carboxylate,

(([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](tert-butyl)amino]carbonyl)oxy)methyl 4-benzoylbenzoate, and

- 5 (([(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl](tert-butyl)amino]carbonyl)oxy)methyl diphenylacetate.

20. A compound according to claim 1 selected from the group

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[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]carbonyl)oxy]methyl 4-fluorobenzoate,

- 15 [[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]carbonyl)oxy]methyl 3,5-dimethylbenzoate,

- 20 [[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]carbonyl)oxy]methyl pivalate,

- 25 [[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]carbonyl)oxy]methyl 3,3-dimethylbutanoate,

- [[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]carbonyl)oxy]methyl 2,2-dimethylbutanoate,

30

[[[(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino]carbonyl)oxy]methyl 2-ethylbutanoate,

- [(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)carbonyl)oxy]methyl thiophene-2-carboxylate,
 5 [(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)carbonyl)oxy]methyl cyclopentylacetate, and
- 10 [(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)carbonyl)oxy]methyl 4-tert-butylbenzoate
 or pharmaceutically acceptable salts thereof.
- 15 21. A compound according to claim 1 selected from the group
 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino)carbonyl)oxy)methyl 1H-indole-2-carboxylate,
- 20 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino)carbonyl)oxy)methyl nicotinate,
- 25 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino)carbonyl)oxy)methyl isonicotinate,
- 30 (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino)-2-oxoethyl)(tert-butyl)amino)carbonyl)oxy)methyl 4-pyrrolidin-1-ylbenzoate,

{{(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl}amino)-2-oxoethyl)(tert-butyl)amino}carbonyl}oxy)methyl 3-methyl-1-benzofuran-2-carboxylate,

5 {{{(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl}amino)-2-oxoethyl)(tert-butyl)amino}carbonyl}oxy)methyl 1-methyl-1H-indole-3-carboxylate,

10 {{{(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl}amino)-2-oxoethyl)(tert-butyl)amino}carbonyl}oxy)methyl quinoline-2-carboxylate,

15 {{{(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl}amino)-2-oxoethyl)(tert-butyl)amino}carbonyl}oxy)methyl 1-benzofuran-2-carboxylate, and

20 {{{(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl}amino)-2-oxoethyl)(tert-butyl)amino}carbonyl}oxy)methyl-1-methyl-1H-pyrrole-2-carboxylate or pharmaceutically acceptable salts thereof.

22. A compound according to claim 1 selected from the group

25 (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-{{(7S,10aR)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl}amino)-2-oxoethyl(propyl)carbamate,

30 (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-{{(7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl}amino)-2-oxoethyl(butyl)carbamate,

(2-oxo-5-phenyl-1,3-dioxol-4-yl)methyl 2-[[[(7R,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl(propyl)carbamate,

- 5 [5-(4-methoxyphenyl)-2-oxo-1,3-dioxol-4-yl]methyl 2-[[[(7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl(propyl)carbamate,

- 10 (2-oxo-5-phenyl-1,3-dioxol-4-yl)methyl 2-[[[(7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl(butyl)carbamate and

- 15 [5-(4-methoxyphenyl)-2-oxo-1,3-dioxol-4-yl]methyl 2-[[[(7S,10aS)-9-(aminocarbonyl)-4,7-bis(dimethylamino)-1,8,10a,11-tetrahydroxy-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahydrotetracen-2-yl]amino}-2-oxoethyl(butyl)carbamate

or pharmaceutically acceptable salts thereof.

- 20 23. A pharmaceutical composition comprising a compound according to anyone of claims 1 to 22, in association with a pharmaceutically acceptable carrier.

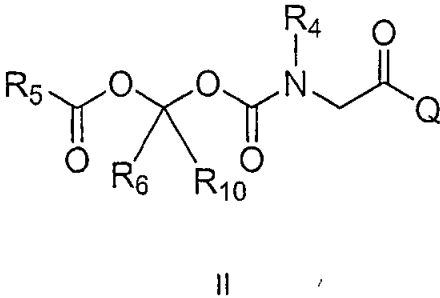
24. A method for the prevention, treatment or control of bacterial infections in warm-blooded animals which comprises providing to said warm-blooded animals an antibacterially effective amount of a compound according to anyone of claims 1 to 22,
25 or a pharmaceutically acceptable salt thereof.

25. Use of a compound according to any one of claims 1 to 22 for the preparation of a medicament for the treatment of bacterial infections.

30

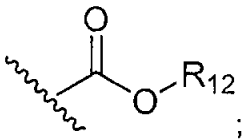
26. A compound according to Formula (II):

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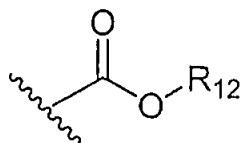
wherein R₄, R₅, R₆, and R₁₀ are as defined in claim 1, and
5 Q is -OR₁₁, Cl, Br, or I;

R₁₁ is H, benzyl optionally substituted with nitro or a moiety of the formula
10



and R₁₂ is alkyl of 1 to 6 carbon atoms.
15

27. A compound according to claim 26 wherein R₄ is t-butyl, R₅ is alkyl of 1 to 6 carbon atoms, and R₁₁ is benzyl optionally substituted with nitro.
28. A compound according to claim 26 wherein R₄ is alkyl of 1 to 6 carbon atoms,
20 R₅ is phenyl optionally substituted and R₁₁ is benzyl optionally substituted with nitro.
29. A compound according to claim 26 wherein R₅ is alkyl of 1 to 6 carbon atoms, R₄ is t-butyl and R₁₁ is H.
- 25 30. A compound according to claim 26 wherein R₅ is alkyl of 1 to 6 carbon atoms, R₄ is t-butyl, Q is



and R₁₂ is alkyl of 1 to 6 carbon atoms.

5

31. A compound according to anyone of claims 26 to 30 wherein R₆ and R₁₀ are H.

32. A compound according to claim 26 selected from the group

10

([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 4-tert-butylbenzoate,

([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 2,2-dimethylbutanoate,

15

([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 2-methylpropanoate,

20

([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl cyclopentanecarboxylate,

([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 4-methylbenzoate,

25

([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl heptanoate,

([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl propionate,

([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl

30

cyclohexanecarboxylate,

- ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 3,5-dimethylbenzoate,
- 5 ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 4-fluorobenzoate,
- ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 3-methylbutanoate,
- 10 benzyl N-(tert-butyl)-N-([[(cyclopentylacetyl)oxy]methoxy]carbonyl)glycinate,
- ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 4-(trifluoromethyl)benzoate,
- 15 ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl cyclopropanecarboxylate,
- ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl adamantane-1-carboxylate,
- 20 ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl pentanoate,
- ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl cyclobutanecarboxylate,
- 25 ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 3-cyclohexylpropanoate,
- benzyl N-(tert-butyl)-N-([[(4-fluorophenoxy)acetyl]oxy]methoxy]carbonyl)glycinate,
- 30 benzyl N-(tert-butyl)-N-([[(cyclohexylacetyl)oxy]methoxy]carbonyl)glycinate,
- ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 2,6-dimethylbenzoate,

- benzyl N-(tert-butyl)-N-(((phenylacetyl)oxy)methoxy)carbonyl)glycinate,
- 5 ((([2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl pivalate,
- (((2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 1-benzofuran-2-
- carboxylate,
- 10 ((([2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 1-methyl-1H-
- pyrrole-2-carboxylate,
- (((2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 1,1'-biphenyl-4-
- carboxylate,
- 15 ((([2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 4-
- methoxybenzoate,
- (((2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 1H-indole-2-
- carboxylate,
- 20 benzyl N-(tert-butyl)-N-(((diphenylacetyl)oxy)methoxy)carbonyl)glycinate,
- (((2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 1-naphthoate,
- 25 ((([2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 2-naphthoate,
- (((2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 1-methyl-1H-
- indole-3-carboxylate,
- 30 ((([2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl quinoline-2-
- carboxylate,
- (((2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl nicotinate,

- ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl isonicotinate,
- ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 2,6-
5 difluorobenzoate,
- ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 2-fluorobenzoate,
- ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 2-
10 (trifluoromethyl)benzoate,
- ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 4-(1H-pyrrol-1-
yl)benzoate,
- 15 ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 1,1'-biphenyl-2-
carboxylate,
- ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 2,4,6-
trimethylbenzoate,
20 ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 4-
isopropoxybenzoate,
- ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 3,4,5-
25 trimethoxybenzoate,
- ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl}oxy)methyl 3,5-
dimethoxybenzoate,
- 30 3-phenyl-acrylic acid (benzyloxycarbonylmethyl-tert-butyl-carbamoyloxy)-methyl
ester,

25
([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 3-methyl-1-benzofuran-2-carboxylate,

benzyl N-[[[3,5-bis(trifluoromethyl)phenyl]acetyl]oxy]methoxy]carbonyl]-N-(tert-butyl)glycinate,

([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 4-(heptyloxy)benzoate,

10 ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 2-(2-phenylethyl)benzoate,

([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 4-(dodecyloxy)benzoate,

15 ([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 4-(acetylamino)benzoate,

([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl anthracene-9-carboxylate and

([[[2-(benzyloxy)-2-oxoethyl](tert-butyl)amino]carbonyl]oxy)methyl 4-benzoylbenzoate.

25 33. A compound according to claim 26 selected from the group:

N-(tert-butyl)-N-([[(4-tert-butylbenzoyl)oxy]methoxy]carbonyl)glycine,

30 N-(tert-butyl)-N-([[(isobutyryloxy)methoxy]carbonyl]glycine,

N-(tert-butyl)-N-([[(cyclopentylcarbonyl)oxy]methoxy]carbonyl)glycine,

N-(tert-butyl)-N-([[(4-methylbenzoyl)oxy]methoxy]carbonyl)glycine,

- N-(tert-butyl)-N-([(heptanoyloxy)methoxy]carbonyl)glycine,
- N-(tert-butyl)-N-([(propionyloxy)methoxy]carbonyl)glycine,
- 5 N-(tert-butyl)-N-([(cyclohexylcarbonyl)oxy]methoxy)carbonyl)glycine,
- N-(tert-butyl)-N-([(3,5-dimethylbenzoyl)oxy]methoxy)carbonyl)glycine,
- 10 N-(tert-butyl)-N-([(4-fluorobenzoyl)oxy]methoxy)carbonyl)glycine,
- N-(tert-butyl)-N-([(3-methylbutanoyl)oxy]methoxy)carbonyl)glycine,
- N-(tert-butyl)-N-([(cyclopentylacetyl)oxy]methoxy)carbonyl)glycine,
- 15 N-(tert-butyl)-N-([(4-(trifluoromethyl)benzoyl)oxy]methoxy)carbonyl)glycine,
- N-(tert-butyl)-N-([(cyclopropylcarbonyl)oxy]methoxy)carbonyl)glycine,
- 20 N-([(1-adamantylcarbonyl)oxy]methoxy)carbonyl)-N-(tert-butyl)glycine,
- N-(tert-butyl)-N-([(pentanoyloxy)methoxy]carbonyl)glycine,
- N-(tert-butyl)-N-([(cyclobutylcarbonyl)oxy]methoxy)carbonyl)glycine,
- 25 N-(tert-butyl)-N-([(3-cyclohexylpropanoyl)oxy]methoxy)carbonyl)glycine,
- N-(tert-butyl)-N-([(cyclohexylacetyl)oxy]methoxy)carbonyl)glycine,
- 30 N-(tert-butyl)-N-([(2,6-dimethylbenzoyl)oxy]methoxy)carbonyl)glycine,
- N-(tert-butyl)-N-([(phenylacetyl)oxy]methoxy)carbonyl)glycine,

- 25²
- N-(tert-butyl)-N-([[(2,2-dimethylpropanoyl)oxy]methoxy]carbonyl)glycine,
- N-([[(1-benzofuran-2-ylcarbonyl)oxy]methoxy]carbonyl)-N-(tert-butyl)glycine,
- 5 N-(tert-butyl)-N-([[(1-methyl-1H-pyrrol-2-yl)carbonyl]oxy]methoxy)carbonyl]glycine,
- N-([[(1,1'-biphenyl-4-ylcarbonyl)oxy]methoxy]carbonyl)-N-(tert-butyl)glycine,
- 10 N-(tert-butyl)-N-([[(4-methoxybenzoyl)oxy]methoxy]carbonyl)glycine,
- N-(tert-butyl)-N-([[(1H-indol-2-ylcarbonyl)oxy]methoxy]carbonyl)glycine,
- N-(tert-butyl)-N-([[(diphenylacetyl)oxy]methoxy]carbonyl)glycine,
- 15 N-(tert-butyl)-N-([[(1-naphthoyloxy)methoxy]carbonyl]glycine,
- N-(tert-butyl)-N-([[(2-naphthoyloxy)methoxy]carbonyl]glycine,
- 20 N-(tert-butyl)-N-([[(1-methyl-1H-indol-3-yl)carbonyl]oxy]methoxy)carbonyl]glycine,
- N-(tert-butyl)-N-([[(quinolin-2-ylcarbonyl)oxy]methoxy]carbonyl)glycine,
- N-(tert-butyl)-N-([[(pyridin-3-ylcarbonyl)oxy]methoxy]carbonyl)glycine,
- 25 N-(tert-butyl)-N-([[(isonicotinoyloxy)methoxy]carbonyl]glycine,
- N-(tert-butyl)-N-([[(2,6-difluorobenzoyl)oxy]methoxy]carbonyl)glycine,
- 30 N-(tert-butyl)-N-([[(2-fluorobenzoyl)oxy]methoxy]carbonyl)glycine,
- N-(tert-butyl)-N-([[(2-(trifluoromethyl)benzoyl]oxy]methoxy]carbonyl]glycine,

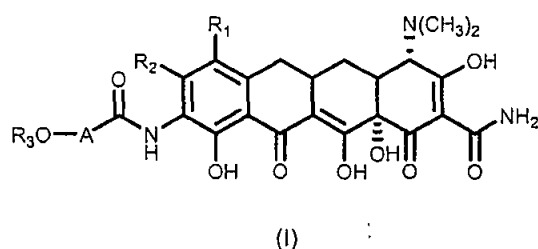
254

- N-(tert-butyl)-N-({[(4-pyrrolidin-1-ylbenzoyl)oxy]methoxy}carbonyl)glycine,
N-({[(1,1'-biphenyl-2-ylcarbonyl)oxy]methoxy}carbonyl)-N-(tert-butyl)glycine,
5 N-(tert-butyl)-N-({[(mesitylcarbonyl)oxy]methoxy}carbonyl)glycine,
N-(tert-butyl)-N-({[(4-isopropoxybenzoyl)oxy]methoxy}carbonyl)glycine,
N-(tert-butyl)-N-({[(3,4,5-trimethoxybenzoyl)oxy]methoxy}carbonyl)glycine,
10 N-(tert-butyl)-N-({[(3,5-dimethoxybenzoyl)oxy]methoxy}carbonyl)glycine,
N-(tert-butyl)-N-({[(2E)-3-phenylprop-2-enoyl]oxy}methoxy}carbonyl]glycine,
15 N-(tert-butyl)-N-({[(3-methyl-1-benzofuran-2-yl)carbonyl]oxy}methoxy}carbonyl]glycine,
N-({[(3,5-bis(trifluoromethyl)phenyl]acetyl)oxy]methoxy}carbonyl)-N-(tert-butyl)glycine,
20 N-(tert-butyl)-N-({[(4-(heptyloxy)benzoyl]oxy}methoxy}carbonyl]glycine,
N-(tert-butyl)-N-({[(2-(2-phenylethyl)benzoyl]oxy}methoxy}carbonyl]glycine,
25 N-(tert-butyl)-N-({[(4-(dodecyloxy)benzoyl]oxy}methoxy}carbonyl]glycine,
N-({[(4-(acetylamino)benzoyl]oxy}methoxy}carbonyl)-N-(tert-butyl)glycine,
N-({[(9-anthrylcarbonyl)oxy]methoxy}carbonyl)-N-(tert-butyl)glycine and
30 N-({[(4-benzoylbenzoyl)oxy]methoxy}carbonyl)-N-(tert-butyl)glycine.

34. A compound according to claim 26 which is

3,3-Dimethyl-butyric acid [tert-butyl-(2-isobutoxycarbonyloxy-2-oxo-ethyl)-carbamoyloxy)-methyl ester.

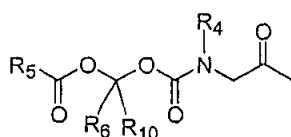
35. A method for the preparation of compounds represented by Formula (I);



10

wherein:

$R_3O - A - CO-$ represents

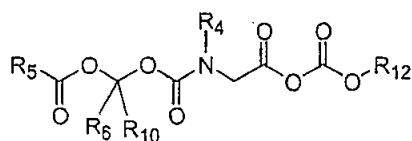


and R_1, R_2, R_4, R_5, R_6 , and R_{10} are as defined in claim 1

15

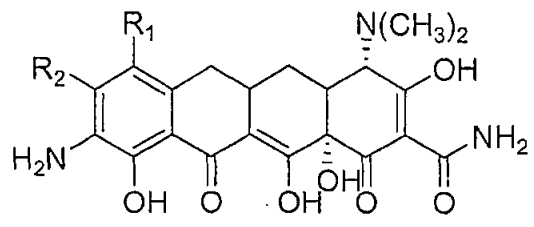
or a pharmaceutically acceptable salt thereof comprising the step of:

a. reacting an activated acyloxycarbamate intermediate of the formula



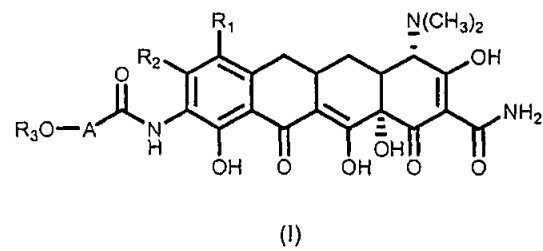
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where R₄, R₅, R₆, and R₁₀ are as defined in claim 1 and R₁₂ is as defined in claim 26 with a 7,8-disubstituted-9-aminotetracycline of the formula

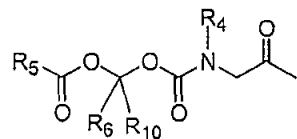


where R₁, and R₂ are as defined in claim 1
in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone and
triethylamine to afford a compound of Formula (I) and, if desired,
5 b. converting the compound of Formula (I) into a pharmaceutically
acceptable salt thereof.

36. A method for the preparation of compounds represented by Formula (I);

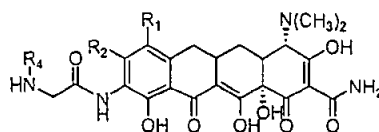


wherein:
R₃O - A - CO- represents

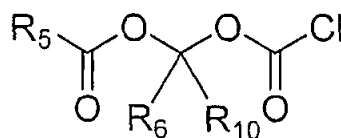


and R₁, R₂, R₄, R₅, R₆, and R₁₀ are as defined in claim 1 or a pharmaceutically
acceptable salt thereof comprising:

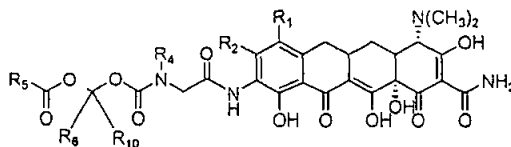
reacting an amine of the formula



wherein R_1 , R_2 , R_4 , R_5 , R_6 , and R_{10} are as defined in claim 1 with a chloro intermediate of the formula

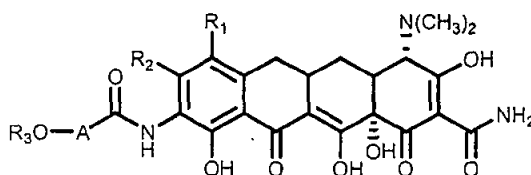


in the presence of an alkali metal carbonate, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone and acetonitrile to afford a compound of the formula



or a pharmaceutically acceptable salt thereof and, if desired, converting the compound of Formula (I) into a pharmaceutically acceptable salt thereof.

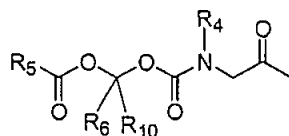
37. A method for the preparation of compounds represented by Formula (I);



(I)

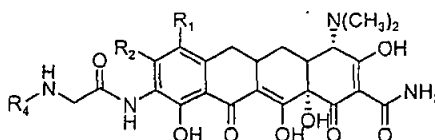
wherein:

$R_3O - A - CO-$ represents

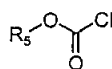


- and R_1 , R_2 , R_4 , R_5 , R_6 , and R_{10} are as defined in claim 1 or a pharmaceutically acceptable salt thereof comprising the step of:

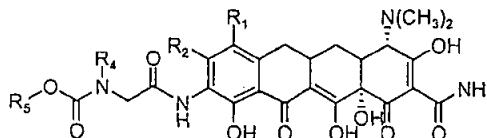
reacting a compound of the formula



- wherein R_1 , R_2 , and R_4 are as defined in claim 1 with a chloro intermediate of the formula

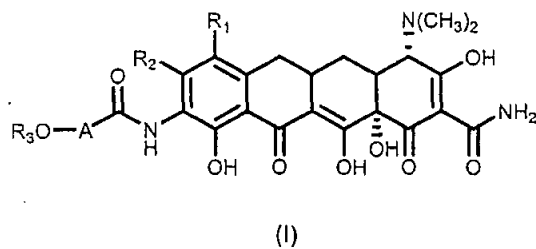


- wherein R_5 is as defined in claim 1 in the presence of an alkali metal carbonate, and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone in acetonitrile to give a compound of Formula I



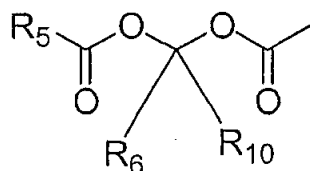
- and, if desired, converting the compound of Formula (I) into a pharmaceutically acceptable salt thereof.

38. A method for the preparation of a compound represented by Formula (I);



wherein:

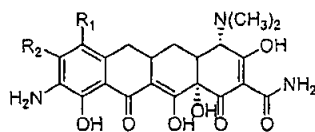
- 5 $R_3O - A - CO-$ represents



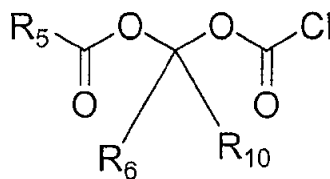
and R_1 , R_2 , R_5 , R_6 , and R_{10} are as defined in claim 1

or a pharmaceutically acceptable salt thereof comprising the step of:

- 10 reacting a 7,8-disubstituted-9-aminotetracycline of the formula



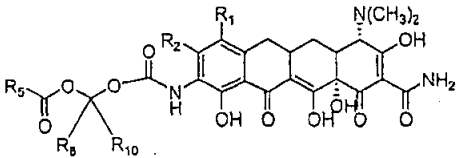
- 15 with a chloro intermediate of the formula



where R_1 , R_2 , R_5 , R_6 , and R_{10} are as defined in claim 1

in the presence of triethylamine and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-

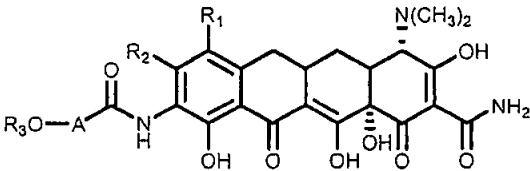
- 20 pyrimidinone to afford a compound of the formula



or a pharmaceutically acceptable salt thereof and, if desired, converting the compound of Formula (I) into a pharmaceutically acceptable salt thereof.

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39. A method for the preparation of a compound represented by Formula (I);



(I)

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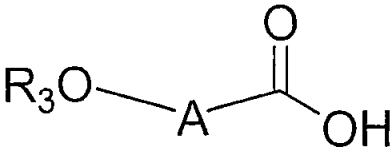
wherein:

A, R₁, R₂, and R₃ are as defined in claim 1

or a pharmaceutically acceptable salt thereof comprising :

15

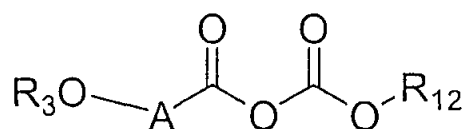
reacting a carboxylic acid of the formula



where A, and R₃ are as defined above

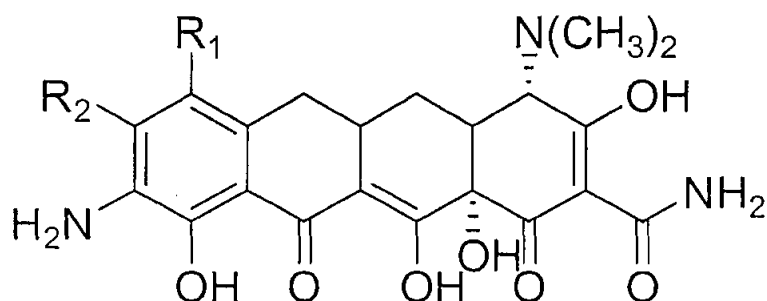
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with a chloroformate ClCO₂R₁₂ where R₁₂ is alkyl of 1 to 6 carbon atoms in the presence of 1,8-bis(dimethylamino)naphthalene in methylene chloride to give a mixed anhydride of the formula

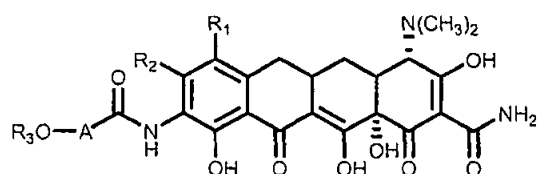


Mixed anhydride

and reacting said mixed anhydride with a 7,8-disubstituted-9-aminotetracycline of the
5 formula



where R₁, and R₂ are as defined above
in the presence of triethylamine and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-
10 pyrimidinone to afford a compound of Formula (I)



(I)

or a pharmaceutically acceptable salt thereof and, if desired, converting the
15 compound of Formula (I) into a pharmaceutically acceptable salt thereof.

20

DERIVADOS DE GLICILCICLINAS SUSTITUIDOS CON 9-AMINOCARBONILO

Esta solicitud reclama la prioridad de la Solicitud Estadounidense No.60/713,112 presentada en Agosto 31, 2005 cuya divulgación completa se incorpora aquí como referencia.

CAMPO DE LA INVENCIÓN

La presente invención se relaciona con derivados de glicilciclinas sustituidas con 9-aminocarbonilo que son útiles como agentes antibióticos y exhiben actividad antibacteriana contra un amplio espectro de organismos incluyendo organismos que son resistentes a las tetraciclinas y otros antibióticos.

ANTECEDENTES DE LA INVENCIÓN

Desde 1947 una variedad de antibióticos de tetraciclina han sido sintetizados y descritos para el tratamiento de enfermedades infecciosas en el hombre y los animales. Las tetraciclinas inhiben la síntesis de la proteína por medio de ligar a la subunidad 30S del ribosoma bacteriano impidiendo el ligado del ARN aminoacilo (Chopra, Handbook of Experimental Pharmacology, Vol. 78, 317-392, Springer-Verlag, 1985). La resistencia a las tetraciclinas emerge entre muchos microorganismos clínicamente importantes los cuales limitan la utilidad de estos antibióticos. Hay dos mecanismos principales de resistencia bacteriana a las tetraciclinas: a) el eflujo dependiente de energía del antibiótico mediado por las proteínas localizadas en la membrana citoplásmica que impide la acumulación intracelular de la tetraciclina (S. B. Levy, et al., Antimicrob. Agents Chemotherapy

33, 1373-1374 (1989); y b) la protección ribosomal mediada por una proteína citoplásmica que interactúa con el ribosoma de modo que la tetraciclina ya no se liga o inhibe a la síntesis de la proteína (A. A. Salyers, B. S. Speers y N. B. Shoemaker, Mol. Microbiol, 4:151-156, 1990). El mecanismo del eflujo de la resistencia es codificado por determinantes de resistencia designados tetA-tetL. Ellos son comunes en muchas bacterias Gram negativas (resistencia a los genes Clase A y E), tal como Enterobacteriaceae, Pseudomonas, Haemophilus y Aeromonas, y en bacterias Gram-positivas (resistencia de los genes Clase K y L), tales como Estafilococos, Bacillus y Streptococos. El mecanismo de protección ribosomal de resistencia es codificado por determinantes de resistencia designados TetM, N y O, es común en el Estafilococos, Streptococos, Campilobacter, Gardnerella, Haemofilus y Micoplasma (A. A. Salyers, B. S. Speers y N. B. Shoemaker, Mol. Microbiol, 4:151-156 1990).

Un compuesto de tetraciclina particularmente útil es el 7-(dimetilamino)-6-demetil-6-deoxitetraciclina, conocido como minociclina (ver la Patente Estadounidense No. 3,148,212, la Patente Estadounidense No. RE 26,253 y la Patente Estadounidense No. 3,226,436 discutidas más adelante). Sin embargo, las cepas que cosechan el tetB (eflujo en bacterias Gram-negativa) como mecanismo, pero no el tetK (eflujo en el Estafilococos) son resistentes a la minociclina. También, las cepas que portan el tetM (protección ribosomal) son resistentes a la minociclina.

Duggar, Patente Estadounidense No. 2,482,055, describe la preparación de Aureomycin.RTM. por medio de la fermentación lo

que tiene actividad antibacterial. Growich et al., Patente Estadounidense No. 3,007,965, describe mejoras en la preparación de la fermentación. Beereboom et al., Patente Estadounidense No. 3,043,875 describe derivados de tetraciclina, Boothe et al., Patente Estadounidense No. 3,148,212, reemitida como Patente Estadounidense No. RE 26,253, y Petisi et al., Patente Estadounidense No. 3,226,436, describe derivados de tetraciclina que son útiles para el tratamiento de infecciones bacterianas. Blackwood et al., Patente Estadounidense No. 3,200,149 describe derivados de tetraciclina que poseen actividad microbiológica. Petisi et al., Patente Estadounidense No. 3,338,963 describe compuestos de tetraciclina que tienen una actividad antibacteriana de amplio espectro. Bitha et al., Patente Estadounidense No. 3,341,585 describe compuestos de tetraciclina que tienen actividad antibacteriana de amplio espectro. Shu, Patente Estadounidense No. 3,360,557 describe 9-hidroxitetraciclinas en las cuales se ha encontrado que poseen actividad antibacteriana. Zambrano, Patente Estadounidense No. 3,360,561 describe un proceso para preparar las 9-nitrotetraciclinas. Martell et al., Patente Estadounidense No. 3,518,306 describe tetraciclinas que poseen actividad antibacterial in vivo.

En la Patente Estadounidense No. 5,021,407 se describe un método para sobreponerse a la resistencia de las bacterias resistentes a al tetraciclina. El método involucra utilizar una composición de agente de bloqueo en conjunto con un antibiótico tipo tetraciclina. La patente no describe compuestos de tetraciclina novedosos que en si mismos tengan una actividad

contra organismos resistentes. Descrito en la Patente Estadounidense No. 5,494,903 se encuentran las 7-sustituidas-9-sustituida amino-6-demetil-6-deoxitetraciclinas que tienen una actividad antibacterial de amplio espectro.

A pesar de los avances hechos para sobreponerse a la resistencia de las bacterias resistentes a la tetraciclina, queda una necesidad de nuevos y mejores antibióticos que solucionen la incidencia incremental de la resistencia. La presente invención suministra tales antibióticos.

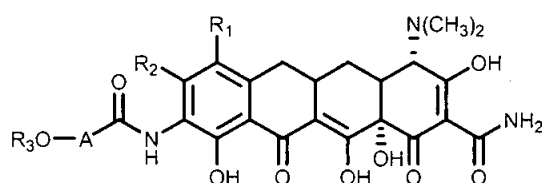
En resumen, ninguna de las patentes anteriores enseña o sugiere derivados novedosos de glicilciclinas de esta solicitud.

RESUMEN DE LA INVENCION

Esta invención está relacionada con derivados de glicilciclinas 9-aminocarbonilo sustituidas representadas por la fórmula I que tienen actividad antibacteriana; con métodos para tratar enfermedades infecciosas en humanos y otros animales cuando se les administran estos nuevos compuestos; con preparaciones farmacéuticas que contienen estos compuestos; y con procesos novedosos para la producción de compuestos de la fórmula I.

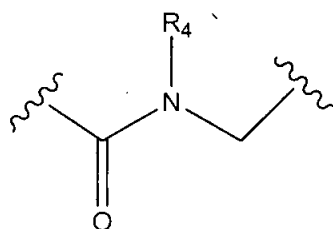
De acuerdo con la presente invención, se ha suministrado compuestos representados por la fórmula (I);

266



(II)

en donde:



A es una parte

o está ausente;

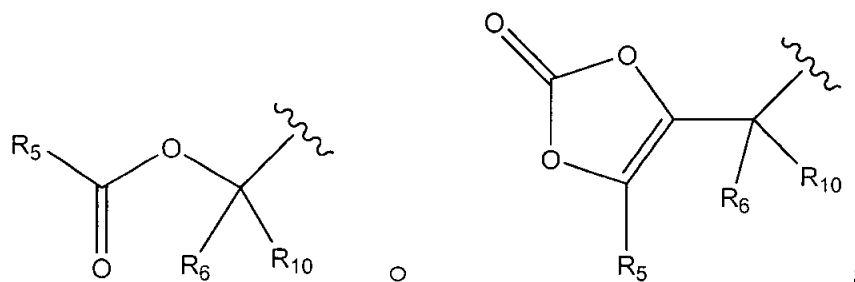
R_1 se selecciona de hidrógeno, -OH, amino, $-NR_7R_8$, halógeno, alquilo de 1 a 12 átomos de carbono, opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de halógeno, amino, ciano, cicloalquilo de 3 a 6 átomos de carbono, alquilo de 1 a 12 átomos de carbono, fenilo, hidroxilo, alcoxi de 1 a 12 átomos de carbono, N-alquilo de 1 a 12 átomos de carbono, N-cicloalquilo de 3 a 6 átomos de carbono, heterociclilo de 3 a 8 átomos en anillo, arilo, ariloxi y N-(alquilo con 1 a 12 átomos de carbono)-arilo, en donde dicho arilo, ariloxi y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alqueno, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcoxicarbonilo, aril-C(O)-, $CH_3-C(O)-NH-$, aralquilo, ariloxi, heterociclilo y fenilo, alqueno de 2 a 12 átomos de carbono

opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de fenilo, heteroarilo, halógeno, amino, ciano, alquilo, hidroxilo, alcoxi, arilo, alquinilo y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alquenilo, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcoxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, y alquinilo de 2 a 12 átomos de carbono opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados del grupo halógeno, amino, ciano, alquilo, hidroxilo, y alcoxi;

R₂ se selecciona de hidrógeno, halógeno, alquilo de 1 a 12 átomos de carbono, opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de halógeno, amino, ciano, cicloalquilo de 3 a 6 átomos de carbono, alquilo de 1 a 12 átomos de carbono, fenilo, hidroxilo, alcoxi de 1 a 12 átomos de carbono, N-alquilo de 1 a 12 átomos de carbono, N-cicloalquilo de 3 a 6 átomos de carbono, heterociclilo de 3 a 8 átomos en anillo, arilo, ariloxi y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo, ariloxi y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alquenilo, hidroxilo, alquilo,

haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcoxycarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, alqueno de 2 a 12 átomos de carbono opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de fenilo, heteroarilo, halógeno, amino, ciano, alquilo, hidroxilo, alcoxi, arilo, alquinilo y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alqueno, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcoxycarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, y alquinilo de 2 a 12 átomos de carbono opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados del grupo halógeno, amino, ciano, alquilo, hidroxilo, y alcoxi;

R₃ es una parte de R₉,



R₄ se selecciona de hidrógeno, alquilo de 1 a 12 átomos de carbono, opcionalmente sustituidos con 1 a 3 sustituyentes

independientemente seleccionados del grupo de halógeno, amino, ciano, cicloalquilo de 3 a 6 átomos de carbono, alquilo de 1 a 12 átomos de carbono, fenilo, hidroxilo, alcoxi de 1 a 12 átomos de carbono, N-alquilo de 1 a 12 átomos de carbono, N-cicloalquilo de 3 a 6 átomos de carbono, heterociclilo de 3 a 8 átomos en anillo, arilo, ariloxi y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo, ariloxi y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alqueno, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, alqueno de 2 a 12 átomos de carbono opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de fenilo, heteroarilo, halógeno, amino, ciano, alquilo, hidroxilo, alcoxi, arilo, alquino y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alqueno, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, alquino de 2 a 12 átomos de carbono opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados del grupo halógeno, amino, ciano, alquilo, hidroxilo, y alcoxi, arilo de 6, 10 o 14

270

átomos de carbono dicho arilo es opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados entre halógeno, nitro, ciano, alqueno, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, N-(alquilo de 1 a 12 átomos de carbono)-arilo, dicho arilo es opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados entre halógeno, nitro, ciano, alqueno, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, aralquilo de 7 a 16 átomos de carbono opcionalmente sustituido, aroilo de 7 a 13 átomos de carbono opcionalmente sustituidos, SR³, heteroarilo opcionalmente sustituido y heteroarilcarbonilo opcionalmente sustituido;

R₅ se selecciona de alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de halógeno, amino, ciano, cicloalquilo de 3 a 6 átomos de carbono, alquilo de 1 a 12 átomos de carbono, fenilo, hidroxilo, alcoxi de 1 a 12 átomos de carbono, N-alquilo de 1 a 12 átomos de carbono, N-cicloalquilo de 3 a 6 átomos de carbono, heterociclilo de 3 a 8 átomos en anillo, arilo de 6, 10 o 14 átomos de carbono, ariloxi y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo, ariloxi y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo, puede ser opcionalmente sustituido con 1 a 3 sustituyentes

221

independientemente seleccionados entre halógeno, nitro, ciano, alqueno, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcoxycarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, aralquilo de 7 a 16 átomos de carbono opcionalmente sustituido, aroilo, -CH₂(CO)OCH₂arilo, dicho arilo es opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados entre halógeno, nitro, ciano, alqueno, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcoxycarbonilo, ariloxi y fenilo, alqueno de 2 a 12 átomos de carbono opcionalmente sustituido, heteroarilo opcionalmente sustituido, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituido, alquino de 2 a 12 átomos de carbono opcionalmente sustituido, cicloalquilo de 3 a 6 átomos en anillo, aril-CH=CH-, cicloalquil-alquilo; y adamantilo;

R₆ se selecciona de hidrógeno, alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de halógeno, amino, ciano, cicloalquilo de 3 a 6 átomos de carbono, alquilo de 1 a 12 átomos de carbono, fenilo, hidroxilo, alcoxi de 1 a 12 átomos de carbono, N-alquilo de 1 a 12 átomos de carbono, N-cicloalquilo de 3 a 6 átomos de carbono, heterociclilo de 3 a 8 átomos en anillo, arilo, ariloxi y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo, ariloxi y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo puede ser opcionalmente sustituido

222

con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alqueno, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, y cicloalquilo de 3 a 6 átomos de carbono;

R₇ y R₈ son cada uno independientemente H o alquilo de 1 a 12 átomos de carbono o R₇ y R₈ cuando son opcionalmente tomados juntos con el átomo de nitrógeno al cual cada uno está sujeto forman un anillo heterociclilo de 3 a 8 miembros;

R₉ es aralquilo de 7 a 16 átomos de carbono opcionalmente sustituido o alquilo de 1 a 12 átomos de carbono;

R₁₀ es H o alquilo de 1 a 12 átomos de carbono;

o una sal farmacéuticamente aceptable de estos.

Una modalidad de esta invención suministra compuestos de la Fórmula I en donde R₁ es -NR₇R₈, R₇ es hidrógeno, R₈ es metilo, etilo, n-propilo, n-butilo, 1-metiletilo, 1-metilpropilo, 2-metilpropilo o 1,1-dimetiletilo o una sal farmacéuticamente aceptable de estos.

Otra modalidad de esta invención suministra compuestos de la Fórmula I en donde R₁ es -NR₇R₈, R₇ es metilo o etilo, R₈ es metilo, etilo, n-propilo, 1-metiletilo, n-propilo, 1-

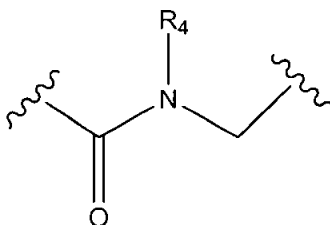
273

metilpropilo, o 2-metilpropilo o una sal farmacéuticamente aceptable de estos.

Una modalidad adicional de esta invención suministra compuestos de la Fórmula I en donde R_1 es $-NR_7R_8$, R_7 y R_8 son tomados juntos con el átomo de nitrógeno al cual cada uno está sujeto forman un anillo heterociclilo de 3 a 8 miembros o una sal farmacéuticamente aceptable de estos.

Otra modalidad de esta invención suministra compuestos de la Fórmula I en donde R_2 es H o una sal farmacéuticamente aceptable de estos.

Otra modalidad de esta invención suministra compuestos de la Fórmula I en donde A es una parte

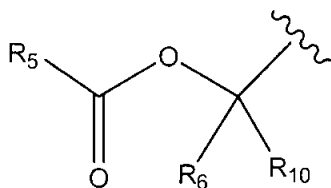


o una sal farmacéuticamente aceptable de esta.

Una modalidad adicional de esta invención suministra compuestos de la Fórmula I en donde A está ausente o una sal farmacéuticamente aceptable de esta.

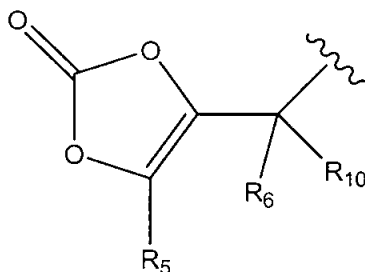
Una modalidad adicional de esta invención suministra compuestos de la Fórmula I en donde R_3 es una parte

224



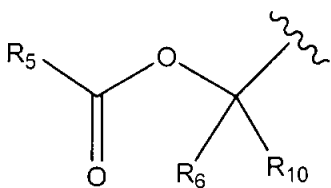
o una sal farmacéuticamente aceptable de esta.

Una modalidad adicional de esta invención suministra compuestos de la Fórmula I en donde R_3 es una parte



o una sal farmacéuticamente aceptable de esta.

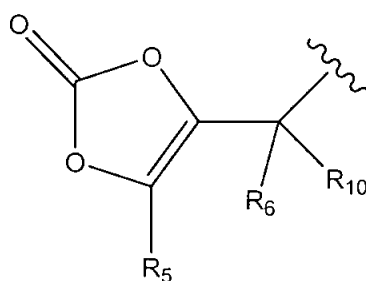
Una modalidad de esta invención suministra compuestos de la Fórmula I en donde R_3 es una parte



y R_6 y R_{10} son H o una sal farmacéuticamente aceptable de estos.

Una modalidad adicional de esta invención suministra compuestos de la Fórmula I en donde R_3 es una parte

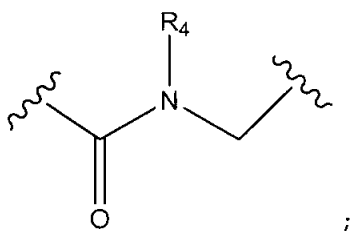
225



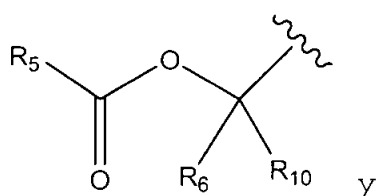
y R_6 y R_{10} son H o una sal farmacéuticamente aceptable de estos.

Una modalidad adicional de esta invención suministra compuestos de la Fórmula I en donde R_3 es R_9 o una sal farmacéuticamente aceptable de estos.

Una modalidad adicional de esta invención suministra compuestos de la Fórmula I en donde A es una parte de,

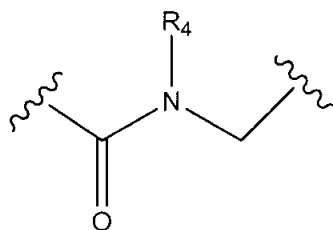


R_3 es una parte de

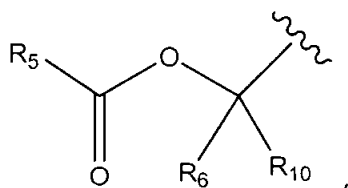


R_5 es arilo de 6 átomos de carbono o una sal farmacéuticamente aceptable de estos.

Una modalidad adicional de esta invención suministra compuestos de la Fórmula I en donde A es una parte



R₃ es una parte,



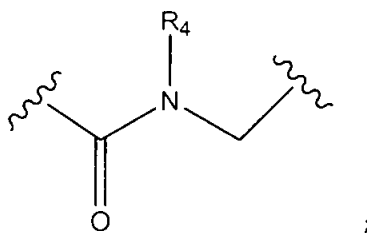
R₄ es 1,1-dimetiletilo y

R₅ es arilo de 6 átomos de carbono o una sal farmacéuticamente aceptable de estos.

Una modalidad adicional de esta invención suministra compuestos de la Fórmula I

en donde:

A es una parte

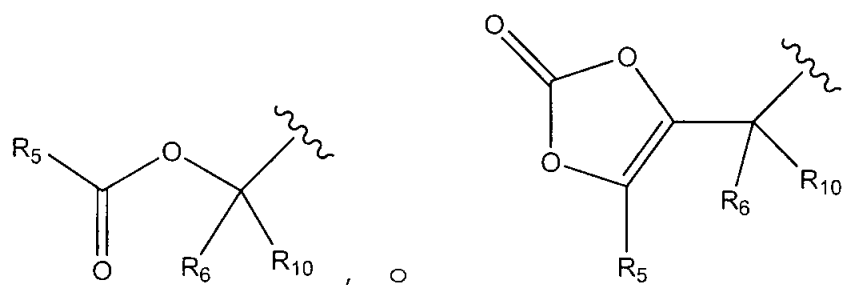


227

R_1 es $-NR_7R_8$;

R_2 es hidrógeno;

R_3 es una parte de



R_4 se selecciona de alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de halógeno, amino, ciano, cicloalquilo de 3 a 6 átomos de carbono, alquilo de 1 a 12 átomos de carbono, fenilo, hidroxilo, alcoxi de 1 a 12 átomos de carbono, N-alquilo de 1 a 12 átomos de carbono, N-cicloalquilo de 3 a 6 átomos de carbono, heterociclilo de 3 a 8 átomos en anillo, arilo, y ariloxi en donde dicho arilo y ariloxi es opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alqueno, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, ariloxi y fenilo;

R_5 se selecciona de alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de halógeno, amino, ciano, cicloalquilo de 3 a 6 átomos de carbono, alquilo de 1 a 12 átomos de carbono, fenilo, hidroxilo,

27A

alcoxi de 1 a 12 átomos de carbono, N-alquilo de 1 a 12 átomos de carbono, N-cicloalquilo de 3 a 6 átomos de carbono, heterociclilo de 3 a 8 átomos en anillo, arilo de 6, 10 o 14 átomos de carbono, y ariloxi en donde dicho arilo, ariloxi y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo, puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados entre halógeno, nitro, ciano, alqueno, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, aralquilo de 7 a 16 átomos de carbono opcionalmente sustituido, aroilo, -CH₂(CO)OCH₂arilo, dicho arilo es opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados entre halógeno, nitro, ciano, alqueno, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, ariloxi y fenilo, heteroarilo opcionalmente sustituido, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituido, cicloalquilo de 3 a 6 átomos en anillo, aril-CH=CH-, cicloalquil-alquilo; y adamantilo;

R₆ es hidrógeno;

R₇ y R₈ son cada uno independientemente H o alquilo de 1 a 12 átomos de carbono;

R₉ es aralquilo de 7 a 16 átomos de carbono opcionalmente sustituido o alquilo de 1 a 12 átomos de carbono;

R₁₀ es H

o una sal farmacéuticamente aceptable de estos.

Modalidades adicionales de la invención son los compuestos específicamente preferidos siguientes de fórmula I o sus sales farmacéuticamente aceptables:

2-metilpropanoato de ({[(2-{[(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(butil)amino]carbonil}oxi)metilo,

4-metoxibenzoato de ({[(2-{[(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(butil)amino]carbonil}oxi)metilo,

4-metilbenzoato de ({[(2-{[(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(butil)amino]carbonil}oxi)metilo,

4-fluorobenzoato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(butil)amino]carbonil}oxi)metilo,

4-metilbenzoato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(propil)amino]carbonil}oxi)metilo,

4-metoxibenzoato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(propil)amino]carbonil}oxi)metilo,

ciclobutanocarboxilato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(propil)amino]carbonil}oxi)metilo,

4-fluorobenzoato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(propil)amino]carbonil}oxi)metilo,

Pivalato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(propil)amino]carbonil}oxi)metilo,

2-metilpropanoato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(propil)amino]carbonil}oxi)metilo,

285

fenilacetato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(propil)amino]carbonil}oxi)metilo,

fenilacetato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(butil)amino]carbonil}oxi)metilo,

pivalato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(butil)amino]carbonil}oxi)metilo

heptanoato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(butil)amino]carbonil}oxi)metilo,

ciclobutanocarboxilato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(butil)amino]carbonil}oxi)metilo,

heptanoato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-

5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-
oxoetil) (propil) amino] carbonil}oxi) metilo,

4-Terc-butilbenzoato de ({ [(2-{ [(5aR,6aS,7S,10aS)-9-
(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-
10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-
2-oxoetil) (butil) amino] carbonil}oxi) metilo,

1,1'-bifenil-4-carboxilato de ({ [(2-{ [(5aR,6aS,7S,10aS)-9-
(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-
10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-
2-oxoetil) (butil) amino] carbonil}oxi) metilo,

3,5-dimetilbenzoato de ({ [(2-{ [(5aR,6aS,7S,10aS)-9-
(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-
10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-
2-oxoetil) (butil) amino] carbonil}oxi) metilo,

1,1'-bifenil-4-carboxilato de ({ [(2-{ [(5aR,6aS,7S,10aS)-9-
(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-
10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-
2-oxoetil) (propil) amino] carbonil}oxi) metilo,

3,5-dimetilbenzoato de ({ [(2-{ [(5aR,6aS,7S,10aS)-9-
(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-
10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-
2-oxoetil) (propil) amino] carbonil}oxi) metilo,

4-Terc-butilbenzoato de (([(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(propil)amino]carbonil}oxi)metilo,

acetato de 1-(([(2-{[(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(butil)amino]carbonil}oxi)etilo,

ciclohexanocarboxilato de (([(2-{[(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(propil)amino]carbonil}oxi)metilo,

ciclohexanocarboxilato de (([(2-{[(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(butil)amino]carbonil}oxi)metilo,

3,3-dimetilbutanoato de (([(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(propil)amino]carbonil}oxi)metilo,

3,3-dimetilbutanoato de (([(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(butil)amino]carbonil}oxi)metilo,

2,2-dimetilbutanoato de ({ [(2- { [(5aR,6aS,7S,10aS) -9-(aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino} -2-oxoetil) (propil) amino] carbonil} oxi) metilo,

ciclopentilacetato de ({ [(2- { [(5aR,6aS,7S,10aS) -9-(aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino} -2-oxoetil) (butil) amino] carbonil} oxi) metilo,

adamantan-1-carboxilato de ({ [(2- { [(5aR,6aS,7S,10aS) -9-(aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino} -2-oxoetil) (butil) amino] carbonil} oxi) metilo,

ciclopentilacetato de ({ [(2- { [(5aR,6aS,7S,10aS) -9-(aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino} -2-oxoetil) (propil) amino] carbonil} oxi) metilo,

adamantan-1-carboxilato de ({ [(2- { [(5aR,6aS,7S,10aS) -9-(aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino} -2-oxoetil) (propil) amino] carbonil} oxi) metilo,

3,3-dimetilbutanoato de ({ [(2- { [(5aR,6aS,7S,10aS) -9-(aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-

245

10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-
2-oxoetil) (Terc-butil) amino] carbonil}oxi) metilo,

4-Terc-butilbenzoato de ({ [(2-{ [(5aR,6aS,7S,10aS) -9-
(aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-
10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-
2-oxoetil) (Terc-butil) amino] carbonil}oxi) metilo,

2,2-dimetilbutanoato de ({ [(2-{ [(5aR,6aS,7S,10aS) -9-
(aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-
10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-
2-oxoetil) (Terc-butil) amino] carbonil}oxi) metilo,

2-metilpropanoato de ({ [(2-{ [(5aR,6aS,7S,10aS) -9- (aminocarbonil) -
4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-
5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-2-
oxoetil) (Terc-butil) amino] carbonil}oxi) metilo,

ciclopentanocarboxilato de ({ [(2-{ [(5aR,6aS,7S,10aS) -9-
(aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-
10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-
2-oxoetil) (Terc-butil) amino] carbonil}oxi) metilo,

4-metilbenzoato de ({ [(2-{ [(5aR,6aS,7S,10aS) -9- (aminocarbonil) -
4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-
5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-2-
oxoetil) (Terc-butil) amino] carbonil}oxi) metilo,

heptanoato de ({ [(2-{ [(5aR,6aS,7S,10aS) -9-(aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino} -2-oxoetil) (Terc-butyl) amino] carbonil} oxi) metilo, y

4-metoxibenzoato de ({ [(2-{ [(5aR,6aS,7S,10aS) -9-(aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino} -2-oxoetil) (Terc-butyl) amino] carbonil} oxi) metilo.

Modalidades adicionales de la invención son los compuestos específicamente preferidos siguientes de fórmula I o sus sales farmacéuticamente aceptables:

2-{ [(5aR,6aS,7S,10aS) -9-(aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino} -2-oxoetil(propil) carbamato de bencilo,

2-{ [(5aR,6aS,7S,10aS) -9-(aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino} -2-oxoetil(propil) carbamato de etilo, y

2-{ [(5aR,6aS,7S,10aS) -9-(aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino} -2-oxoetil(propil) carbamato de isobutilo.

28

Modalidades adicionales de la invención son los siguientes compuestos específicamente preferidos de fórmula I o sus sales farmacéuticamente aceptables

tiofen-2-carboxilato de ($\{[(2-\{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino\}-2-oxoetil)(butil)amino]carbonil\}oxi)metilo,$

tiofen-2-carboxilato de ($\{[(2-\{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino\}-2-oxoetil)(propil)amino]carbonil\}oxi)metilo,$

tiofen-3-carboxilato de ($\{[(2-\{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino\}-2-oxoetil)(propil)amino]carbonil\}oxi)metilo,$

tiofen-3-carboxilato de ($\{[(2-\{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino\}-2-oxoetil)(butil)amino]carbonil\}oxi)metilo,$

2-furoato de ($\{[(2-\{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino\}-2-oxoetil)(butil)amino]carbonil\}oxi)metilo,$ y

288

2-furoato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(propil)amino]carbonil}oxi)metilo.

Modalidades adicionales de la invención son los siguientes compuestos preferidos específicamente de fórmula I o sus sales farmacéuticamente aceptables

propionato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

ciclohexanocarboxilato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

3,5-dimetilbenzoato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

4-fluorobenzoato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

28^a

3-metilbutanoato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

ciclopentilacetato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

4-(trifluorometil)benzoato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

ciclopropanocarboxilato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

adamantan-1-carboxilato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(Terc-butil)carbamato de butilo,

2-{ [(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-2-oxoetil (Terc-butil) carbamato de isobutilo,

2-{ [(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-2-oxoetil (Terc-butil) carbamato de metilo,

pentanoato de ({ [(2-{ [(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-2-oxoetil) (Terc-butil) amino] carbonil} oxi) metilo,

ciclobutanocarboxilato de ({ [(2-{ [(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-2-oxoetil) (Terc-butil) amino] carbonil} oxi) metilo,

3-ciclohexilpropanoato de ({ [(2-{ [(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-2-oxoetil) (Terc-butil) amino] carbonil} oxi) metilo,

(4-fluorofenoxi) acetato de ({ [(2-{ [(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-

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10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-
2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

ciclohexilacetato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-
4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-
5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-
oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

2,6-dimetilbenzoato de ({[(2-{[(5aR,6aS,7S,10aS)-9-
(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-
10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-
2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

fenilacetato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-
bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-
5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-
oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

pivalato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-
bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-
5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-
oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

1,1'-bifenil-4-carboxilato de ({[(2-{[(5aR,6aS,7S,10aS)-9-
(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-
10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-
2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

2a2

1-naftoato de ({ [(2- { [(5aR,6aS,7S,10aS) -9- (aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino} -2-oxoetil) (Terc-butil) amino] carbonil} oxi) metilo,

2-naftoato de ({ [(2- { [(5aR,6aS,7S,10aS) -9- (aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino} -2-oxoetil) (Terc-butil) amino] carbonil} oxi) metilo,

2,6-difluorobenzoato de ({ [(2- { [(5aR,6aS,7S,10aS) -9- (aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino} -2-oxoetil) (Terc-butil) amino] carbonil} oxi) metilo,

2-fluorobenzoato de ({ [(2- { [(5aR,6aS,7S,10aS) -9- (aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino} -2-oxoetil) (Terc-butil) amino] carbonil} oxi) metilo,

2-(trifluorometil)benzoato de ({ [(2- { [(5aR,6aS,7S,10aS) -9- (aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino} -2-oxoetil) (Terc-butil) amino] carbonil} oxi) metilo,

1,1'-bifenil-2-carboxilato de ({ [(2- { [(5aR,6aS,7S,10aS) -9- (aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino} -2-oxoetil) (Terc-butil) amino] carbonil} oxi) metilo,

2,4,6-trimetilbenzoato de ({ [(2-{ [(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-2-oxoetil) (Terc-butil) amino] carbonil} oxi) metilo,

4-isopropoxibenzoato de ({ [(2-{ [(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-2-oxoetil) (Terc-butil) amino] carbonil} oxi) metilo,

3,4,5-trimetoxibenzoato de ({ [(2-{ [(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-2-oxoetil) (Terc-butil) amino] carbonil} oxi) metilo,

3,5-dimetoxibenzoato de ({ [(2-{ [(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-2-oxoetil) (Terc-butil) amino] carbonil} oxi) metilo,

(2E)-3-fenilprop-2-enoato de ({ [(2-{ [(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-2-oxoetil) (Terc-butil) amino] carbonil} oxi) metilo,

[3,5-bis(trifluorometil) fenil]acetato de ({ [(2-{ [(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-

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octahidrotetracen-2-il] amino}-2-oxoetil) (Terc-butyl) amino] carbonil}oxi) metilo,

4-(heptiloxi)benzoato de ({ [(2-{ [(5aR, 6aS, 7S, 10aS) -9-(aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-2-oxoetil) (Terc-butyl) amino] carbonil}oxi) metilo,

2-(2-feniletil)benzoato de ({ [(2-{ [(5aR, 6aS, 7S, 10aS) -9-(aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-2-oxoetil) (Terc-butyl) amino] carbonil}oxi) metilo,

4-(dodeciloxi)benzoato de ({ [(2-{ [(5aR, 6aS, 7S, 10aS) -9-(aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-2-oxoetil) (Terc-butyl) amino] carbonil}oxi) metilo,

4-(acetilamino)benzoato de ({ [(2-{ [(5aR, 6aS, 7S, 10aS) -9-(aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-2-oxoetil) (Terc-butyl) amino] carbonil}oxi) metilo,

antraceno-9-carboxilato de ({ [(2-{ [(5aR, 6aS, 7S, 10aS) -9-(aminocarbonil) -4,7-bis(dimetilamino) -1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino}-2-oxoetil) (Terc-butyl) amino] carbonil}oxi) metilo,

4-benzoilbenzoato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo, y

difenilacetato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo.

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4-fluorobenzoato de [{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}carbonil)oxi]metilo,

3,5-dimetilbenzoato de [{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}carbonil)oxi]metilo,

pivalato de [{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}carbonil)oxi]metilo,

3,3-dimetilbutanoato de [({[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}carbonil)oxi]metilo,

2,2-dimetilbutanoato de [({[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}carbonil)oxi]metilo,

2-etilbutanoato de [({[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}carbonil)oxi]metilo,

tiofen-2-carboxilato de [({[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}carbonil)oxi]metilo,

ciclopentilacetato de [({[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}carbonil)oxi]metilo, y

4-Terc-butilbenzoato de [({[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}carbonil)oxi]metilo.

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1H-indol-2-carboxilato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

nicotinato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

isonicotinato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

4-pirrolidin-1-ilbenzoato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

3-metil-1-benzofuran-2-carboxilato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

1-metil-1H-indol-3-carboxilato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

quinolin-2-carboxilato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

1-benzofuran-2-carboxilato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo, y

({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metil-1-metil-1H-pirrol-2 carboxilato.

Modalidades adicionales de la invención son los siguientes compuestos específicamente preferidos de fórmula I o sus sales farmacéuticamente aceptables

2-{[(7S,10aR)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-

2-il]amino}-2-oxoetil(propil)carbamato de (5-metil-2-oxo-1,3-dioxol-4-il)metilo,

2-{[(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(butil)carbamato de (5-metil-2-oxo-1,3-dioxol-4-il)metilo,

2-{[(7R,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(propil)carbamato,

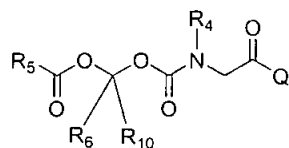
[5-(4-metoxifenil)-2-oxo-1,3-dioxol-4-il]metilo 2-{[(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(propil)carbamato de (2-oxo-5-fenil-1,3-dioxol-4-il)metilo,

2-{[(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(butil)carbamato de (2-oxo-5-fenil-1,3-dioxol-4-il)metilo y

2-{[(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(butil)carbamato de [5-(4-metoxifenil)-2-oxo-1,3-dioxol-4-il]metilo.

2da

Una modalidad adicional de esta invención son los compuestos representados por la Fórmula (II):



(II)

en donde:

R₄ se selecciona de hidrógeno, alquilo de 1 a 12 átomos de carbono, opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de halógeno, amino, ciano, cicloalquilo de 3 a 6 átomos de carbono, alquilo de 1 a 12 átomos de carbono, fenilo, hidroxilo, alcoxi de 1 a 12 átomos de carbono, N-alquilo de 1 a 12 átomos de carbono, N-cicloalquilo de 3 a 6 átomos de carbono, heterociclilo de 3 a 8 átomos en anillo, arilo, ariloxi y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo, ariloxi y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alquenilo, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, alquenilo de 2 a 12 átomos de carbono opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de fenilo, heteroarilo, halógeno, amino, ciano, alquilo,

hidroxilo, alcoxi, arilo, alquinilo y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alquenilo, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcoxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, alquinilo de 2 a 12 átomos de carbono opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados del grupo halógeno, amino, ciano, alquilo, hidroxilo, y alcoxi, arilo de 6, 10 o 14 átomos de carbono dicho arilo es opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados entre halógeno, nitro, ciano, alquenilo, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcoxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, N-(alquilo de 1 a 12 átomos de carbono)-arilo, dicho arilo es opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados entre halógeno, nitro, ciano, alquenilo, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcoxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, aralquilo de 7 a 16 átomos de carbono opcionalmente sustituido, aroilo de 7 a 13 átomos de carbono opcionalmente sustituidos, SR³, heteroarilo opcionalmente sustituido y heteroarilcarbonilo opcionalmente sustituido;

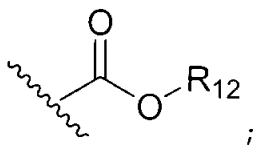
R₅ se selecciona de alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de halógeno, amino, ciano, cicloalquilo de 3 a 6 átomos de carbono, alquilo de 1 a 12 átomos de carbono, fenilo, hidroxilo, alcoxi de 1 a 12 átomos de carbono, N-alquilo de 1 a 12 átomos de carbono, N-cicloalquilo de 3 a 6 átomos de carbono, heterociclilo de 3 a 8 átomos en anillo, arilo de 6, 10 o 14 átomos de carbono, ariloxi y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo, ariloxi y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo, puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados entre halógeno, nitro, ciano, alquenoilo, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, aralquilo de 7 a 16 átomos de carbono opcionalmente sustituido, aroilo, -CH₂(CO)OCH₂arilo, dicho arilo es opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados entre halógeno, nitro, ciano, alquenoilo, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, ariloxi y fenilo, alquenoilo de 2 a 12 átomos de carbono opcionalmente sustituido, heteroarilo opcionalmente sustituido, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituido, alquinilo de 2 a 12 átomos de carbono opcionalmente sustituido, cicloalquilo de 3 a 6 átomos en anillo, aril-CH=CH-, cicloalquil-alquilo; y adamantilo;

R_6 se selecciona de hidrógeno, alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de halógeno, amino, ciano, cicloalquilo de 3 a 6 átomos de carbono, alquilo de 1 a 12 átomos de carbono, fenilo, hidroxilo, alcoxi de 1 a 12 átomos de carbono, N-alquilo de 1 a 12 átomos de carbono, N-cicloalquilo de 3 a 6 átomos de carbono, heterociclilo de 3 a 8 átomos en anillo, arilo, ariloxi y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo, ariloxi y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alquenilo, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, aril-C(O)-, $\text{CH}_3\text{-C(O)-NH-}$, aralquilo, ariloxi, heterociclilo y fenilo, y cicloalquilo de 3 a 6 átomos de carbono;

R_{10} es H o alquilo de 1 a 12 átomos de carbono;

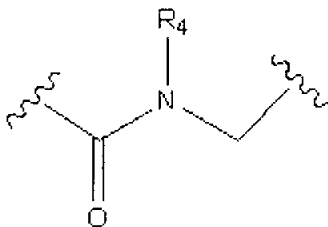
Q es $-\text{OR}_{11}$, Cl, Br o I;

R_{11} es H, bencilo opcionalmente sustituido con nitro o una parte de la fórmula

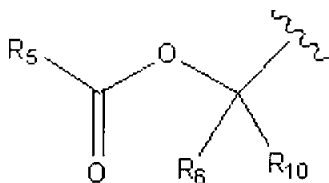


R₁₂ es alquilo de 1 a 6 átomos de carbono.

Los compuestos que tienen la Fórmula II son útiles como intermediarios químicos para hacer los compuestos que tienen Fórmula I y sus sales farmacéuticamente aceptables en donde A: es una parte



y R₃ es una parte



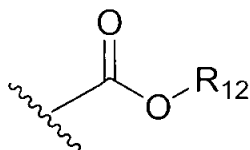
En donde R₄ y R₅ son como se definió anteriormente

Una modalidad de la invención suministra compuestos de la Fórmula II en donde R₄ es t-butilo, R₅ es alquilo de 1 a 6 átomos de carbono, y R₁₁ es bencilo opcionalmente sustituido con nitro.

Otra modalidad de la invención suministra compuestos de la Fórmula II en donde R₄ es alquilo de 1 a 6 átomos de carbono, R₅ es fenilo opcionalmente sustituido y R₁₁ es bencilo opcionalmente sustituido con nitro.

Una modalidad de la invención suministra compuestos de la Fórmula II en donde R_5 es alquilo de 1 a 6 átomos de carbono, R_4 es t-butilo y R_{11} es H.

Una modalidad adicional de la invención suministra compuestos de la Fórmula II en donde R_5 es alquilo de 1 a 6 átomos de carbono, R_4 es t-butilo, Q es $-OR_{11}$, R_{11} es



y R_{12} es alquilo de 1 a 6 átomos de carbono.

Otra modalidad de la invención suministra compuestos de la Fórmula II en donde R_6 y R_{10} son H.

Modalidades adicionales de la invención suministran los siguientes compuestos específicamente preferidos de la Fórmula II o sus sales farmacéuticamente aceptables.

4-Terc-butilbenzoato de ({[[2-(benciloxi)-2-oxoetil] (Terc-butil)amino]carbonil}oxi)metilo,

2,2-dimetilbutanoato de ({[[2-(benciloxi)-2-oxoetil] (Terc-butil)amino]carbonil}oxi)metilo,

2-metilpropanoato de ({[[2-(benciloxi)-2-oxoetil] (Terc-butil)amino]carbonil}oxi)metilo,

305

ciclopentanocarboxilato de ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl) amino] carbonil} oxi) metilo,

4-metilbenzoato de ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl) amino] carbonil} oxi) metilo,

heptanoato de ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl) amino] carbonil} oxi) metilo,

propionato de ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl) amino] carbonil} oxi) metilo,

ciclohexanocarboxilato de ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl) amino] carbonil} oxi) metilo,

3,5-dimetilbenzoato de ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl) amino] carbonil} oxi) metilo,

4-fluorobenzoato de ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl) amino] carbonil} oxi) metilo,

3-metilbutanoato ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl) amino] carbonil} oxi) metilo,

N-(Terc-butyl)-N-

({ [(ciclopentilacetil) oxi] metoxi} carbonil) glicinato de bencilo,

4-(trifluorometil)benzoato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo,

ciclopropanocarboxilato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo,

adamantan-1-carboxilato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo,

pentanoato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo,

ciclobutanocarboxilato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo,

({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo
3-ciclohexilpropanoato,

N-(Terc-butil)-N-([(4-fluorofenoxi) acetil] oxi} metoxi) carbonil] glicinato de bencilo,

N-(Terc-butil)-N-([(ciclohexilacetil) oxi] metoxi} carbonil) glicinato de bencilo,

2,6-dimetilbenzoato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo,

N-(Terc-butil)-N-([(fenilacetil) oxi] metoxi} carbonil) glicinato de bencilo,

pivalato de ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl)amino]carbonil}oxi)metilo

1-benzofuran-2-carboxilato de ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl)amino]carbonil}oxi)metilo,

1-metil-1H-pirrol-2-carboxilato de ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl)amino]carbonil}oxi)metilo,

1,1'-bifenil-4-carboxilato de
({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl)amino]carbonil}oxi)metilo,

4-metoxibenzoato de ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl)amino]carbonil}oxi)metilo,

1H-indol-2-carboxilato de ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl)amino]carbonil}oxi)metilo,

N-(Terc-butyl)-N-({ [(difenilacetil)oxi]metoxi}carbonil)glicinato
de bencilo,

1-naftoato de ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl)amino]carbonil}oxi)metilo,

2-naftoato ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl)amino]carbonil}oxi)metilo,

307

1-metil-1H-indol-3-carboxilato de ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl) amino] carbonil} oxi) metilo,

quinolin-2-carboxilato de ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl) amino] carbonil} oxi) metilo,

nicotinato de ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl) amino] carbonil} oxi) metilo,

isonicotinato de ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl) amino] carbonil} oxi) metilo,

2,6-difluorobenzoato de [2-(benciloxi)-2-oxoetil] (Terc-butyl) amino] carbonil} oxi) metilo,

2-fluorobenzoato de 2-(benciloxi)-2-oxoetil] (Terc-butyl) amino] carbonil} oxi) metilo,

2-(trifluorometil)benzoato de [2-(benciloxi)-2-oxoetil] (Terc-butyl) amino] carbonil} oxi) metilo,

4-(1H-pirrol-1-il)benzoato de [2-(benciloxi)-2-oxoetil] (Terc-butyl) amino] carbonil} oxi) metilo,

1,1'-bifenil-2-carboxilato de ({ [[2-(benciloxi)-2-oxoetil] (Terc-butyl) amino] carbonil} oxi) metilo,

2,4,6-trimetilbenzoato de [2-(benciloxi)-2-oxoetil] (Terc-butyl) amino] carbonil} oxi) metilo,

4-isopropoxibenzoato de [2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil}oxi) metilo,

3,4,5-trimetoxibenzoato de 2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil}oxi) metilo,

3,5-dimetoxibenzoato de 2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil}oxi) metilo,

Éster de (benciloxicarbonilmetil-Terc-butil-carbamoiloxi)-metilo de ácido 3-fenil-acrílico,

3-metil-1-benzofuran-2-carboxilato de ({[[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil}oxi) metilo,

N-{([3,5-bis(trifluorometil) fenil] acetil}oxi) metoxi] carbonil}-N-(Terc-butil) glicinato de bencilo,

4-(heptiloxi)benzoato de ({[[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil}oxi) metilo,

2-(2-feniletíl)benzoato de ({[[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil}oxi) metilo,

4-(dodeciloxi)benzoato de ({[[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil}oxi) metilo,

4-(acetilamino)benzoato de ({[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

antraceno-9-carboxilato de ({[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo y

4-benzoilbenzoato de ({[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo.

Modalidades adicionales de la invención son los siguientes compuestos específicamente preferidos de la Fórmula II o sus sales farmacéuticamente aceptables.

N-(Terc-butyl)-N-({[4-Terc-butylbenzoil]oxi]metoxi}carbonil)glicina,

N-(Terc-butyl)-N-({[isobutitrioxi]metoxi]carbonil}glicina,

N-(Terc-butyl)-N-({[ciclopentilcarbonil]oxi]metoxi]carbonil)glicina,

N-(Terc-butyl)-N-({[4-metilbenzoil]oxi]metoxi]carbonil)glicina,

N-(Terc-butyl)-N-({[heptanoiloxi]metoxi]carbonil}glicina,

N-(Terc-butyl)-N-({[propioniloxi]metoxi]carbonil}glicina,

N-(Terc-butyl)-N-({[ciclohexilcarbonil]oxi]metoxi]carbonil)glicina,

311

N- (Terc-butyl) -N- ({ [(3,5-
dimetilbenzoil)oxi]metoxi}carbonil)glicina,

N- (Terc-butyl) -N- ({ [(4-fluorobenzoil)oxi]metoxi}carbonil)glicina,

N- (Terc-butyl) -N- ({ [(3-metilbutanoil)oxi]metoxi}carbonil)glicina,

N- (Terc-butyl) -N-
({ [(ciclopentilacetil)oxi]metoxi}carbonil)glicina,

N- (Terc-butyl) -N- [({ [4-
(trifluorometil)benzoil]oxi}metoxi)carbonil]glicina,

N- (Terc-butyl) -N-
({ [(ciclopropilcarbonil)oxi]metoxi}carbonil)glicina,

N- ({ [(1-adamantilcarbonil)oxi]metoxi}carbonil) -N- (Terc-
butyl)glicina,

N- (Terc-butyl) -N- { [(pentanoiloxi)metoxi]carbonil}glicina,

N- (Terc-butyl) -N-
({ [(ciclobutilcarbonil)oxi]metoxi}carbonil)glicina,

N- (Terc-butyl) -N- ({ [(3-
ciclohexilpropanoil)oxi]metoxi}carbonil)glicina,

3/2

N-(Terc-butil)-N-([[(4-fluorofenoxi)acetil]oxi]metoxi)carbonil]glicina

N-(Terc-butil)-N-([[(ciclohexilacetil)oxi]metoxi]carbonil)glicina,

N-(Terc-butil)-N-([[(2,6-dimetilbenzoil)oxi]metoxi]carbonil)glicina,

N-(Terc-butil)-N-([[(fenilacetil)oxi]metoxi]carbonil)glicina,

N-(Terc-butil)-N-([[(2,2-dimetilpropanoil)oxi]metoxi]carbonil)glicina,

N-([[(1-benzofuran-2-ilcarbonil)oxi]metoxi]carbonil)-N-(Terc-butil)glicina,

N-(Terc-butil)-N-([[(1-metil-1H-pirrol-2-il)carbonil]oxi]metoxi)carbonil]glicina,

N-([[(1,1'-bifenil-4-ilcarbonil)oxi]metoxi]carbonil)-N-(Terc-butil)glicina,

N-(Terc-butil)-N-([[(4-metoxibenzoil)oxi]metoxi]carbonil)glicina,

N-(Terc-butil)-N-([[(1H-indol-2-ilcarbonil)oxi]metoxi]carbonil)glicina,

N-(Terc-butil)-N-([[(difenilacetil)oxi]metoxi]carbonil)glicina,

N-(Terc-butil)-N-{[(1-naftoiloxi)metoxi]carbonil}glicina,

N-(Terc-butil)-N-{[(2-naftoiloxi)metoxi]carbonil}glicina,

N-(Terc-butil)-N-[(1-metil-1H-indol-3-il)carbonil]oxi}metoxi)carbonil]glicina,

N-(Terc-butil)-N-{[(quinolin-2-ilcarbonil)oxi]metoxi}carbonil}glicina,

N-(Terc-butil)-N-{[(piridin-3-ilcarbonil)oxi]metoxi}carbonil}glicina,

N-(Terc-butil)-N-{[(isonicotinoiloxi)metoxi]carbonil}glicina,

N-(Terc-butil)-N-{[(2,6-difluorobenzoil)oxi]metoxi}carbonil}glicina,

N-(Terc-butil)-N-{[(2-fluorobenzoil)oxi]metoxi}carbonil}glicina,

N-(Terc-butil)-N-[(2-(trifluorometil)benzoil]oxi}metoxi)carbonil]glicina,

N-(Terc-butil)-N-{[(4-pirrolidin-1-ilbenzoil)oxi]metoxi}carbonil}glicina,

N-{[(1,1'-bifenil-2-ilcarbonil)oxi]metoxi}carbonil)-N-(Terc-butil)glicina,

N-(Terc-butyl)-N-([(mesitilcarbonil)oxi]metoxi)carbonil)glicina,

N-(Terc-butyl)-N-([(4-isopropoxibenzoil)oxi]metoxi)carbonil)glicina,

N-(Terc-butyl)-N-([(3,4,5-trimetoxibenzoil)oxi]metoxi)carbonil)glicina,

N-(Terc-butyl)-N-([(3,5-dimetoxibenzoil)oxi]metoxi)carbonil)glicina,

N-(Terc-butyl)-N-([((2E)-3-fenilprop-2-enoil)oxi]metoxi)carbonil)glicina,

N-(Terc-butyl)-N-([((3-metil-1-benzofuran-2-il)carbonil)oxi]metoxi)carbonil)glicina,

N-([((3,5-bis(trifluorometil)fenil)acetil)oxi]metoxi)carbonil)-
N-(Terc-butyl)glicina,

N-(Terc-butyl)-N-([(4-(heptiloxi)benzoil)oxi]metoxi)carbonil)glicina,

N-(Terc-butyl)-N-([(2-(2-feniletil)benzoil)oxi]metoxi)carbonil)glicina,

N-(Terc-butyl)-N-([(4-(dodeciloxi)benzoil)oxi]metoxi)carbonil)glicina,

3/6

N-([([4-(acetilamino)benzoil]oxi}metoxi)carbonil)-N-(Terc-butyl)glicina,

N-([([9-antrilcarbonil]oxi}metoxi}carbonil)-N-(Terc-butyl)glicina
y

N-([([4-benzoilbenzoil]oxi}metoxi}carbonil)-N-(Terc-butyl)glicina

Una modalidad adicional de la invención es el siguiente compuesto específicamente preferido de la Fórmula II o sus sales farmacéuticamente aceptables.

Éster de [Terc-butyl-(2-isobutoxicarboniloxi-2-oxo-etil)-carbamoiloxi)-metilo de ácido 3,3-Dimetil-butírico.

DEFINICIONES

Para los compuestos de la invención definidos anteriormente y referidos aquí amoenos que se especifique otra cosa los siguientes términos son definidos:

El término alquilo significa una porción alquilo lineal o ramificada de 1 a 12 átomos de carbono opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de halógeno, amino, ciano, cicloalquilo de 3 a 6 átomos de carbono, alquilo de 1 a 12 átomos de carbono, fenilo, hidroxilo, alcoxi de 1 a 12 átomos de carbono, N-alquilo de 1 a 12 átomos de carbono, N-cicloalquilo de 3 a 6 átomos de carbono, heterociclilo

de 3 a 8 átomos en anillo, arilo, ariloxi y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo, ariloxi y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alquenilo, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcoxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo. En algunas modalidades de la invención 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 de la invención alquilo es 1,1-dimetiletilo también llamado t-butilo. En algunas modalidades de la invención cuando el alquilo es un grupo metilo en donde la sustitución opcional es dos anillos fenilo independientes. Ejemplos no limitativos de alquilo son metilo, etilo, n-propilo, 1-metiletilo, n-butilo, 1-metilpropilo, 2-metilpropilo y 1,1- dimetiletil.

El término alquenilo significa una cadena de carbono lineal o ramificada de 2 a 12 átomos de carbono tiene por lo menos un sitio de insaturación opcionalmente sustituido independientemente con 1 a 3 sustituyentes seleccionados del grupo opcionalmente sustituido independientemente con 1 a 3 sustituyentes seleccionados entre el grupo fenilo, heteroarilo, halógeno, amino, ciano, alquilo, hidroxilo, alcoxi, arilo, alquinilo y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano,

alquenilo, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcoxycarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo. En algunas modalidades de la invención alquenilo es una porción vinilo de -CH₂=CH-.

Como se usa aquí el término alcoxi se refiere a alquil-O- en donde alquilo es como se definió anteriormente. Ejemplos no limitativos incluyen: metoxi y etoxi.

Como se usa aquí el término arilo significa una porción aromática que tiene 6, 10 o 14 átomos de carbono preferiblemente 6 a 10 átomos de carbono, opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alquenilo, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcoxycarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo. En particular, arilo es fenilo o naftilo opcionalmente sustituido con 1 a 3 sustituyentes.

El término aralquilo como se usa aquí de 7 a 16 átomos de carbono significa un alquilo sustituido con un grupo arilo en el cual el grupo arilo y alquilo son como se definieron anteriormente. Ejemplos no limitativos de los grupos aralquilo incluyen bencilo y fenetilo y similares.

Perhaloalquilo como se usa aquí significa una porción alquilo de 1 a 6 átomos de carbono en el cual cada átomo de

hidrógeno se sustituye con un átomo de halógeno, un ejemplo ilustrativo es trifluorometilo.

Fenilo como se usa aquí se refiere a un anillo aromático de carbono de 6 miembros.

Como se usa aquí el término alquinilo incluye ambas cadenas lineales y porciones ramificadas que contienen 2 a 12 átomos de carbono que tienen por lo menos un enlace triple de carbono a carbono opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados del grupo entre halógeno, amino, ciano, alquilo de 1 a 12 átomos de carbono, hidroxilo, y alcoxi de 1 a 12 átomos de carbono.

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

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

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

El término heteroarilo significa un anillo aromático monocíclico, heterocíclico de 5 a 6 átomos en anillo que contienen 1 a 4 heteroátomos independientemente seleccionados de O, N y S o anillos aromáticos bicíclicos de 8 a 20 átomos en anillo que contiene 1 a 4 heteroátomos independientemente seleccionados de O, N y S. Anillos heteroarilo pueden ser opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo alquilo, halógeno, ciano, nitro, hidroxilo, amino, alquilamino, dialquilamino, alcoxi, ariloxi, $-\text{CH}_2\text{OCOCH}_3$ y carboxi. Non-limiting heteroarilo moieties opcionalmente sustituido incluye: furanilo, benzofuranilo, benzotienilo, tienilo, piridinilo, quinolinilo, tetrazolilo, imidazol, tiazolilo y similares.

En donde los términos se utilizan en combinación, la definición para cada parte individual de la combinación se aplica a menos que se defina de otra manera. Por ejemplo, aralquilo se refiere a un grupo arilo, y alquilo se refiere al grupo alquilo como se definió anteriormente. También, ariloxi se refiere a un grupo aril-.

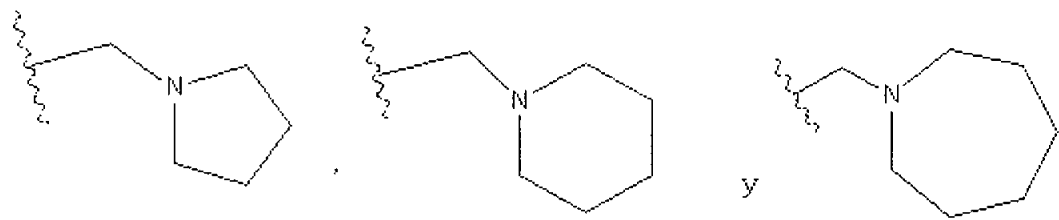
El término heteroarilcarbonilo significa un grupo heteroaril-C(O)- en el cual el grupo heteroarilo es como se definió previamente.

El término heterociclilo como se usa aquí representa un anillo saturado de 3 a 8 átomos en anillo que contiene 1 a 3 heteroátomos seleccionados de nitrógeno, oxígeno y azufre. En algunas modalidades de la invención se prefiere un anillo

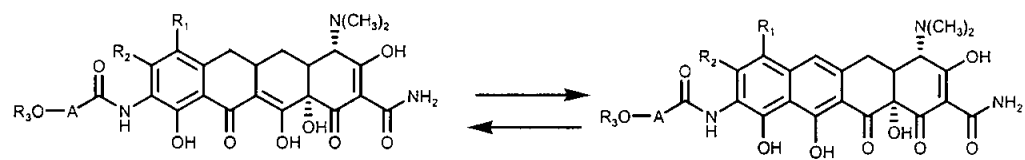
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saturado de 5 o 6 átomos en anillo. Ejemplos representativos son pirrolidilo, piperidilo, piperazinilo, morfolinilo, tiomorfolinilo, aziridinilo, tetrahidrofuranilo y similares.

El término alquilheterociclilo significa un grupo alquilheterociclilo en en cual el grupo alquilo y heterociclilo son independientemente como se definió antes. Ejemplos no limitativos de grupos alquilheterociclilo incluyen porciones de las fórmulas:



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



La presente invención de acuerdo a lo anterior suministra una composición farmacéutica que comprende un compuesto de esta invención en combinación o asociación con un vehículo farmacéuticamente aceptable. En particular, la presente invención

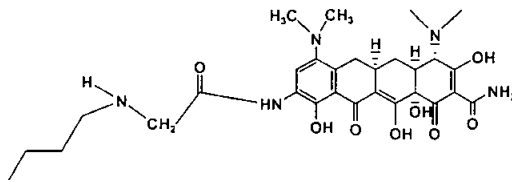
suministra una composición farmacéutica que comprende una cantidad efectiva de un compuesto de esta invención y un vehículo farmacéuticamente aceptable.

Esponja de protón es [1,8-bis(dimetilamino)naftaleno,N,N',N'-tetrametil-1,8-naftalenodiamina].

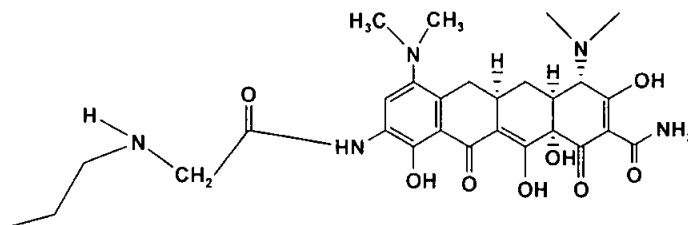
El carbonato de metal álcali incluye lito, potasio y carbonato de sodio.

DMPU es 1,3-dimetil-3,4,5,6-tetrahidro-2(1H)-pirimidinona.

N-butil-glicilciclina (N-bu-glicil) es



N-propil-glicilciclina (N-prop-glicil) es



DESCRIPCIÓN DE LAS MODALIDADES PREFERIDAS

Los compuestos de esta invención pueden ser preparados de acuerdo con los siguientes esquemas: (1) a partir de materiales

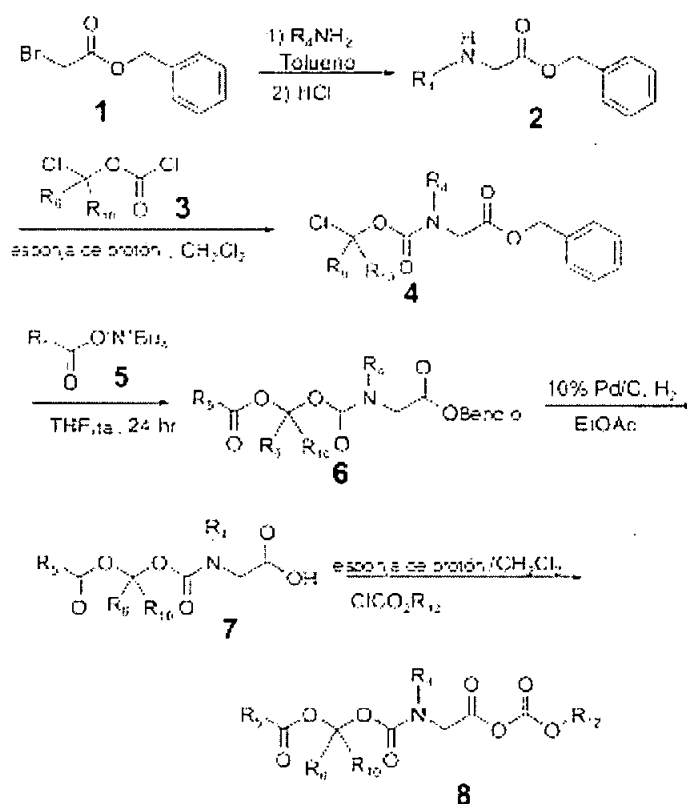
de partida comercialmente disponibles o: (2) de materiales de partida conocidos que pueden ser preparados según se describió en los procedimientos de la literatura o: (3) de nuevos intermedios descritos en los esquemas y en procedimientos experimentales.

La síntesis del intermedio aciloxi 8 es mostrada en el esquema 1. La reacción de la amina R_4NH_2 , preferiblemente t-butilamina con el éster 1 suministra el amino éster sustituido 2. La preparación del intermedio 4 se lleva acabo utilizando la esponja de protón como base para efectuar la acilación del amino éster 2 sustituido con cloroformato de clorometilo 3. El tratamiento de intermedio 4 con la sal de tetrabutilamonio 5 de ácidos carboxílicos da el bencilo protegido por el intermedio aciloxi 6. El grupo de protección de bencilo es removido por remoción catalítica para dar ácido carboxílico 7 el cual es activado a un anhídrido mezclado con cloroformato $ClCO_2R_{12}$ en donde R_{12} es alquilo de 1 a 6 átomos de carbono, por ejemplo, cloroformato de iso-butilo para dar el intermedio de aciloxi carbamato 8. En una ruta alterna, ésteres de sililo pueden ser opcionalmente utilizados en lugar del éster de bencilo del intermedio 4, tratar con el ácido carboxílico apropiado seguido por el desbloqueo del éster de sililo con cloruro de tetrabutilamnio o bromuro de magnesio para proporcionar ácido carboxílico 7. Opcionalmente, al ácido carboxílico 7 puede ser activado por medio del uso de agentes de acoplamiento no limitados a bicarbonato de di-t-butilo (Boc_2O); por ejemplo, benzotriazol-1-il-oxi-tris-(dimetilamino)-hexafluorofosfato de fosfonio (también conocido como asBop); hexafluorofosfato de

324

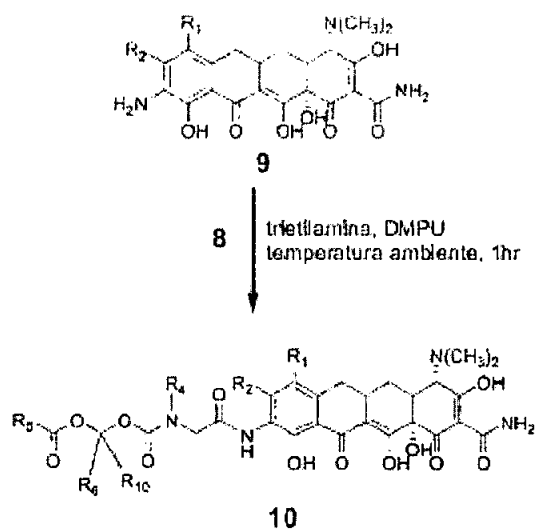
benzotriazol-1-il-oxi-tris-pirrolidino-fosfono (también conocido como PyBop); O-benzotriazol-N,N,N',N'-tetrametil-uronio-hexafluoro-fosfato (HBTU); hexafluorofosfato de Bromotris-pirrolidino-fosfonio; yoduro de 2-Cloro-N-metilpiridinio (CMPI); diciclohexilcarbodiimida (DCC); 1,3-diisopropilcarbodiimida (DIC); clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (EDC); o Carbonil diimidazol.

ESQUEMA 1



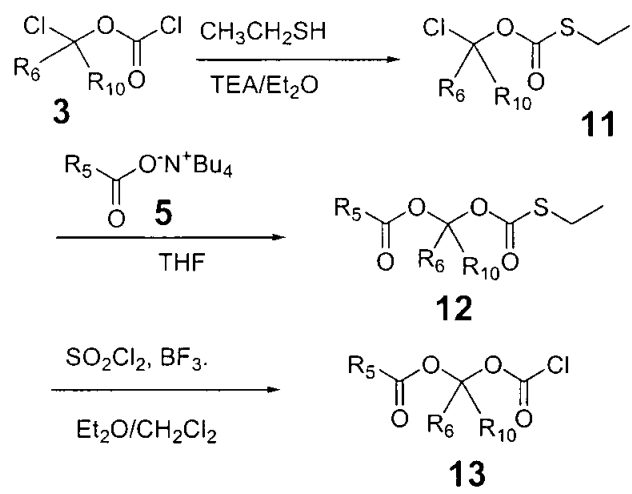
como se muestra en el esquema 2, la reacción del intermedio de aciloxicarbamato activado 8 con 7,8-disustituido-9-aminotetraciclina 9 en la presencia de trietilamina y DMPU da aciloxicarbamato 10.

Esquema 2



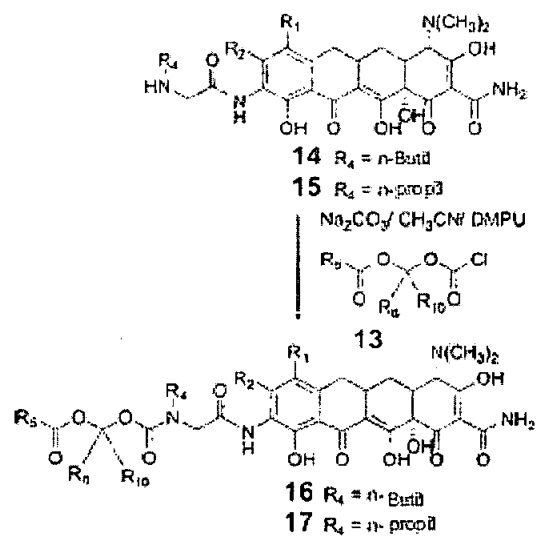
Compuestos de carbamato de aciloxi adicionales pueden ser sintetizados por vías que se muestran en los Esquemas 3 y 4. El tratamiento de cloroformato de clorometilo 3 con etanotiol en la presencia de trietilamina (TEA) da carbonotioato 11. El compuesto 12 se prepara haciendo reaccionar carbonotioato 11 con sal de tetrabutylamnio de ácido carboxílico 5 en tetrahidrofurano. La clorinación del compuesto 12 con cloruro de sulfurilo en la presencia de cantidad catalítica de trifluoroeterato de boro proporciona un intermedio de 13 (utilizando los métodos descritos en M. Folkmann y F.J. Lund, *Synthesis*, Diciembre 1990, 1159-1166).

Esquema 3



Como se ve adicionalmente en el Esquema 4 los aciloxicarbamatos 16 y 17 en donde R_4 es preferiblemente n-butilo o n-propilo son sintetizados por medio del tratamiento de 14 o 15 en donde R_4 es preferiblemente n-butilo o n-propilo con el intermedio de cloro 13 para dar aciloxicarbamatos 16 y 17 respectivamente.

Esquema. 4

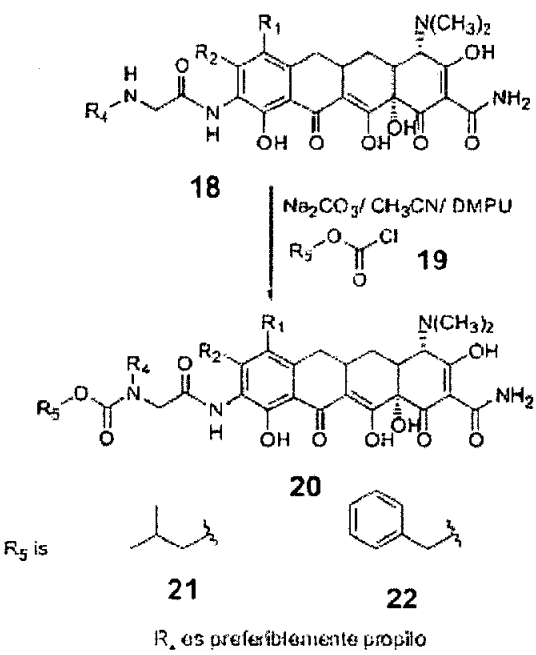


Como se muestra en el esquema 5, los carbamatos de glicilciclina en donde R_4 es preferiblemente propilo 18 pueden

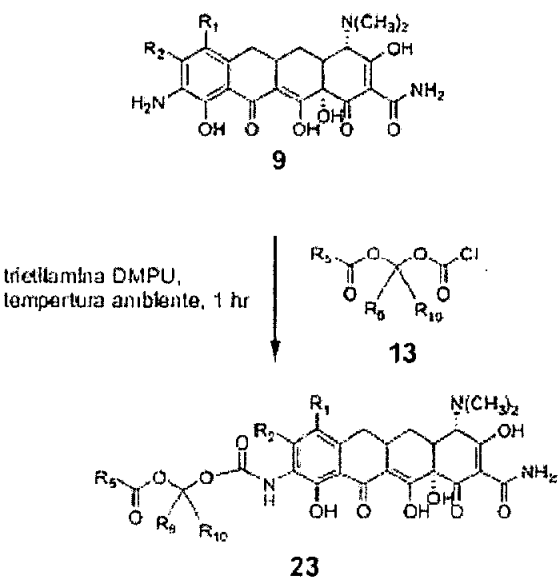
327

también ser preparados por medio de la reacción con el intermedio de cloro 19 en la presencia de un carbonato de metal álcali preferiblemente carbonato de sodio, y DMPU en acetonitrilo para proporcionar los compuestos preferidos (21 y 22).

Esquema 5



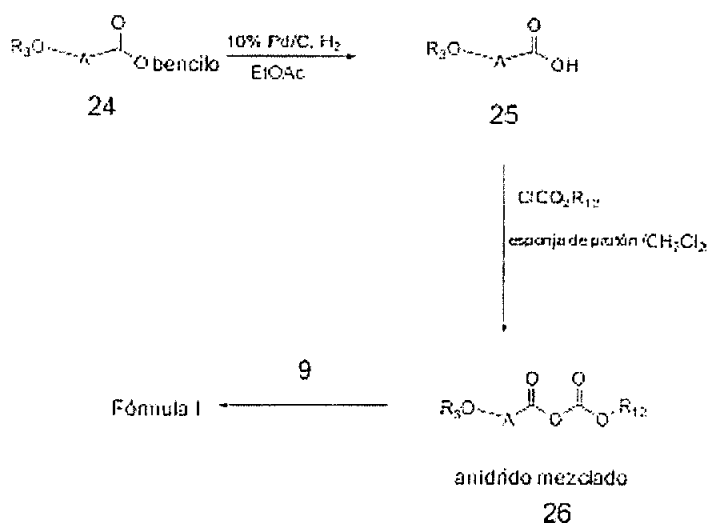
Esquema 6



Como se muestra en el esquema 6, la reacción del intermedio de cloro 13 con 7,8-disustituido-9-aminotetraciclina 9 en la presencia de trietilamina y DMPU da carbamato 23.

Como se muestra adicionalmente en el Esquema 7, los compuestos de la Fórmula I pueden ser en general preparados por medio de remover el grupo de protección de bencilo del intermedio aciloxi protegido por bencilo 24 para dar ácido carboxílico 25 el cual es activado a un anhídrido mezclado con un cloroformato $\text{ClCO}_2\text{R}_{12}$ en donde R_{12} es alquilo de 1 a 6 átomos de carbono, por ejemplo cloroformato de iso-butilo para dar el intermedio aciloxicarbamato 26. Reacción adicional de 7,8-disustituido-9-aminotetraciclina 9 con aciloxicarbamato mezclado con el intermedio anhídrido 26 en la presencia de trietilamina y DMPU proporciona compuestos de la Fórmula (I).

Esquema 7



Las reacciones se llevan a cabo en un disolvente apropiado a los reactivos y materiales empleados y adecuados para que la transformación se lleve acabo. Se entiende por aquellos versados en la técnica de síntesis orgánica que las diversas

funcionalidades presentes en la molécula deben ser consistentes con las transformaciones químicas propuestas. Esto puede requerir el fusionamiento para ordenar las etapas sintéticas, los grupos de protección y si se requiere, las condiciones de desprotección. Los sustituyentes sobre los materiales de partida pueden ser incompatibles con algunas de las condiciones de la reacción. Tales restricciones a los sustituyentes que son compatibles con las condiciones de reacción serán evidentes para aquellos versados en la técnica.

Algunos de los compuestos de los esquemas descritos aquí anteriormente tienen centros de asimetría. Los compuestos, pueden, por lo tanto, existir en por lo menos dos frecuentemente más formas estereoisoméricas. La presente invención involucra todos los estereoisómeros de los compuestos sean libres de otros estereoisómeros o mezclados con otros estereoisómeros en cualquier proporción y por lo tanto incluye, por ejemplo, mezcla racémica de enantiómeros lo mismo que la mezcla diastereomérica de isómeros. La configuración absoluta de cualquier compuesto puede ser determinada por cristalografía de rayos X convencional.

Los compuestos de la invención pueden ser obtenidos como complejos de metal tales como aluminio, calcio, hierro, magnesio, manganeso y sales complejas; sales inorgánicas y orgánicas y aductos de base Mannich correspondientes utilizando métodos conocidos por aquellos versados en la técnica (Richard C. Larock, Comprehensive Organic Transformations, VCH Publishers, 411-415, 1989). Preferiblemente, los compuestos de la invención son obtenidos como sales inorgánicas tales como sales hidrclóricas,

hidrobrómicas, hidroyódicas, fosfóricas, nítricas o de sulfato; o sales orgánicas tales como acetato, benzoato, citrato, cisteína u otros aminoácidos fumarato, glicolato, maleato, succinato, tartrato alquilsulfonato o arilsulfonato. En todos los casos, la formación de sales ocurre con el grupo C(4)-dimetilamino. Las sales son preferidas para la administración oral y parenteral.

Procedimientos de Ensayo Farmacológico Estándar

Métodos para la evaluación antibacterial in vitro.

Concentración inhibitoria mínima (MIC)

Ensayo de susceptibilidad antimicrobiana. Las actividades in vitro de los antibióticos son determinados por el método de microdilución en caldo según se recomendó por el Comité Nacional de Estándares de Laboratorio (NCCLS) (1). El caldo Mueller-Hinton II (MHBII) (BBL Cockeysville, MD) es el medio empleado en los procedimientos de ensayo. Las placas microtítulo que contienen las diluciones seriales de cada agente antimicrobiano son inoculadas con cada organismo para proporcionar la densidad apropiada (10^5 CFU/ml) en un volumen final de 100 μ l. las placas son incubadas durante 18 a 22 horas a 75° C en aire ambiente. La concentración inhibitoria mínima para todos los aislados es definida como la concentración menor de agente antimicrobiano que inhibe completamente el crecimiento del organismo según se detectó por el ojo sin ayuda.

1. Métodos para los Ensayos de Susceptibilidad de Dilución Antimicrobiana para Bacterias que Crecen Aeróbicamente; Estándares Aprobados M7-A5, Vol. 20. Comité Nacional para Estándares de Laboratorio Clínico, Wayne, PA.

Procedimientos de Ensayo Farmacológico Estándar

Se presentan en las Tablas I a XIII compuestos representativos de Fórmula I los cuales fueron evaluados contra un panel de 40 cepas de bacterias Gram-positivo y Gram-negativo por preincubación en agua, suero de ratón o suero humano. Los compuestos representativos fueron primeramente incubados en suero de ratón durante 1 hora antes al ensayo in vitro contra un panel de cepas de bacteria seleccionadas Gram-positivo y Gram-negativo. Todos los compuestos fueron también preincubados en agua durante 1 hora antes de los ensayos como controles. Los compuestos representativos de Fórmula I fueron incubados en suero humano antes de la determinación del MIC. Los compuestos representativos de la Fórmula I que demostraron una actividad in vivo fueron adicionalmente sometidos a diversos ensayos de estabilidad. Un resumen de los datos de ensayo in vitro en ejemplos representativos de la Fórmula I se muestran en la Tabla 1. Los datos expandidos in vitro de ejemplos seleccionados (87 y 27) se muestran en las Tablas 2 y 5 respectivamente. Los MIC de los ejemplos representativos de Fórmula I se dan en las Tablas III y IV. La Tabla VI presente la actividad in vitro e in vivo de ejemplos representativos de los compuestos de Fórmula I contra el *Staphylococcus aureus* Smith en ratones. La tabla 7 presenta la actividad in vivo (oral, iv) e in vitro (MIC) de ejemplos

representativos de compuestos de Fórmula I contra el E. coli en ratones. La Tabla 8 presenta la actividad in vivo (oral, iv) e in vitro (MIC) de ejemplos representativos de compuestos de Fórmula I, contra el Staphylococcus aureus Smith en ratones. La Tabla 9 presenta la actividad in vitro (MIC) de ejemplos representativos de los compuestos de Fórmula I contra el E. Coli en suero humano y agua y también contra el Staphylococcus en suero humano y agua.

La Tabla 10 presenta una dosis oral única in vivo (SOD) y dosis intravenosa única (SIV) y sus datos ED₅₀ para los ejemplos representativos de compuestos de Fórmula I contra el Staphylococcus. Smith y el E. Coli #311 en mamíferos.

TABLA I

ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE
FÓRMULA I
CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

	Suero de		Suero de		Suero de		Suero de		Suero de	
	ratón		ratón		ratón		ratón		ratón	
	Ejemplo	Agua	Ejemplo	Agua	Ejemplo	Agua	Ejemplo	Agua	Ejemplo	Agua
1	1	2	2	3	3	3	3	3	4	Ejemplo 4
E. coli GC 2236	1	16	4	32	1	>64	1	>64	1	64
E. coli GC 2231	1	64	4	64	2	>64	2	>64	1	64
E. coli GC 2235	0.50	16	2	64	1	>64	1	>64	1	64
E. coli GC 2232	0.50	16	2	64	2	>64	2	>64	1	64
E. coli GC 2233	1	16	1	64	1	>64	1	>64	1	64
E. coli GC 2234	0.50	16	1	64	1	>64	1	>64	1	64
E. coli GC 2270	0.50	16	1	64	1	>64	1	>64	1	64
E. coli GC 2271	0.50	16	1	64	1	>64	1	>64	0.50	64
E. coli GC 2272	1	16	1	64	1	>64	1	>64	1	64
E. coli GC 4559	1	32	1	64	2	>64	2	>64	2	>64
E. coli GC 4560	0.50	2	0.25	4	0.50	32	0.25	8	0.25	8
E. coli GC 6465	8	>64	8	64	8	>64	8	>64	4	>64
E. coli GC 3226	1	32	4	64	2	>64	2	>64	2	64
E. coli GC 2203	0.50	16	2	64	1	>64	1	>64	1	64
E. coli GC 1073	1	32	4	64	2	>64	2	>64	1	>64
Salmonella spp. GC 235	1	64	8	>64	2	>64	2	>64	2	>64

TABLA I (Cont)
 ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE
 FÓRMULA I
 CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

	Suero de ratón	Suero de		Suero de		Suero de		Suero de		Suero de		Agua Ejemplo
		Agua Ejemplo	ratón Ejemplo	Agua Ejemplo	ratón Ejemplo	Agua Ejemplo	ratón Ejemplo	Agua Ejemplo	ratón Ejemplo	Agua Ejemplo	ratón Ejemplo	
	1	1	2	2	3	3	4	3	4	4	4	
Salmonella spp. GC												
566	2	64	8	>64	4	>64	4	>64	4	>64	>64	
S. cholerasius GC												
1355	8	>64	>64	>64	16	>64	8	>64	8	>64	>64	
S. typhimurium GC												
2172	4	>64	>64	>64	8	>64	4	>64	4	>64	>64	
P. aeruginosa GC												
2214	32	>64	>64	>64	32	>64	32	>64	32	>64	>64	
S. aureus GC 1131	1	4	2	4	2	4	1	4	1	4	4	
S. aureus GC 6466	1	1	1	2	1	4	0.50	2	0.50	2	2	
S. aureus GC 6467	4	4	4	8	4	32	2	32	2	8	8	
S. aureus GC 1079	2	4	8	8	2	32	1	4	1	4	4	
S. aureus GC 4536	2	4	2	4	2	4	1	4	0.50	4	4	
S. aureus GC 2216	1	4	2	4	1	4	1	8	1	4	4	
S. aureus GC 6335	2	4	8	8	2	8	2	8	2	4	4	
S. aureus GC 6469	2	8	2	4	4	32	2	32	2	16	16	

TABLA I (Cont)
 ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA I
 CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

	Suero de		Suero de		Suero de		Suero de		Suero de	
	ratón	Agua	ratón	Agua	ratón	Agua	ratón	Agua	ratón	Agua
	Ejemplo 1	Ejemplo 1	Ejemplo 2	Ejemplo 2	Ejemplo 3	Ejemplo 3	Ejemplo 3	Ejemplo 3	Ejemplo 4	Ejemplo 4
S. epidermidis GC 4935	2	8	8	8	4	8	2	4	2	4
E. faecalis GC 4555	1	4	2	4	1	8	1	8	1	8
E. faecalis GC 2265	1	4	4	8	2	32	2	8	2	8
E. faecalis GC 2267	2	8	4	4	2	32	1	8	1	8
E. faecalis GC 2242	1	4	4	4	2	16	1	4	1	4
E. faecium GC 4556	1	4	4	8	2	16	1	4	1	4
E. faecium GC 2243	1	2	1	4	1	4	0.50	2	0.50	2
S. pneumoniae* GC 4465	0.50	0.25	0.50	0.25	0.12	0.25	<0.06	0.12	0.12	0.12
S. pneumoniae+ GC 4465	2	2	2	4	1	2	2	4	2	4
S. pyogenes GC 4563	0.25	0.50	0.25	0.25	0.12	0.25	0.12	0.25	0.12	0.25
S. agalactiae GC 4564	0.50	1	2	2	1	2	0.25	0.50	0.25	0.50
C. albicans GC 3066	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64

TABLA II
 ACTIVIDAD ANTIBACTERIAL DE DERIVADOS DE GLICILCICLINAS SUSTITUIDOS CON 9-AMINOCARBONILO DE FÓRMULA I
 CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

	Suero de		Suero de		Suero de		Suero de	
	ratón		ratón		ratón		ratón	
	Ejemplo 5	Agua Ejemplo 5	Ejemplo 6	Agua Ejemplo 6	Ejemplo 7	Agua Ejemplo 7	Ejemplo 8	Agua Ejemplo 8
E. coli GC 2236	2	16	2	8	0.25	2	1	
E. coli GC 2231	2	64	2	64	2	16	2	
E. coli GC 2235	1	16	1	8	0.50	4	1	
E. coli GC 2232	2	32	2	32	0.50	4	1	
E. coli GC 2233	2	32	2	16	0.50	4	1	
E. coli GC 2234	1	32	1	16	1	4	1	
E. coli GC 2270	1	16	1	8	0.50	4	1	
E. coli GC 2271	1	16	1	8	0.50	4	1	
E. coli GC 2272	1	32	1	16	0.50	4	1	
E. coli GC 4559	2	32	2	16	1	8	1	
E. coli GC 4560	0.50	4	0.25	2	0.25	0.50	0.50	
E. coli GC 6465	8	>64	4	>64	16	>64	8	
E. coli GC 3226	2	32	2	16	0.50	8	2	
E. coli GC 2203	1	32	2	16	0.50	4	1	
E. coli GC 1073	2	32	2	16	0.50	8	1	
Salmonella spp. GC 235	2	32	2	16	2	8	4	
Salmonella spp. GC 566	4	64	4	64	1	16	4	

TABLA II (Cont)
 ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE
 FÓRMULA I
 CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

	Suero de			Suero de			Suero de			Suero de			Agua Ejemplo
	ratón Ejemplo	Agua Ejempl	o 5	ratón Ejempl	o 6	Agua Ejempl	ratón Ejempl	o 7	Agua Ejempl	ratón Ejempl	o 8	Agua Ejemplo	
S. cholerasius													
GC 1355	16	>64		16		>64	16		>64	32		>64	
S. typhimurium													
GC 2172	8	>64		8		>64	4		>64	8		>64	
P. aeruginosa GC													
2214	32	>64		32		>64	16		>64	32		>64	
S. aureus GC													
1131	0.50	1		0.50		1	1		1	1		2	
S. aureus GC													
6466	0.25	0.50		0.25		1	0.50		0.50	0.50		1	
S. aureus GC													
6467	2	4		2		4	4		4	4		8	
S. aureus GC													
1079	2	2		2		4	1		4	2		4	
S. aureus GC													
4536	1	1		0.50		2	1		1	0.50		2	
S. aureus GC													
2216	0.50	2		0.50		2	0.50		0.50	0.50		4	
S. aureus GC													
6335	0.50	1		0.50		2	1		1	1		4	

TABLA II (Cont)
 ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA I

CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)												
		Suero de			Suero de			Suero de				
		ratón	Agua	ratón	Agua	ratón	Agua	ratón	Agua			
		Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	
		5	5	6	6	7	7	7	7	8	8	
E. faecalis	GC	1	4	1	4	0.50	1	0.50	1	0.50	8	
E. faecalis	GC	2	4	2	4	1	2	2	2	2	8	
E. faecalis	GC	2	4	1	4	1	2	2	2	2	8	
E. faecalis	GC	1	2	1	2	1	1	1	1	1	4	
E. faecium	GC	1	2	1	2	0.50	1	0.50	1	1	4	
E. faecium	GC	0.50	1	0.50	2	0.25	0.12	0.25	0.12	0.25	2	
S. pneumoniae*		<0.06	0.12	0.12	0.25	0.25	0.25	0.25	0.12	<0.06	0.25	
GC 4465		2	4	2	2	4	2	4	2	1	4	
S. pneumoniae+		0.12	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.12	0.50	
GC 4465												
S. pyogenes	GC											
4563												
S. agalactiae	GC											
4564												
c. albicans	GC											
3066		>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	

337

TABLA III

ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA I

CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

	Suero de			Suero de			Suero de		
	ratón			ratón			ratón		
	Ejemplo	Agua	Suero de	Ejemplo	Agua	Suero de	Ejemplo	Agua	Agua
	9	9	10	10	o 10	11	11	11	12
E. coli GC 2236	1	8	0.50	8	0.50	8	1	16	16
E. coli GC 2231	2	64	2	32	2	64	2	64	64
E. coli GC 2235	0.50	4	0.25	4	0.25	4	1	16	16
E. coli GC 2232	1	8	0.50	8	1	16	0.50	32	32
E. coli GC 2233	0.50	4	0.50	8	0.25	8	1	32	32
E. coli GC 2234	0.50	8	0.50	8	0.50	16	1	16	16
E. coli GC 2270	0.50	4	0.50	8	0.50	8	0.50	32	32
E. coli GC 2271	0.50	8	0.25	8	0.25	4	0.50	16	16
E. coli GC 2272	0.50	8	0.50	8	0.25	4	1	16	16
E. coli GC 4559	1	8	0.50	16	0.50	32	1	64	64
E. coli GC 4560	0.25	1	0.12	0.12	0.12	0.12	0.25	1	1
E. coli GC 6465	4	>64	8	>64	8	>64	8	>64	>64
E. coli GC 3226	2	16	0.50	16	0.50	>64	2	64	64
E. coli GC 2203	0.50	4	0.50	8	0.25	16	1	32	32
E. coli GC 1073	1	8	0.50	16	0.50	16	1	64	64
Salmonella spp. GC 235	1	8	0.50	32	0.50	64	1	64	64
Salmonella spp. GC 566	2	64	2	>64	2	>64	4	>64	>64
S. cholerasius GC 1355	64	>64	16	>64	32	>64	16	>64	>64

TABLA III (Cont)

ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE
FÓRMULA I
CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

		Suero de ratón		Suero de ratón		Suero de ratón		Suero de ratón		Suero de ratón		Suero de ratón	
		Ejemplo	Agua	Ejemplo	Agua	Ejemplo	Agua	Ejemplo	Agua	Ejemplo	Agua	Ejemplo	Agua
		9	9	10	10	11	11	12	12	13	13	14	14
S. typhimurium	GC	8	>64	4	>64	4	>64	4	>64	4	>64	4	>64
2172													
P. aeruginosa	GC 2214	16	>64	16	>64	16	>64	16	>64	16	>64	16	>64
S. aureus	GC 1131	<0.06	0.25	0.12	0.12	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
S. aureus	GC 6466	0.12	0.12	0.12	0.12	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
S. aureus	GC 6467	1	2	2	2	4	4	4	4	4	4	4	4
S. aureus	GC 1079	2	1	0.50	1	2	4	2	4	2	4	2	4
S. aureus	GC 4536	0.50	0.50	0.25	0.50	0.25	0.50	0.50	0.50	0.50	0.50	0.50	0.50
S. aureus	GC 2216	0.25	0.50	0.25	0.50	0.25	0.50	0.50	0.50	0.50	0.50	0.50	0.50
S. aureus	GC 6335	0.25	0.50	0.25	0.50	0.25	0.50	1	1	1	1	1	1
S. aureus	GC 6469	1	2	1	2	4	4	4	4	4	4	4	4
S. epidermidis	GC												
4935		0.25	1	0.50	1	1	1	1	1	1	1	1	1
E. faecalis	GC 4555	0.50	2	0.50	1	0.50	1	0.50	1	0.50	1	0.50	1

TABLA III (Cont)
 ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE
 FÓRMULA I
 CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

		Suero de				Suero de				Suero de			
		ratón	Agua	ratón	Agua	ratón	Agua	ratón	Agua	ratón	Agua	ratón	Agua
		Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo
		9	9	10	10	11	11	11	11	12	12	12	12
E. faecalis	GC	1	2	1	1	2	4	2	8				
E. faecalis	GC	1	2	1	2	2	2	2	8				
E. faecalis	GC	0.50	1	0.25	0.50	0.25	0.50	2	4				
E. faecium	GC	0.25	0.50	0.25	0.50	0.25	0.50	1	4				
E. faecium	GC	0.25	0.50	<0.06	0.12	0.12	0.25	0.50	4				
S. pneumoniae*	GC	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	0.12				
S. pneumoniae+	GC	2	2	1	1	2	2	4	8				
S. pyogenes	GC	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	0.12	0.25				
S. agalactiae	GC	0.12	0.25	<0.06	0.12	<0.06	<0.06	0.25	0.25				
C. albicans	GC	>64	>64	>64	>64	>64	>64	>64	>64				

TABLA IV
 ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA I
 CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

	Suero de ratón	Agua Ejemplo	Suero ratón	de Agua Ejemplo	Suero ratón	de Agua Ejemplo	Suero de ratón	de Agua
	Ejemplo 13	13	Ejemplo 14	14	Ejemplo 15	15	Ejemplo 16	Ejemplo 16
E. coli GC 2236	2	8	>64	>64	>64	64	>64	>64
E. coli GC 2231	2	16	>64	>64	>64	>64	>64	>64
E. coli GC 2235	2	8	32	64	32	16	64	64
E. coli GC 2232	2	8	>64	>64	>64	>64	>64	>64
E. coli GC 2233	2	8	>64	>64	>64	>64	>64	>64
E. coli GC 2234	1	8	>64	>64	>64	>64	>64	>64
E. coli GC 2270	1	8	>64	>64	64	>64	>64	>64
E. coli GC 2271	2	8	>64	>64	64	>64	>64	>64
E. coli GC 2272	2	8	>64	>64	>64	>64	>64	>64
E. coli GC 4559	4	16	>64	>64	>64	>64	>64	>64
E. coli GC 4560	1	4	4	4	1	2	4	4
E. coli GC 6465	8	>64	>64	>64	>64	>64	>64	>64
E. coli GC 3226	2	16	>64	>64	>64	64	>64	>64
E. coli GC 2203	2	8	32	64	32	16	64	64
E. coli GC 1073	2	16	>64	>64	>64	>64	>64	>64
Salmonella spp.								
GC 235	2	16	>64	>64	>64	>64	>64	>64

TABLA IV (Cont)

	Suero de		Suero de		Suero de		Suero de		Suero de	
	ratón	Agua	ratón	Agua	ratón	Agua	ratón	Agua	ratón	Agua
	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo
	13	13	14	14	15	15	16	16	16	16
Salmonella spp. GC										
566	8	64	>64	>64	>64	>64	>64	>64	>64	>64
S. cholerasius GC										
1355	16	>64	>64	>64	>64	>64	>64	>64	>64	>64

TABLA IV (Cont)

ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA

I

CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

	Suero de			Suero de			Suero de		
	ratón	Agua	ratón	ratón	Agua	ratón	ratón	Agua	ratón
	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo
	13	13	14	14	14	15	15	16	16
S. typhimurium GC 2172	8	64	>64	>64	>64	>64	>64	>64	>64
P. aeruginosa GC 2214	32	>64	>64	>64	>64	>64	>64	>64	>64
S. aureus GC 1131	2	2	1	2	2	2	4	2	4
S. aureus GC 6466	1	2	2	8	2	2	4	4	8
S. aureus GC 6467	4	8	2	4	16	8	16	8	8
S. aureus GC 1079	4	4	1	2	2	2	4	2	4
S. aureus GC 4536	1	2	2	2	2	2	4	2	4
S. aureus GC 2216	2	4	2	4	2	2	4	2	4
S. aureus GC 6335	2	4	1	4	4	4	4	4	4
S. aureus GC 6469	4	8	2	4	4	4	8	4	8
S. epidermidis GC 4935	4	8	8	8	16	16	16	8	8
E. faecalis GC 4555	2	4	2	8	8	4	8	4	8

TABLA IV (Cont)

ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA

I

CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

	Suero de		Suero de		Suero de		Suero de		Suero de	
	ratón	Agua	ratón	Agua	ratón	Agua	ratón	Agua	ratón	Agua
	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo
	13	13	14	14	15	15	16	16	16	16
E. faecalis GC 2265	4	8	2	8	8	8	4	8	4	8
E. faecalis GC 2267	4	8	2	8	8	8	4	8	4	8
E. faecalis GC 2242	4	8	2	8	8	8	8	8	8	8
E. faecium GC 4556	2	8	4	8	8	8	4	8	4	8
E. faecium GC 2243	2	4	2	4	8	8	4	8	4	8
S. pneumoniae* GC 4465	0.50	0.50	2	4	2	2	4	4	4	4
S. pneumoniae+ GC 4465	8	8	4	4	4	4	8	4	8	8
S. pyogenes GC 4563	0.50	1	2	4	2	2	4	2	4	8
S. agalactiae GC 4564	1	2	16	16	8	8	16	8	16	16
c. albicans GC 3066	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64

ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA I
CONCENTRACIÓN INHIBITORIA MÍNIMA MIC(UG/ML)

TABLA V

	Suero de		Suero de		Suero de		Suero de	
	ratón	Ejemplo	ratón	Ejemplo	ratón	Ejemplo	ratón	Ejemplo
		21		22		23		24
	Ejemplo 21							
E. coli GC 2236	1	>64	2	>64	2	>64	1	>64
E. coli GC 2231	1	>64	2	>64	2	>64	2	>64
E. coli GC 2235	0.50	>64	1	>64	1	>64	0.50	>64
E. coli GC 2232	1	>64	2	>64	1	>64	0.50	>64
E. coli GC 2233	1	>64	2	>64	2	>64	1	>64
E. coli GC 2234	0.50	>64	1	>64	1	>64	0.50	>64
E. coli GC 2270	1	>64	1	>64	1	>64	0.50	>64
E. coli GC 2271	0.50	>64	1	>64	1	>64	0.50	>64
E. coli GC 2272	1	>64	1	>64	1	>64	1	>64
E. coli GC 4559	1	>64	2	>64	2	>64	1	>64
E. coli GC 4560	0.25	>64	0.50	>64	0.50	8	0.25	64
E. coli GC 6465	4	>64	8	>64	4	>64	8	>64
E. coli GC 3226	8	>64	8	>64	8	>64	1	>64
E. coli GC 2203	0.50	>64	1	>64	1	>64	0.50	>64
E. coli GC 1073	1	>64	2	>64	1	>64	1	>64
Salmonella spp. GC 235	2	>64	2	>64	2	>64	1	>64
Salmonella spp. GC 566	4	>64	4	>64	4	>64	2	>64
S. cholerae GC 1355	16	>64	16	>64	16	>64	32	>64

TABLA V (CONT)
 ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA I
 CONCENTRACIÓN INHIBITORIA MÍNIMA MIC(UG/ML)

	Suero de		Suero de		Suero de		Suero de		Suero de		Suero de	
	ratón	Agua	ratón	Agua	ratón	Agua	ratón	Agua	ratón	Agua	ratón	Agua
	Ejemplo 21	Ejemplo 21	Ejemplo 22	Ejemplo 22	Ejemplo 23	Ejemplo 23	Ejemplo 23	Ejemplo 23	Ejemplo 24	Ejemplo 24	Ejemplo 24	Ejemplo 24
S. typhimurium GC 2172	4	>64	8	>64	4	>64	8	>64	8	>64	>64	>64
P. aeruginosa GC 2214	>64	>64	>64	>64	>64	>64	16	>64	16	>64	>64	>64
S. aureus GC 1131	1	64	1	4	1	2	1	2	1	2	2	2
S. aureus GC 6466	1	64	0.50	2	0.25	0.50	0.25	0.50	0.25	0.50	0.50	0.50
S. aureus GC 6467	4	>64	4	>64	4	8	4	8	4	>64	>64	>64
S. aureus GC 1079	4	>64	2	32	2	4	2	4	2	64	64	64
S. aureus GC 4536	2	32	1	2	1	2	1	2	1	4	4	4
S. aureus GC 2216	1	64	1	4	1	4	0.50	4	0.50	4	4	4
S. aureus GC 6335	2	64	2	8	2	4	2	4	2	16	16	16
S. aureus GC 6469	4	>64	4	64	4	4	4	4	4	>64	>64	>64
S. epidermidis GC 4935	2	64	2	16	2	4	2	4	2	16	16	16
E. faecalis GC 4555	1	64	2	64	1	4	1	4	1	64	64	64
E. faecalis GC 2265	1	64	2	64	1	4	2	4	2	32	32	32
E. faecalis GC 2267	2	64	4	64	2	8	4	8	4	64	64	64
E. faecalis GC 2242	2	32	2	32	2	4	2	4	2	4	4	4
E. faecium GC 4556	2	64	2	64	2	4	1	4	1	32	32	32
E. faecium GC 2243	0.50	8	1	8	0.50	4	0.50	4	0.50	2	2	2
S. pneumoniae* GC 4465	0.25	0.50	0.50	1	0.12	0.12	<0.06	0.12	<0.06	<0.06	<0.06	<0.06

TABLA V (CONT)

ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE
FÓRMULA I
CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

	Suero de				Suero de			
	Suero de		Suero de		Suero de		Suero de	
	ratón	Agua	ratón	Agua	ratón	Agua	ratón	Agua
	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo
21	21	22	22	23	23	24	24	24
S. pneumoniae+ GC 4465	4	4	4	16	4	8	2	1
S. pyogenes GC 4563	0.25	0.12	0.50	1	0.12	0.25	<0.06	<0.06
S. agalactiae GC 4564	0.50	8	1	8	0.25	0.25	0.50	8
c. albicans GC 3066	>64	>64	>64	>64	>64	>64	>64	>64

TABLA VI

ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA

I

CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

	Suero de				Suero de				Suero de			
	ratón		Agua		ratón		Agua		ratón		Agua	
	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo
	25	25	25	26	26	26	27	27	27	28	28	28
E. coli GC 2236	2	64		2			>64	0.50	64	0.50		>64
E. coli GC 2231	2	>64		4			>64	1	>64	1		>64
E. coli GC 2235	1	32		1			64	0.50	64	0.50		>64
E. coli GC 2232	1	>64		1			>64	0.50	64	0.50		>64
E. coli GC 2233	2	32		2			>64	0.50	64	0.50		>64
E. coli GC 2234	1	>64		1			>64	0.50	64	0.25		>64
E. coli GC 2270	1	>64		1			>64	0.50	64	0.50		>64
E. coli GC 2271	1	32		1			>64	0.50	64	0.25		>64
E. coli GC 2272	2	64		2			64	0.50	32	0.50		>64
E. coli GC 4559	2	>64		2			>64	0.50	>64	0.50		>64
E. coli GC 4560	0.50	2		0.50			8	0.25	1	0.25		>64
E. coli GC 6465	8	>64		8			>64	4	>64	8		>64
E. coli GC 3226	2	>64		2			>64	0.50	>64	0.50		>64
E. coli GC 2203	1	>64		1			>64	0.50	>64	0.50		>64
E. coli GC 1073	2	>64		2			>64	0.50	>64	0.50		>64
Salmonella spp. GC												
235	2	>64		2			>64	1	>64	0.50		>64
Salmonella spp. GC												
566	4	>64		4			>64	1	>64	2		>64
S. cholerae GC												
1355	32	>64		32			>64	16	>64	16		>64

324

ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLINAS DE FÓRMULA I

	Suero de ratón			Suero de ratón			Suero de ratón			Suero de ratón		
	Ejemplo	Agua	ratón	Ejemplo	Agua	ratón	Ejemplo	Agua	ratón	Ejemplo	Agua	ratón
	25	25	26	26	26	27	27	27	28	28	28	28
S. typhimurium GC 2172	8	>64	16		>64	4		>64	8		>64	>64
P. aeruginosa GC 2214	32	>64	32		>64	8		>64	16		>64	>64
S. aureus GC 1131	0.50	0.50	0.50		0.50	0.12		0.25	0.50		0.25	32
S. aureus GC 6466	0.25	0.25	0.25		0.25	0.12		0.25	0.50		0.25	4
S. aureus GC 6467	2	2	1		4	2		2	4		2	64
S. aureus GC 1079	1	2	1		2	1		2	2		2	64
S. aureus GC 4536	0.50	0.50	0.25		0.50	0.12		0.12	0.50		0.50	32
S. aureus GC 2216	0.50	1	0.50		0.50	0.25		0.25	0.50		0.25	32
S. aureus GC 6335	0.50	0.50	0.50		1	0.25		0.50	1		0.50	16
S. aureus GC 6469	2	4	1		2	1		2	4		2	64
S. epidermidis GC 4935	1	2	1		2	0.25		1	1		1	32
E. faecalis GC 4555	1	2	1		4	0.25		1	0.25		0.25	64
E. faecalis GC 2265	2	2	2		8	1		2	2		2	64
E. faecalis GC 2267	2	4	2		4	1		2	2		2	64
E. faecalis GC 2242	2	2	2		4	0.50		0.50	0.50		0.50	4
E. faecium GC 4556	1	4	1		4	0.50		1	0.50		0.50	32
E. faecium GC 2243	0.50	1	1		2	0.12		0.25	0.25		0.25	0.25
S. pneumoniae* GC 4465	0.12	0.25	0.25		0.25	<0.06		<0.06	<0.06		<0.06	<0.06

TABLA VI (CONT)

ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA
I
CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

	Suero de ratón		Suero de ratón		Suero de ratón		Suero de ratón		Suero de ratón		Suero de ratón	
	Ejemplo	Agua	Ejemplo	Agua	Ejemplo	Agua	Ejemplo	Agua	Ejemplo	Agua	Ejemplo	Agua
	25	25	26	26	27	27	28	28	29	29	30	30
S. pneumoniae+ GC 4465	4	4	4	4	1	2	2	2	2	2	2	2
S. pyogenes GC 4563	0.12	0.25	0.25	0.25	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06	<0.06
S. agalactiae GC 4564	0.50	0.50	1	2	0.12	0.12	0.25	0.25	0.25	0.25	0.25	0.25
c. albicans GC 3066	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64

TABLA VII

ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA

I

CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

	Suero de ratón		Suero de ratón		Suero humano		Suero de ratón		Suero humano	
	Agua Ejemplo 42	Ejemplo 42	Agua Ejemplo 43	Ejemplo 43	Agua Ejemplo 43	Ejemplo 43	Agua Ejemplo 44	Ejemplo 44	Agua Ejemplo 44	Ejemplo 44
E. coli GC 2236	>64	4	>64	>64	>64	0.50	>64	2	>64	>64
E. coli GC 2231	>64	4	>64	>64	>64	0.50	>64	2	>64	>64
E. coli GC 2235	>64	4	>64	>64	>64	0.25	>64	2	>64	>64
E. coli GC 2232	>64	4	>64	>64	>64	0.50	>64	2	>64	>64
E. coli GC 2233	>64	4	>64	>64	>64	0.50	>64	2	>64	>64
E. coli GC 2234	>64	4	>64	>64	>64	0.25	>64	2	>64	>64
E. coli GC 2270	>64	4	>64	>64	>64	0.25	>64	2	>64	>64
E. coli GC 2271	>64	4	>64	>64	>64	0.25	>64	2	>64	>64
E. coli GC 2272	>64	4	>64	>64	>64	0.50	>64	2	>64	>64
E. coli GC 4559	>64	8	>64	>64	>64	0.50	>64	4	>64	>64
E. coli GC 4560	8	2	8	32	<0.06	16	4	2	4	4
E. coli GC 6465	>64	16	>64	>64	>64	2	>64	8	>64	>64
E. coli GC 3226	>64	16	>64	>64	>64	1	>64	4	>64	>64
E. coli GC 2203	>64	8	>64	>64	>64	0.50	>64	2	>64	>64
E. coli GC 1073	>64	8	>64	>64	>64	0.50	>64	4	>64	>64
Salmonella spp.										
GC 235	>64	16	>64	>64	>64	0.50	>64	4	>64	>64
Salmonella spp.										
GC 566	>64	32	>64	>64	>64	2	>64	8	>64	>64

TABLA VII (CONT)

ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA
I I
CONCENTRACIÓN INHIBITORIA MÍNIMA MIC(UG/ML)

	Suero de ratón		Suero de ratón		Suero de ratón		Suero humano		Suero de ratón		Suero humano		Suero de ratón		Suero humano	
	Agua Ejemplo	42	Agua Ejemplo	42	Agua Ejemplo	43	Agua Ejemplo	43	Agua Ejemplo	43	Agua Ejemplo	44	Agua Ejemplo	44	Agua Ejemplo	44
S. cholerae GC 1355	>64	64	>64	>64	>64	>64	4	>64	>64	>64	>64	>64	16	>64	>64	>64
S. typhimurium GC 2172	>64	64	>64	>64	>64	>64	2	>64	>64	>64	>64	>64	8	>64	>64	>64
P. aeruginosa GC 2214	>64	>64	>64	>64	>64	>64	16	>64	>64	>64	>64	>64	>64	>64	>64	>64
S. aureus GC 1131	4	2	2	2	64	64	1	16	16	16	4	2	2	2	2	2
S. aureus GC 6466	4	2	4	4	64	64	0.50	16	16	16	2	2	2	2	2	2
S. aureus GC 6467	8	4	4	4	>64	>64	0.50	32	32	32	4	2	2	2	2	2
S. aureus GC 1079	4	2	4	4	64	64	1	32	32	32	4	2	2	2	2	2
S. aureus GC 4536	8	2	4	4	32	32	1	16	16	16	4	2	2	2	2	2
S. aureus GC 2216	4	2	2	2	64	64	0.50	32	32	32	2	2	2	2	2	2
S. aureus GC 6335	4	2	4	4	64	64	1	64	64	64	4	4	2	2	4	4
S. aureus GC 6469	4	2	4	4	>64	>64	1	32	32	32	4	2	2	2	2	2

TABLA VII (CONT)
 ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA
 I
 CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

	Suero de ratón		Suero de ratón		Suero humano		Suero de ratón		Suero humano		Suero de ratón		Suero humano	
	Agua	Ejemplo	Agua	Ejemplo	Agua	Ejemplo	Agua	Ejemplo	Agua	Ejemplo	Agua	Ejemplo	Agua	Ejemplo
	42	42	42	42	43	43	43	43	43	43	44	44	44	44
S. epidermidis GC														
4935	8	4	4	4	32	2	4	4	4	2	4	4	4	4
E. faecalis GC														
4555	4	2	4	4	32	0.50	8	4	4	2	4	4	4	4
E. faecalis GC														
2265	8	2	4	4	32	0.50	8	4	4	2	2	4	4	4
E. faecalis GC														
2267	4	2	4	4	32	0.50	4	4	4	2	4	4	4	4
E. faecalis GC														
2242	8	4	4	4	16	0.50	4	4	4	2	4	4	4	4
E. faecium GC 4556	8	2	4	4	16	0.50	8	4	4	2	4	4	4	4
E. faecium GC 2243	4	2	4	4	0.25	0.12	0.25	4	4	2	4	4	4	4
S. pneumoniae* GC														
4465	4	2	4	4	0.50	<0.06	1	2	2	1	2	4	4	4
S. pneumoniae+ GC														
4465	8	4	8	8	2	2	2	4	4	4	4	4	4	4
S. pyogenes GC														
4563	4	2	4	4	<0.06	<0.06	<0.06	2	2	1	4	4	4	4
S. agalactiae GC														
4564	8	2	8	8	2	<0.06	2	4	4	1	4	4	4	4
C. albicans GC														
3066	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64

TABLA VIII
 ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA
 I

CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)																
Agua Ejemplo 45	Suero de ratón Ejemplo 45		Suero humano Ejemplo 45		Agua Ejemplo 46		Suero de ratón Ejemplo 46		Suero humano Ejemplo 46		Agua Ejemplo 47		Suero de ratón Ejemplo 47		Suero humano Ejemplo 47	
E. coli GC 2236	16	1	4	4	64	0.50	4	>64	1	32						
E. coli GC 2231	32	1	4	4	64	0.50	4	>64	1	32						
E. coli GC 2235	16	0.50	4	4	64	0.50	4	>64	1	16						
E. coli GC 2232	16	1	4	4	64	0.50	4	>64	1	16						
E. coli GC 2233	16	1	4	4	64	0.50	4	>64	0.50	16						
E. coli GC 2234	16	0.50	4	4	64	0.50	4	>64	1	16						
E. coli GC 2270	32	0.50	4	4	>64	0.50	4	>64	0.50	16						
E. coli GC 2271	16	0.50	4	4	64	0.50	4	>64	1	16						
E. coli GC 2272	16	1	8	8	64	1	4	>64	1	16						
E. coli GC 4559	64	1	8	8	>64	1	8	>64	2	64						
E. coli GC 4560	2	0.25	0.50	0.50	4	0.50	1	16	1	4						
E. coli GC 6465	>64	2	16	16	>64	2	16	>64	2	>64						
E. coli GC 3226	64	1	8	8	>64	1	16	>64	2	32						
E. coli GC 2203	32	0.50	4	4	>64	0.50	8	>64	1	32						
E. coli GC 1073	64	1	8	8	>64	1	8	>64	2	32						
Salmonella spp.																
GC 235	>64	1	8	8	>64	1	16	>64	2	64						
Salmonella spp.																
GC 566	>64	2	32	32	>64	2	16	>64	4	>64						

TABLA VIII (CONT)
 ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA

I									
CONCENTRACIÓN INHIBITORIA MÍNIMA MIC(UG/ML)									
	Suero de ratón		Suero humano		Suero de ratón		Suero humano		
	Ejemplo 45	Ejemplo 46	Ejemplo 45	Ejemplo 46	Ejemplo 46	Ejemplo 47	Ejemplo 46	Ejemplo 47	
S. cholerae									
GC 1355	>64	4	32	>64	2	32	>64	4	>64
S. typhimurium									
GC 2172	>64	2	32	>64	2	32	>64	4	>64
P. aeruginosa									
GC 2214	>64	16	>64	>64	16	>64	>64	32	>64
S. aureus GC									
1131	1	0.50	0.50	0.50	0.50	0.50	2	1	2
S. aureus GC									
6466	0.50	0.25	0.25	0.25	0.25	0.25	2	1	1
S. aureus GC									
6467	2	1	1	1	1	0.50	4	1	2
S. aureus GC									
1079	1	0.50	0.12	0.50	0.50	0.50	2	1	2
S. aureus GC									
4536	1	0.50	0.50	0.50	0.50	0.50	4	1	1
S. aureus GC									
2216	1	1	0.50	1	0.50	0.50	2	1	1
S. aureus GC									
6335	2	1	0.50	1	1	0.50	2	1	2
S. aureus GC									
6469	1	1	0.50	1	1	0.50	4	1	2
S. epidermidis									
GC 4935	2	1	1	2	1	1	4	2	4

355

TABLA VIII (CONT)
 ANTIBACTERIAL ACTIVITY OF derivados de glicilciclinas sustituidos con 9-aminocarbonilo OF
 FORMULA I
 CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

	Suero de ratón		Suero humano		Agua Ejemplo		Suero de ratón Ejemplo		Suero humano Ejemplo		Agua Ejemplo		Suero de ratón Ejemplo		Suero humano Ejemplo		Agua Ejemplo		Suero de ratón Ejemplo		Suero humano Ejemplo	
	O 45	Ejempl 45	O 45	Ejempl 45	O 45	Ejempl 45	O 46	Ejempl 46	O 46	Ejempl 46	O 46	Ejempl 46	O 47	Ejempl 47	O 47	Ejempl 47	O 47	Ejempl 47	O 47	Ejempl 47	O 47	Ejempl 47
E. faecalis GC 4555	2	1		2		2	0.50		0.50		2		0.50		0.50		4		1		4	
E. faecalis GC 2265	4	0.50		1		2	0.50		0.50		2		0.50		1		4		1		4	
E. faecalis GC 2267	2	0.50		1		2	0.50		0.50		2		0.50		1		4		1		4	
E. faecalis GC 2242	2	1		1		1	0.50		0.50		1		0.50		1		4		1		4	
E. faecium GC 4556	2	1		1		1	0.50		0.50		1		0.50		1		4		1		4	
E. faecium GC 2243	2	0.50		1		0.50	0.25		0.25		0.50		0.25		0.25		2		0.50		2	
S. pneumoniae* GC 4465	0.50	0.25		0.25		0.12	0.12		0.12		0.12		0.12		0.12		0.50		0.25		0.50	
S. pneumoniae+ GC 4465	4	2		2		1	1		1		1		1		1		4		2		2	
S. pyogenes GC 4563	0.50	0.25		0.25		0.25	0.12		0.12		0.25		0.12		0.25		0.25		0.12		0.25	
S. agalactiae GC 4564	0.50	0.25		0.50		0.25	0.25		0.25		0.25		0.25		0.25		1		0.50		1	
c. albicans GC 3066	>64	>64		>64		>64	>64		>64		>64		>64		>64		>64		>64		>64	

TABLA IX

ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA

I

CONCENTRACIÓN INHIBITORIA MÍNIMA MIC(UG/ML)

	Suero de ratón				Suero de ratón humano				Suero humano				Suero de ratón humano			
	Agua Ejemplo	48	48	48	Agua Ejemplo	49	49	49	de ratón Ejemplo	49	49	49	Agua Ejemplo	50	50	50
E. coli GC 2236	64	0.25	16	16	16	0.50	0.50	4	4	32	1	8	32	1	8	8
E. coli GC 2231	64	0.50	16	16	16	0.50	0.50	8	8	64	1	8	64	1	8	8
E. coli GC 2235	32	0.25	16	16	8	0.50	0.50	4	4	32	1	4	32	1	4	4
E. coli GC 2232	64	0.25	16	16	16	0.50	0.50	4	4	32	1	8	32	1	8	8
E. coli GC 2233	64	0.25	16	16	8	0.25	0.25	4	4	32	1	8	32	1	8	8
E. coli GC 2234	64	0.50	16	16	16	0.25	0.25	4	4	64	1	8	64	1	8	8
E. coli GC 2270	64	0.50	16	16	16	0.50	0.50	4	4	32	1	8	32	1	8	8
E. coli GC 2271	32	0.25	8	8	8	0.25	0.25	4	4	32	1	4	32	1	4	4
E. coli GC 2272	64	0.25	8	8	8	0.50	0.50	2	2	32	1	4	32	1	4	4
E. coli GC 4559	>64	0.25	32	16	16	0.50	0.50	8	8	64	2	16	64	2	16	16
E. coli GC 4560	2	0.12	1	1	1	0.12	0.12	0.50	0.50	4	0.50	2	4	0.50	2	2
E. coli GC 6465	>64	2	>64	>64	>64	2	2	32	32	>64	2	16	>64	2	16	16
E. coli GC 3226	>64	0.50	32	16	16	0.50	0.50	8	8	32	1	8	32	1	8	8
E. coli GC 2203	64	0.25	16	16	8	0.25	0.25	4	4	32	1	8	32	1	8	8
E. coli GC 1073	64	0.50	32	32	32	0.50	0.50	8	8	32	2	8	32	2	8	8
Salmonella spp. GC 235	>64	0.50	32	32	32	1	1	16	16	>64	2	32	>64	2	32	32
Salmonella spp. GC 566	>64	2	>64	64	64	2	2	32	32	>64	4	32	>64	4	32	32
S. cholerae GC 1355	>64	4	>64	>64	>64	4	4	64	64	>64	4	64	>64	4	64	64

357

TABLA IX (Cont.)
 ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA
 I
 CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

	Suero de Suero		Suero de Suero		Suero de Suero		Suero de Suero	
	Agua	ratón humano	Agua	ratón humano	Agua	ratón humano	Agua	ratón humano
	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo
	48	48	48	49	49	49	50	50
S. typhimurium GC 2172	>64	4	>64	>64	4	32	>64	4
P. aeruginosa GC 2214	>64	16	>64	>64	32	>64	>64	32
S. aureus GC 1131	0.25	0.25	0.25	0.50	0.50	0.50	1	0.50
S. aureus GC 6466	0.12	0.12	0.12	0.12	0.12	0.12	0.25	0.25
S. aureus GC 6467	2	1	0.50	2	1	1	2	0.25
S. aureus GC 1079	1	0.25	0.25	0.50	0.50	0.50	2	0.50
S. aureus GC 4536	0.25	0.25	0.25	0.25	0.25	0.25	0.50	0.25
S. aureus GC 2216	0.50	0.25	0.25	0.50	0.25	0.25	2	0.50
S. aureus GC 6335	2	2	2	2	1	1	1	1
S. aureus GC 6469	1	0.50	1	1	1	1	2	1
S. epidermidis GC 4935	1	0.50	0.50	2	1	1	4	2
E. faecalis GC 4555	2	0.12	4	4	0.25	0.50	4	2

359

TABLA X
 ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA I
 CONCENTRACIÓN INHIBITORIA MÍNIMA MIC(UG/ML)

	Agua		Suero de		Suero humano		Agua		Suero de		Suero humano		Agua		Suero de		Suero humano	
	Ejemplo	51	ratón	Ejemplo	51	humano	Ejemplo	52	ratón	Ejemplo	52	humano	Ejemplo	53	ratón	Ejemplo	53	humano
E. coli GC 2236	>64	2	32	8	1	8	32	32	1	8	32	32	1	16	1	16	16	16
E. coli GC 2231	>64	2	32	16	1	8	32	32	1	8	32	32	1	16	1	16	16	16
E. coli GC 2235	>64	1	32	4	0.50	4	32	32	0.50	4	32	32	0.50	8	0.50	8	8	8
E. coli GC 2232	>64	2	32	8	0.50	4	32	32	0.50	4	32	32	0.50	8	0.50	8	8	8
E. coli GC 2233	>64	2	32	8	0.50	8	32	32	0.50	8	32	32	1	16	1	16	16	16
E. coli GC 2234	>64	1	32	8	0.50	4	32	32	0.50	4	32	32	0.50	8	0.50	8	8	8
E. coli GC 2270	>64	1	32	4	0.50	4	32	32	0.50	4	32	32	1	8	1	8	8	8
E. coli GC 2271	>64	1	32	4	0.50	4	32	32	0.50	4	32	32	0.50	8	0.50	8	8	8
E. coli GC 2272	>64	2	32	4	0.50	4	32	32	0.50	4	32	32	0.25	8	0.25	8	8	8
E. coli GC 4559	>64	2	32	8	1	8	32	32	1	8	32	32	1	16	1	16	16	16
E. coli GC 4560	32	1	8	2	0.25	2	8	2	0.25	2	2	2	0.50	2	0.50	2	2	2
E. coli GC 6465	>64	4	32	64	2	16	32	64	2	16	16	16	>64	32	4	32	32	32
E. coli GC 3226	>64	2	64	16	1	16	64	16	1	16	16	16	32	16	1	16	16	16
E. coli GC 2203	>64	2	32	8	0.50	8	32	8	0.50	8	32	32	1	16	1	16	16	16
E. coli GC 1073	>64	2	64	4	1	8	64	4	1	8	64	64	32	16	1	16	16	16
Salmonella spp. GC 235	>64	2	64	16	1	16	64	16	1	16	16	16	64	64	2	64	64	64
Salmonella spp. GC 566	>64	4	64	64	2	32	64	64	2	32	32	32	>64	32	2	32	32	32
S. cholerae GC 1355	>64	8	>64	>64	4	>64	>64	>64	4	>64	>64	>64	>64	>64	8	>64	>64	>64
S. typhimurium GC 2172	>64	8	64	64	4	64	64	64	4	64	64	64	>64	>64	4	>64	>64	>64

30

TABLA X (CONT)

ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA I
CONCENTRACIÓN INHIBITORIA MÍNIMA MIC(UG/ML)

	Suero de		Suero humano		Agua		Suero de ratón		Suero humano		Agua		Suero de ratón		Suero humano		Suero de ratón		Suero humano	
	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo
P. aeruginosa GC 2214	51	64	>64	64	>64	52	64	>64	52	>64	52	>64	52	64	>64	52	64	53	53	>64
S. aureus GC 1131	1	0.50	1	0.50	2	2	0.50	1	0.50	1	2	1	0.50	1	1	1	1	1	1	1
S. aureus GC 6466	1	0.25	1	0.25	2	2	0.25	0.25	0.50	1	2	0.50	0.50	0.50	0.50	1	0.50	0.50	0.50	0.50
S. aureus GC 6467	2	0.50	2	0.50	4	4	1	1	0.50	4	4	2	0.50	2	4	4	1	1	1	1
S. aureus GC 1079	2	0.50	2	0.50	2	2	1	1	0.50	1	2	2	0.50	1	1	1	0.50	0.50	0.50	0.50
S. aureus GC 4536	1	0.50	1	0.50	2	2	0.50	0.50	0.50	0.50	2	2	0.50	0.50	0.50	1	0.25	0.50	0.50	0.50
S. aureus GC 2216	1	0.50	1	0.50	4	4	0.50	0.50	0.50	1	4	1	0.50	1	1	1	0.50	0.50	0.50	0.50
S. aureus GC 6335	1	0.50	1	0.50	4	4	0.50	0.50	1	2	4	1	1	1	2	1	0.50	0.50	0.50	0.50
S. aureus GC 6469	2	1	2	1	4	4	1	1	0.50	2	4	2	0.50	1	2	2	1	1	1	1
S. epidermidis GC 4935	4	2	4	2	4	4	2	2	1	4	4	4	1	1	4	2	1	2	2	2
E. faecalis GC 4555	16	1	16	1	4	4	8	8	0.50	2	2	2	0.50	0.50	2	0.50	0.50	2	2	2
E. faecalis GC 2265	8	1	8	1	4	4	4	4	1	4	4	4	1	1	4	1	1	0.50	0.50	0.50
E. faecalis GC 2267	16	2	16	2	4	4	4	4	0.50	4	4	4	0.50	0.50	4	0.50	0.50	2	2	2

TABLA X (CONT)

TABLA XI
 I
 ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA
 I
 CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

	Suero de		Suero humano		Suero de		Suero humano		Suero de		Suero humano		Suero de		Suero humano	
	ratón		Ejemplo		ratón		Ejemplo		ratón		Ejemplo		ratón		Ejemplo	
	58	58	58	58	59	59	59	59	59	59	60	60	60	60	60	60
E. coli GC 2236	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2231	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2235	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2232	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2233	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2234	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2270	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2271	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2272	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 4559	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 4560	4	4	4	4	4	4	4	4	4	4	2	1	1	1	1	1
E. coli GC 6465	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 3226	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 2203	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
E. coli GC 1073	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Salmonella spp.																
GC 235	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Salmonella spp.																
GC 566	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
S. cholerasius																
GC 1355	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
S. typhimurium																
GC 2172	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64

TABLA XI (CONT)

ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE
FÓRMULA I
CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)

	Suero de ratón		Suero humano		Agua		Suero de ratón		Suero humano		Agua		Suero de ratón		Suero humano	
	Ejemplo	58	Ejemplo	58	Ejemplo	59	Ejemplo	59	Ejemplo	59	Ejemplo	60	Ejemplo	60	Ejemplo	60
P. aeruginosa																
GC 2214	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
S. aureus GC																
1131	4	2	4	4	4	4	4	4	4	4	8	8	2	2	2	2
S. aureus GC																
6466	4	2	4	8	8	8	4	4	4	4	8	8	4	4	4	4
S. aureus GC																
6467	4	2	4	4	4	4	4	4	4	4	8	8	4	4	4	4
S. aureus GC																
1079	8	2	4	8	8	8	4	4	2	2	4	4	2	2	2	2
S. aureus GC																
4536	4	2	4	4	4	4	4	4	4	4	4	4	2	2	2	2
S. aureus GC																
2216	4	2	4	4	4	4	4	4	4	4	4	4	2	2	2	2
S. aureus GC																
6335	4	4	4	4	4	4	4	4	4	4	8	8	8	8	8	8
S. aureus GC																
6469	4	2	4	4	4	4	4	4	4	4	4	4	2	2	2	2
S. epidermidis																
GC 4935	8	4	4	4	4	4	4	4	4	4	16	16	8	8	8	8
E. faecalis GC																
4555	8	4	4	4	4	4	4	4	4	4	4	4	4	4	4	2

E. faecalis GC	4	4	4	4	4	4	4	8	8	4
2265										
E. faecalis GC	4	2	4	4	4	4	4	8	8	4
2267										
E. faecalis GC	4	2	4	4	4	4	4	8	8	4
2242										
E. faecium GC	4	2	4	4	4	4	4	4	4	4
4556										
E. faecium GC	4	2	4	4	4	4	8	4	2	2
2243										
S. pneumoniae*	2	2	4	4	4	4	4	2	1	1
GC 4465										
S. pneumoniae+	8	4	4	4	8	4	8	4	4	2
GC 4465										
S. pyogenes GC	4	4	4	4	4	4	4	2	1	0.50
4563										
S. agalactiae	8	8	16	8	8	8	8	4	4	4
GC 4564										
c. albicans GC	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
3066										

TABLA XII
 ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9 -AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE
 FÓRMULA I

	CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)									
	Agua		Suero de ratón		Suero humano		Suero de ratón		Suero humano	
	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo
	61	61	61	62	62	62	62	62	63	63
E. coli GC	16	0.50	4	4	0.50	8	>64	1	>64	>64
E. coli GC	32	1	8	8	0.50	4	>64	1	>64	>64
E. coli GC	16	0.50	4	4	0.50	2	>64	0.50	>64	>64
E. coli GC	16	0.50	4	8	1	2	>64	1	>64	>64
E. coli GC	16	1	8	8	2	4	>64	1	>64	>64
E. coli GC	16	0.50	8	8	1	2	>64	1	64	64
E. coli GC	16	0.50	4	8	0.50	2	>64	0.50	64	64
E. coli GC	16	0.50	4	4	1	2	>64	0.50	>64	>64
E. coli GC	8	0.50	4	8	1	4	>64	1	>64	>64
E. coli GC	64	1	8	16	1	8	>64	2	>64	>64
E. coli GC	1	0.25	1	0.50	0.25	0.50	16	0.50	2	2
E. coli GC	>64	1	32	>64	2	8	>64	2	>64	>64

TABLA XII (CONT.)
 ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE
 FÓRMULA I

		CONCENTRACIÓN INHIBITORIA MÍNIMA MIC (UG/ML)									
		Suero de ratón		Suero humano		Agua Ejemplo		Suero de ratón Ejemplo		Suero humano Ejemplo	
		Ejemplo 61	Ejemplo 61	Ejemplo 61	Ejemplo 61	Ejemplo 62	Ejemplo 62	Ejemplo 62	Ejemplo 62	Ejemplo 62	Ejemplo 63
S. typhimurium											
GC 2172	>64	1	64	>64	>64	2	16	>64	2	>64	>64
P. aeruginosa											
GC 2214	>64	8	>64	>64	>64	16	>64	>64	32	>64	>64
S. aureus GC 1131	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	1	1	1
S. aureus GC 6466	0.50	0.50	0.50	0.25	0.25	0.50	0.50	0.50	2	0.50	1
S. aureus GC 6467	1	0.50	0.50	0.50	0.50	1	0.50	0.50	16	2	4
S. aureus GC 1079	1	0.25	0.50	0.50	0.50	1	0.50	0.50	8	1	2
S. aureus GC 4536	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	4	1	1
S. aureus GC 2216	1	0.50	0.50	0.50	0.50	0.50	0.50	0.50	4	1	1
S. aureus GC 6335	1	0.50	1	0.50	0.50	1	0.50	0.50	4	1	1
S. aureus GC 6469	2	0.50	0.50	1	1	1	0.50	0.50	16	1	2
S.	1	0.50	1	0.50	0.50	0.50	0.50	0.50	4	2	2

epidermidis
GC 4935
E. faecalis
GC 4555
E. faecalis
GC 2265
E. faecalis
GC 2267
E. faecalis
GC 2242

2	1	2	1	1	0.50	4	1	2
2	0.50	2	1	0.50	0.50	8	1	2
2	0.50	2	1	0.50	0.50	16	1	2
2	0.50	2	0.50	0.50	0.50	1	1	1

TABLA XIII

ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA

I

CONCENTRACIÓN INHIBITORIA MÍNIMA MIC(UG/ML)

	Suero de		Suero de		Suero de		Suero de		Agua
	ratón	Agua	ratón	Agua	ratón	Agua	ratón	Agua	
	Ejemplo 108	Ejemplo 108	Ejemplo 109	Ejemplo 109	Ejemplo 109	Ejemplo 109	Ejemplo 110	Ejemplo 110	
E. coli GC									
2236	0.50	2	0.50	1	0.50	2	1	2	
E. coli GC									
2231	2	4	0.50	1	1	2	4	8	
E. coli GC									
2235	0.50	1	0.25	0.50	0.50	1	0.50	1	
E. coli GC									
2232	1	2	0.50	1	0.50	2	1	2	
E. coli GC									
2233	0.50	1	0.25	0.50	1	2	0.50	1	
E. coli GC									
2234	0.50	2	0.12	0.25	0.25	2	1	2	
E. coli GC									
2270	0.50	1	0.25	0.50	0.25	2	1	1	
E. coli GC									
2271	0.50	0.50	0.12	0.25	0.25	1	1	2	
E. coli GC									
2272	0.25	0.50	0.25	0.25	0.50	2	1	1	
E. coli GC									
4559	0.50	1	0.12	0.25	1	2	2	2	
III									

E. coli GC 4560	0.12	0.25	<0.06	<0.06	0.25	0.25	0.25	0.25	0.50
E. coli GC 6465	8	64	1	4	4	16	64	>64	
E. coli GC 3226	0.50	1	0.50	1	1	4	2	4	
E. coli GC 2203	0.50	1	0.50	1	0.50	2	1	4	
E. coli GC 1073	0.50	2	0.50	1	1	4	2	8	
Salmonella spp. GC 235	1	4	1	2	1	4	4	8	
Salmonella spp. GC 566	1	8	2	4	2	4	16	32	
S. cholerae GC 1355	32	64	8	32	8	32	>64	>64	

TABLA XIII (CONT)

ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA I
CONCENTRACIÓN INHIBITORIA MÍNIMA MIC(UG/ML)

	Suero de ratón	Agua	Suero de ratón	Agua	Suero de ratón Ejemplo 109	Agua Ejemplo 109	Suero de ratón Ejemplo 110	Agua Ejemplo 110
	Ejemplo 108	Ejemplo 108	Ejemplo 109	Ejemplo 109	Ejemplo 109	Ejemplo 109	Ejemplo 110	Ejemplo 110
S. typhimurium GC 2172	4	32	4	16	4	16	64	>64
P. aeruginosa GC 2214	16	32	16	>64	32	>64	>64	>64
S. aureus GC 1131	0.25	0.50	1	2	1	4	2	4
S. aureus GC 6466	0.50	1	0.50	1	0.50	4	1	2
S. aureus GC 6467	2	8	2	4	2	8	32	>64
S. aureus GC 1079	2	4	2	4	2	8	16	16
S. aureus GC 4536	0.50	1	1	2	1	4	4	4
S. aureus GC 2216	0.50	1	1	2	0.50	8	2	4
S. aureus GC 6335	1	2	2	4	1	4	8	8
S. aureus GC 6469	0.25	1	1	2	2	8	32	32
S. epidermidis GC 4935	1	2	2	4	2	8	4	8
E. faecalis GC 4555	0.50	0.50	0.50	1	0.50	1	1	2
E. faecalis GC 2265	1	2	1	2	1	4	8	4

TABLA XIII (CONT)

ACTIVIDAD ANTIBACTERIAL DE DERIVADOS 9-AMINOCARBONIL SUSTITUIDOS DE GLICILCLICINAS DE FÓRMULA
I
CONCENTRACIÓN INHIBITORIA MÍNIMA MIC(UG/ML)

	Suero de		Suero de		Suero de		Suero de		Suero de		Suero de	
	ratón	Agua	ratón	Agua	ratón	Agua	ratón	Agua	ratón	Agua	ratón	Agua
	Ejemplo	Ejempl	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo	Ejemplo
	108	o 108	109	109	109	109	109	109	110	110	110	110
E. faecalis GC 2267	1	2	1	2	1	4	1	4	8	4	4	4
E. faecalis GC 2242	0.50	1	1	1	1	2	1	2	1	1	1	1
E. faecium GC 4556	0.50	1	1	2	1	2	1	2	1	2	2	2
E. faecium GC 2243	0.50	0.50	0.50	0.50	0.50	1	0.50	1	0.50	0.50	0.50	0.50
S. pneumoniae* GC 4465	0.12	0.12	<0.06	0.12	<0.06	0.12	<0.06	0.25	0.25	0.12	0.12	0.12
S. pneumoniae+ GC 4465	1	2	1	1	1	2	1	2	4	2	2	2
S. pyogenes GC 4563	0.12	0.12	<0.06	0.12	0.12	0.25	0.12	0.25	0.12	<0.06	<0.06	<0.06
S. agalactiae GC 4564	0.12	0.12	0.12	0.25	<0.06	0.25	<0.06	0.25	0.25	0.25	0.25	0.25
c. albicans GC 3066	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64

375

Tabla 1. Actividad in vitro (MIC)^a de ejemplos representativos de fórmula I

Número Ej	Concentración de inhibición mínima MIC (µg/ml)			
	E.coli (Suero de ratón)	E.coli (Agua)	Staph (Suero de ratón)	Staph (Agua)
1	0.5-1	16-64	1-4	1-8
2	1-4	32-64	1-8	2-8
3	1-2	>64	1-4	4-32
4	0.5-2	64->64	0.5-2	2-16
5	1-2	16-64	0.25-2	0.5-4
6	1-2	8-64	0.5-2	1-4
7	0.25-2	2-16	0.5-4	0.5-4
8	1-2	16->64	0.5-4	1-8
9	0.5-2	4-64	<0.06-2	0.12-2
10	0.25-2	4-32	0.25-2	0.12-2
11	0.25-2	4->64	0.25-4	0.25-4
12	0.5-2	16-64	0.5-4	1-16
13	1-4	8-16	1-4	2-8
14	32->64	64->64	1-8	2-8
15	32->64	32->64	2-16	4-16
16	16->16	64->64	2-8	4-8
17	0.5-2	32-64	1-4	2-32
18	0.5-2	4-8	1-4	1-4
19	0.5-2	32->64	0.5-4	1-8
20	0.5-2	>64	1-4	64->64
21	0.5-8	>64	1-4	32->64
22	1-8	>64	0.5-4	2->64
23	1-8	>64	0.25-4	0.5-8
24	0.5-2	>64	0.25-4	0.5->64
25	1-2	32->64	0.25-2	0.5-4
26	1-4	64->64	0.25-1	0.25-4
27	0.5-1	32->64	0.12-2	0.12-2
28	0.25-1	>64	0.5-4	4-64
29	0.5-1	>64	0.25-2	1-4
30	0.5-1	32->64	0.25-2	1-8
31	0.5-1	16->64	0.25-2	0.5-4
32	0.5-1	1-4	0.25-2	0.5-4
33	0.5-2	32->64	0.12-2	0.12-2

^a Rango de MIC (Concentración de inhibición mínima) para E. coli y Staph., incluyendo MRSA que son seleccionados de estos E. coli y Staph., presentados en las Tablas I-XIII.

Tabla 1 (Cont)

Número Ej	Concentración de inhibición mínima MIC ^a ($\mu\text{g/ml}$)			
	E.coli (Suero de ratón)	E.coli (Agua)	Staph (Suero de ratón)	Staph (Agua)
34	0.5-1	4-16	0.25-4	0.25-4
35	4-8	8-64	2-4	2-4
36	2-8	8-32	2-4	4-16
37	2-4	4-32	1-4	2-4
38	0.5-4	64->64	0.5-2	1-8
39	1-4	16-32	1-4	2-16
40	1-2	16->64	0.25-2	0.25-2
41	0.5-4	16-64	0.5-4	1-8
42	4-16	>64	2-4	4-8
43	0.25-2	>64	0.5-2	32->64
44	2-8	>64	2	2-4
45	0.5-2	16->64	0.25-1	0.5-2
46	0.5-2	64->64	0.25-1	0.25-2
47	0.5-2	>64	1-2	2-4
48	0.25-2	32->64	0.12-2	0.12-2
49	0.25-2	8->64	0.12-1	0.12-2
50	1-2	32-64	0.25-2	0.25-4
51	1-2	>64	0.25-2	1-4
52	0.5-1	4-16	0.5-1	2-4
53	0.25-1	16-64	0.25-1	0.5-2
54	0.5-1	>64	0.5-2	1-4
55	0.5-8	64->64	1-2	2-8
56	0.25-2	8>64	0.25-1	1-4
57	0.5-4	>64	0.5-2	4-16
58	>64	>64	2-4	4-8
59	32->64	>64	4	4-8
60	32->64	64->64	2-8	4-16
61	0.5-1	8->64	0.25-0.5	0.5-2
62	0.5-2	4->64	0.5-1	0.25-1
63	0.5-2	>64	0.5-2	2-16
64	<0.12 - <0.12 -	<0.12 - 1	<0.12 - 0.25	<0.12 - 0.5
65	0.5	16	<0.12 - 0.5	<0.12 - 1
66	>128 <0.12 -	>128	1-16 <0.12 -	2-16
67	0.25 <0.12 -	8-32	0.25 <0.12 -	<0.12 - 1
68	1	2-8	0.25	<0.12 - 1

^a Rango de MIC (Concentración de inhibición mínima) para E. coli y Staph., incluyendo MRSA que son seleccionados de estos E. coli y Staph., presentados en las Tablas I-XIII.

Tabla 1 (Cont)

Número Ej	Concentración de inhibición mínima MIC ^a ($\mu\text{g/ml}$)			
	E.coli (Suero de ratón)	E.coli (Agua)	Staph (Suero de ratón)	Staph (Agua)
	<0.12 -		<0.12 -	
69	0.5	8-64	0.25	<0.12 - 1
70	4-8	>64	1-4	2-4
	0.12-			
71	0.25	>64	0.5-1	32-64
72	0.5-1	>64	0.5-1	4-8
73	0.5-1	>64	1-4	4-8
74	0.25-1	>64	0.5-4	64->64
75	16->64	>64	8-16	16-32
76	16->64	>64	8-16	8-32
77	8->64	>64	2-4	4-32
78	16-64	>64	8	8-32
79	16->64	>64	4	4-8
80	16->64	64->64	4-8	4-16
81	0.5-1	8-16	0.5-2	4-8
82	64->64	>64	4-16	4-8
83	64->64	>64	8-32	2-16
84	2-4	>64	0.5-2	0.5-4
85	1-2	>64	1-2	4-16
86	8-16	>64	2-8	8
87	64->64	>64	32-64	>64
88	0.5-2	8-16	1-4	4-16
89	0.25-1	4-8	0.5-1	1-4
90	2-4	>64	0.25-2	1-16
91	0.5-2	>64	0.12-0.25	0.25-2
92	4-8	>64	4	8-32
93	1-4	64->64	1-2	32-64
94	32-64	>64	16-32	>64
95	>64	>64	16->64	>64
96	0.25-1	64->64	0.25-1	4-16
97	4-8	>64	1-4	4-8
98	1-4	>64	0.5-2	2-4
99	1-2	>64	0.5-2	2-4
100	2	64->64	0.5-1	2-4
101	1	16-32	0.5-2	4-16
102	0.5-1	>64	0.5-1	64->64
103	8-16	>64	8-16	64->64
104	8-16	>64	16-64	64->64
105	2	>64	1-2	16->64

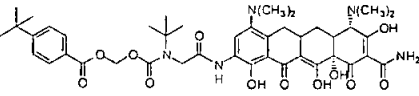
^a Rango de MIC (Concentración de inhibición mínima) para E. coli y Staph., incluyendo MRSA que son seleccionados de estos E. coli y Staph., presentados en las Tablas I-XIII.

324

Número Ej	Tabla 1 (Cont) Concentración de inhibición mínima MIC ^a (µg/ml)			
	E.coli (Suero de ratón)	E.coli (Agua)	Staph (Suero de ratón)	Staph (Agua)
106	>64	>64	>64	>64
107	>64	0.5-1	2-8	0.5-1
108	0.5-2	0.5-4	0.25-2	1-8
109	0.25-1	1-4	0.5-2	4-8
110	0.5-4	1-8	1-32	2->64
111	0.25-1	1-4	0.5-8	1-16
112	1-4	2-8	2-8	4-16
113	1-4	2-16	4-16	4-32

^a Rango de MIC (Concentración de inhibición mínima) para E. coli y Staph., incluyendo MRSA que son seleccionados de estos E. coli y Staph., presentados en las Tablas I-XIII.

Tabla 2. Actividad in vitro (MIC) del Ejemplo 87.

Ejemplo 87			
			
	agua	Suero de ratón	Suero humano
E. coli, tet (A-D), eflujo	>64	0.25-0.5	>64
E. coli, tet (M,S,O) Tet (M)	>64	0.25-0.5	>64
E. coli (susceptible)	>64	0.5	>64
E. coli (IMP)	32	<0.06	16
S. aureus, tet (M)	64	0.5	16
S. aureus, tet (K), eflujo	64	1	32
S. aureus (susceptible) ^a	32	1	16
Enterococcus spp.	0.25-32	0.12-0.5	0.25-8
Streptococcus spp.	0.5-2	<0.06	1-2
C. albicans	>64	>64	>64

^a Cepa utilizada para los ensayos in vivo

379

Ejemplos representativos de compuestos de Fórmula I se evalúan adicionalmente para eficacia oral, estabilidad en fisiología pH en suero de ratón y plasma humano.

Tabla 3. Actividad in vitro (MIC)^a of ejemplos representativos de compuestos de Fórmula I

Concentración de inhibición mínima (MIC), µg/mL				
Ej. No.	E. coli (Suero de de ratón)	E. coli (agua)	Staph. (Suero de ratón)	Staph. (agua)
1	0.5-1	16-64	1-4	1-8
2	1-4	32-64	1-8	2-8
3	1-2	>64	1-4	4-32
4	0.5-2	64->64	0.5-2	2-16
12	0.5-2	16-64	0.5-4	1-16
13	1-4	8-16	1-4	2-8
17	0.5-2	32-64	1-4	2-32
18	0.5-2	4-8	1-4	1-4
20	0.5-2	>64	1-4	64->64
21	0.5-8	>64	1-4	32->64
22	1-8	>64	0.5-4	2->64
23	1-8	>64	0.25-4	0.5-8
29	0.5-1	>64	0.25-2	1-4
30	0.5-1	32->64	0.25-2	1-8
34	0.5-1	4-16	0.25-4	0.25-4
36	2-8	8-32	2-4	4-16
38	0.5-4	64->64	0.5-2	1-8
39	1-4	16-32	1-4	2-16

^a Rango de MIC (Concentración de inhibición mínima) para E. coli y Staph., incluyendo MRSA que son seleccionados de estos E. coli y Staph., presentados en las Tablas I-XIII.

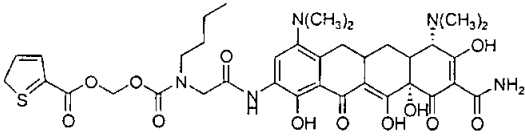
Tabla 4. Actividad in vitro (MIC)^a of ejemplos representativos de compuestos de Fórmula I

340

Concentración de inhibición mínima (MIC), µg/mL				
Ej. No.	E. coli (Suero de ratón)	E. coli (agua)	Staph. (Suero de ratón)	Staph. (agua)
5	1-2	16-64	0.25-2	0.5-4
6	1-2	8-64	0.5-2	1-4
7	0.25-2	2-16	0.5-4	0.5-4
8	1-2	16->54	0.5-4	1-8
9	0.5-2	4-64	0.06-1	0.12-2
10	0.25-2	4-32	0.25-2	0.12-2
11	0.25-2	4->64	0.25-4	0.25-4
19	0.5-2	32->64	0.5-4	1-8
24	0.5-2	>64	0.25-4	0.5->64
25	1-2	32->64	0.25-2	0.5-4
26	1-4	64->64	0.25-1	0.25-4
27	0.5-1	32->64	0.12-2	0.12-2
28	0.25-1	>64	0.5-4	4-64
31	0.5-1	16->64	0.25-2	0.5-4
33	0.5-2	32->64	0.12-2	0.12-2
35	4-8	8-64	2-4	2-4
40	1-2	16->64	0.25-2	0.25-2
41	0.5-4	16-64	0.5-4	1-8

^a Rango de MIC (Concentración de inhibición mínima) para E. coli y Staph. incluyendo MRSA que son seleccionados de estos E. coli y Staph., presentados en las Tablas I-XIII.

Tabla 5. Actividad in vitro (MIC) del Ejemplo 27

Ejemplo 27			
			
	agua	Suero de ratón	Suero humano
E. coli, tet (A-D), eflujo	64->64	0.5-1	4-16
E. coli, tet (M,S,O) Tet (M)	0.5	0.5	4-8
E. coli (susceptible)	0.5	0.5	16
E. coli (IMP)	0.25	0.25	0.5
S. aureus, tet	0.12	0.12	0.25

341

(M)			
S. aureus, tet	1	1	1
(K), eflujo			
S. aureus	0.12	0.12	0.5
(susceptible) ^a			
Enterococcus	0.12-1	0.12-1	0.5-2
spp.			
Streptococcus	<0.06-	<0.06-	0.12-2
spp.	0.12	0.12	
C. albicans	>64	>64	>64

^a Cepa utilizada para ensayo in vivo

Ejemplos representativos de compuestos de Fórmula I se ensayan para la eficacia oral utilizando S. aureus Smith en ratones. En resumen de actividades in vivo e in vitro de compuestos de seleccionados se listan en la Tabla 6.

Tabla 6. Actividad in vitro e in vivo de los ejemplos representativos de compuestos de Fórmula I contra Staph. aureus Smith en ratones.

ED ₅₀ mg/kg (Staph μ g/mL (Staph aureus aureus Smith) Smith)			
Ej. No.	SOD ^b	SIV ^c	MIC ^a
42	5.68	1.43	8
44	4	0.75	4
45	5.9	0.66	1
47	14	1.2	4
48	10.1	1.1	0.25
49	16	0.92	0.25
50	16.88	1.65	0.5
52	10.69	1.29	2
53	5.08	0.73	1
54	8.4	0.83	0.5
87	12.82	0.83	32

^a MIC (Concentración de inhibición mínima)

^b SOD (Dosis unitaria oral)

382

^c SIV (Dosis unitaria intravenosa)

Ejemplos representativos de compuestos de Fórmula I se ensayan in vivo contra bacterias Gram-negativa (E. coli) en ratones. Los resultados de los ensayos (MIC, oral y IV) se listan en la Tabla 7.

Tabla 7. Actividad in vivo (oral, iv) e in vitro (MIC)^a de los ejemplos representativos de compuestos de Fórmula I contra E. coli en ratones .

Ej. No.	ED ₅₀ mg/kg		μg/mL
	(E. coli)		(E. coli)
	SOD ^b	SIV ^c	MIC
5	>64	3.17	>64
42	30.3	3.1	>64
44	42.8	2.85	>64
45	64	1.8	64
48	29.8	1.7	>64
49	49	2.2	64
50	29.8	1.7	>64
52	43.7	3.78	8
53	46.88	2.25	32
54	29.2	2.16	>64
87	60.4	3.6	>64

^a MIC (Concentración de inhibición mínima)

^b SOD (Dosis unitaria oral)

^c SIV (Dosis unitaria intravenosa)

Los resultados de los ensayos de actividad in vivo se muestran en la Tabla 8 para ejemplos representativos de compuestos de Fórmula I.

343

Tabla 8. Actividad in vivo (oral, iv) e in vitro (MIC)^a de ejemplos los representativos de compuestos de Fórmula I, contra Staph aureus Smith en ratones .

Ej. No.	ED ₅₀ mg/kg (Staph aureus Smith)		μg/mL (Staph aureus Smith)
	SOD ^b	SIV ^c	MIC
1	4.7	0.6	4
5	8.51	0.5	1
19	8.05	0.31	1
26	8.79	0.43	0.5
27	3.9	0.44	0.12
28	6.61	0.6	32
33	4.91	0.48	0.12
35	3.5	0.43	4
36	5.15	0.84	8
38	5.3	0.6	2
40	4.65	0.39	0.5

^a MIC (Concentración de inhibición mínima)

^b SOD (Dosis unitaria oral)

^c SIV (Dosis unitaria intravenosa)

Tabla 9 Concentración de inhibición mínima (MIC), μg/mL				
Ej. No.	E.coli (Suero humano)	E.coli (Agua)	Staph (Suero humano)	Staph (Agua)
4	8-32	32->64	0.5-4	2-8
19	8-32	16->64	0.12-1	0.25-4
27	4-16	64->64	0.25-2	0.5-4
42	>64	>64	2-4	4-8
43	>64	>64	4-64	32->64
44	>64	>64	2-4	2-4
45	4-16	16->64	0.12-1	0.5-2
46	4-16	64->64	0.25-1	0.25-2
47	16->64	>64	1-4	2-4
48	8->64	32->64	0.12-2	0.12-2
49	4-32	8->64	0.12-1	0.12-2
50	4-16	32-64	0.25-2	0.25-4
51	32-64	>64	0.25-2	1-4
52	4-16	4-16	0.5-4	2-4
53	8-16	16-64	0.5-2	0.5-2
54	16-32	>64	0.5-2	1-4

385

55	32->64	64->64	1-4	2-8
56	4-32	8->64	0.25-2	1-4
57	>64	>64	1-8	4-16
58	>64	>64	4	4-8
59	>64	>64	2-4	4-8
60	32->64	64->64	2-8	4-16
61	4-32	8->64	0.5-1	0.5-2
62	2-8	4->64	0.5	0.25-1
63	64->64	>64	1-4	2-16
102	64->64		>64	
105	64>64		8->64	

Tabla 10

Ej. No.	ED ₅₀ (mg/kg)		ED ₅₀ mg/kg		IV - RAT			PO - RAT		
	Staph Smith		E. coli #311		Cmax	AUC	T1/2	Cmax	AUC	%BA
	SOD	SIV	SOD	SIV						
1										
2	13.27	0.71								
3	16.05	0.59								
4	11.6	0.39	>32	>2						
5	8.51	0.5								
6	20.05	0.87								
7	16.1	0.52								
8	16.63	0.48								
9	11.27	0.32								
10	13.62	0.36								
11	30.27	0.59								
12	15.02	1								
13	10.98	0.82								
14	>32	>2								
16	>32	>2								
17	59.9	1.07								
18	29.02	0.6								
19	8.05	0.31	>32	>2						
20	19.4	0.6								
21	>32	0.77								
22	18.77	0.43								

386

382

Tabla 10 (cont)

Ej. No.	SOD	SIV	SOD	SIV	Cmax	AUC	T1/2	Cmax	AUC	%BA
23	19.01	0.47								
24	27	0.59								
25	15.71	0.56								
26	8.79	0.43								
27	3.9	0.44	>32	>2						
28	6.61	0.6	>32	>2						
29	13.67	0.43								
30	15.1	0.41								
31	11.11	0.31								
32	7.7	0.56								
33	4.91	0.45								
34	12.86	0.71								
35	3.5	0.43								
36	5.15	0.84								
37	4.1	0.55								
38	5.3	0.6								
39	13.3	0.6								
40	4.65	0.39								
41	11.3	0.83								
42	5.68	1.43	30.3	3.1	4.1	1.6	5.1	0.22	0.64	8.1
43	12.82	0.83	60.4	3.6						
44	4	0.75	42.8	2.85	6.5	2.4	3.5	0.05	0.27	2.3
45	5.9	0.66	64	1.8						
46	8.4	0.83	29.2	2.16						
47	14	1.2	>64	3.17						
48	10.1	1.1	29.8	1.7						
49	16.6	0.92	49	2.2						

388

Tabla 10 (cont)

Ej. No.	ED ₅₀ (mg/kg) Staph Smith		ED ₅₀ mg/kg E. coli #311		IV - RAT 2 mg/kg		PO - RAT 20 mg/kg	
	SOD	SIV	SOD	SIV	Cmax	AUC	Cmax	AUC
50	16.88	1.65	>64	2.59				
52	10.69	1.29	43.7	3.78				
53	5.08	0.73	46.88	2.25				
54	>16	1.17	>32	3.72				
55	>16	1.81	32	4.69				
56	>16	0.79						
57	6.36	1.17						
58								
59								
60			>32	>8				
61			>32	2-4				
62			>32	4-8				
63			>32	4-8				
71	>32	1	>32	>4				
74	>32	1.08	>32	>4				
81	16-32	>4						
82	21.97	0.52						
90	16-32	0.5-1						
91	11.73	1.21						
93	>32	0.5-1						
96	16-32	1-2	>32	2-4				
102	19.81	1.59	>32	2-4				
108	>32	>2						
109	19.94	0.76						
110	31.94	0.6						
112	6.12	0.48						
113	7.01	0.4						

Tabla 10 (cont)

Cuando los compuestos de la invención se emplean como antibacteriales, ellos pueden ser combinados con uno o más vehículos farmacéuticamente aceptables, por ejemplo, solventes, diluyentes, y similares y se pueden administrar oralmente como en forma de tabletas, cápsulas, polvos dispersables, gránulos, o suspensiones que los contienen, por ejemplo, de aproximadamente 0.05 a 5% de agente de suspensión, jarabes que contienen por ejemplo, aproximadamente 10 a 50% de azúcar, y elíxires que contienen, por ejemplo, 20 a 50% de etanol, y similares, o parenteralmente en la forma de soluciones estériles inyectables o suspensiones que contienen cerca de aproximadamente 0.05 a 5% de agente de suspensión en un medio isotónico. Tales preparaciones farmacéuticas pueden contener, por ejemplo, cerca de aproximadamente 25 a aproximadamente 90% del ingrediente activo en combinación con el vehículo, más usualmente entre aproximadamente 5% a aproximadamente 60% por peso.

Una cantidad efectiva del compuesto de 2.0 mg/kg del peso del cuerpo a 100.0 mg/kg del peso del cuerpo se puede administrar de una a cinco veces por día mediante cualquier ruta de administración típica incluyendo pero no limitada a oral, parenteral (incluyendo subcutánea, intravenosa, intramuscular, inyección intrasternal o técnicas de infusión), tópica o rectal, en formulaciones de dosis unitarias que contienen portadores farmacéuticamente aceptables no tóxicos convencionales, adyuvantes y vehículos. Se entiende, sin embargo, que es nivel de dosis específica y la frecuencia de dosificación para cualquier paciente en particular se puede variar y dependerá de una variedad de factores que incluyen la actividad del compuesto

específico empleado, la edad, el peso del cuerpo, salud en general, sexo, dieta, modo y tiempo de administración, índice de excreción, combinación de droga, la severidad de la condición particular, y la terapia que experimente el huésped.

Estos compuestos activos se pueden administrar oralmente como también mediante rutas intravenosas, intramusculares, o subcutáneas. Los vehículos sólidos incluyen almidón, lactosa, fosfato de dicalcio, celulosa microcristalina, sucrosa y caolín, los vehículos líquidos incluyen agua estéril, polietilenglicoles, tensoactivos no iónicos, aceites comestibles tales como maíz, maní, aceites de sésamo, como sean apropiados a la naturaleza del ingrediente activo y a la forma de administración particular deseada. Los adyuvantes empleados de costumbre en la preparación de las composiciones farmacéuticas ventajosamente se pueden incluir, tales como agentes saborizantes, agentes colorantes, agentes de preservación, y antioxidantes, por ejemplo, vitamina E, ácido ascórbico, BHT y BHA.

Las composiciones farmacéuticas preferidas desde el punto de vista de fácil preparación y administración son las composiciones sólidas, particularmente tabletas y cápsulas llenas de líquido o llenas de sólidos. Se prefiere la administración oral de los compuestos.

Estos compuestos activos se pueden administrar parenteral o intraperitonealmente. Las soluciones o suspensiones de estos compuestos activos se pueden preparar como una base libre o una sal farmacéuticamente aceptable en agua convenientemente mezclada

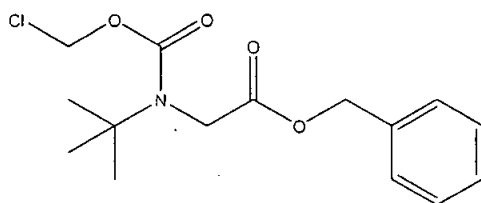
con un tensoactivo tal como hidroxipropilcelulosa. Las dispersiones también se pueden preparar en glicerol, líquido, polietilenglicoles, y mezclas de estos en aceites. Bajo condiciones ordinarias de almacenamiento y uso, estas preparaciones contienen un preservativo para prevenir el crecimiento de microorganismos.

Las formas inyectables de uso farmacéuticamente adecuadas incluyen soluciones o dispersiones estériles acuosas y polvos estériles para la preparación extemporánea de soluciones o dispersiones inyectables estériles. En todos los casos, la forma debe ser estéril y debe ser fluida para que exista fácil administración con jeringa. Debe ser estable bajo condiciones de fabricación y almacenamiento y se debe preservar contra la acción contaminante de microorganismos tales como bacteria y hongos. Los vehículos pueden ser un solvente o medio de dispersión que contiene, por ejemplo, agua, etanol, poliol (por ejemplo, glicerol, propilenglicol, y polietilenglicol líquido), mezclas adecuadas de estos y aceites vegetales.

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

El compuesto de Referencia 1

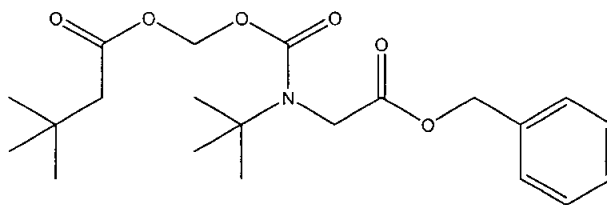
Éster de bencilo de ácido (Terc-butil-clorometoxicarbonil-amino)-acídico.



A una solución de Éster de bencilo de ácido Terc-butilamino-acético en diclorometano se agrega dos equivalentes de [1,8-bis(dimetilamino)naftaleno, N,N,N',N'-tetrametil-1,8-naftalenodiamina]. La mezcla de reacción se enfría luego en un baño de hielo y se agrega un equivalente de cloroformato de clorometilo. La reacción luego se calienta a temperatura ambiente y se continúa la agitación durante 24 hr. Esta luego se lava con agua y luego con solución salina.

El compuesto de Referencia 2

Éster de (benciloxycarbonilmetil-Terc-butil-carbamoiiloxi)-metilo de ácido 3,3-Dimetil-butírico



Ácido terc-butilacético e hidróxido de tetrabutylamonio 1.0 M en metanol se agitan durante una hora, el metanol se remueve y se agrega THF. A esta solución se agrega luego N-(Terc-butil)-N-[(clorometoxi)carbonil]glicinato de bencilo y se agita a temperatura ambiente durante 24 hr. El solvente se remueve y el residuo se diluye con éter, entonces se lava con agua, luego con

solución salina. Este se seca sobre sulfato de magnesio, se filtra y el solvente se remueve. MS (ESI) m/z 394.25

El compuesto de Referencias 3-55 (Tabla A)

Siguiendo substancialmente el método descrito anteriormente en el Compuesto de Referencia 2 utilizando éster de bencilo de ácido (Terc-butil-clorometoxicarbonil-amino)-acídico del Compuesto de Referencia 1 y el ácido carboxílico apropiado, los compuestos de Referencias 3-55 de esta invención que se listan abajo en la Tabla A están preparados.

Tabla A

Comp. de Ref. No.	Nombre	Espectro
3	4-Terc-butilbenzoato de ({[[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 456.23
4	2,2-dimetilbutanoato de ({[[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo	MS m/z 01-400386LMS;
5	2-metilpropanoato de ({[[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 366.24; HRMS: calculado para C19H27NO6 + Na+, 388.17306; encontrado (ESI+, [M+NA]1+), 388.17295;
6	ciclopentanocarboxilato de ({[[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 392.23;
7	4-metilbenzoato de ({[[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 414.24; MS (ESI) m/z 436.23; HRMS: calculado para

395

Comp. de Ref. No.	Nombre	Espectro
		C ₂₃ H ₂₇ N ₆ O ₆ + Na ⁺ , 436.17306; encontrado (ESI ⁺ , [M+NA] ¹⁺), 436.17291;
8	heptanoato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 408.24;
9	propionato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 352.17; HRMS: calculado para C ₁₈ H ₂₅ N ₆ O ₆ + H ⁺ , 352.17546; encontrado (ESI ⁺ , [M+H] ⁺), 352.17551;
10	ciclohexanocarboxilato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 406.26;
11	3,5-dimetilbenzoato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo MS (ESI) m/z 428.25; MS (ESI) m/z 87.54;	MS (ESI) m/z 428.25; MS (ESI) m/z 87.54;
12	4-fluorobenzoato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 418.2; MS (ESI) m/z 440.2;
13	3-metilbutanoato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 380.27; HRMS: calculado para C ₂₀ H ₂₉ N ₆ O ₆ + Na ⁺ , 402.18871; encontrado (ESI ⁺ , [M+NA] ¹⁺), 402.18882;
14	N- (Terc-butil) -N- ({[(ciclopentilacetil) oxi] metoxi} carbonil) glicinato De bencilo	MS (ESI) m/z 406.2;
15	4- (trifluorometil) benzoato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (CI (ISOBUTANO)) m/z 468.13;

396

Comp. de Ref. No.	Nombre	Espectro
16	ciclopropanocarboxilato de ({[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 364.26;
17	adamantan-1-carboxilato de ({[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 458.3;
18	pentanoato de ({[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 380.2;
19	ciclobutanocarboxilato de ({[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 378.2; MS (ESI) m/z 400.2;
20	3-ciclohexilpropanoato de ({[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 434.3; MS (ESI) m/z 451.3; HRMS: calculado para C24H35NO6 + Na+, 456.23566; encontrado (ESI+, [M+NA] 1+), 456.23661;
21	N-(Terc-butil)-N-(({[4-fluorofenoxi]acetil}oxi)metoxi)carbonil]glicinato de bencilo	
22	N-(Terc-butil)-N-(({[ciclohexilacetil]oxi}metoxi)carbonil)glicinato de bencilo	MS (ESI) m/z 420.2; MS (ESI) m/z 442.2;
23	2,6-dimetilbenzoato de ({[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 428.2;
24	N-(Terc-butil)-N-(({[fenilacetil]oxi}metoxi)carbonil)glicinato de bencilo	MS (ESI) m/z 414.2; MS (ESI) m/z 436.2; HRMS: calculado para C23H27NO6 + H+, 414.19112; encontrado (ESI+, [M+H] 1+), 414.19143;
25	Pivalato de ({[2-(benciloxi)-2-oxoetil](Terc-	MS (ESI) m/z 380.1;

322

Comp. Ref. No.	de	Nombre	Espectro
		butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 781.3; HRMS: calculado para C20H29NO6 + H+, 380.20677; encontrado (ESI+, [M+H] 1+), 380.20649;
26		1-benzofuran-2-carboxilato de ({ [2- (benciloxi) -2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 440; MS (ESI) m/z 901.1; HRMS: calculado para C24H25NO7 + H+, 440.17038; encontrado (ESI+, [M+H] 1+), 440.17005;
27		1-metil-1H-pirrol-2-carboxilato de ({ [2- (benciloxi) -2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 403.3; MS (ESI) m/z 827.7;
28		1,1'-bifenil-4-carboxilato de ({ [2- (benciloxi) -2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 476.2; HRMS: calculado para C28H29NO6 + Na+, 498.18871; encontrado (ESI+, [M+NA] 1+), 498.18857;
29		4-metoxibenzoato de ({ [2- (benciloxi) -2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 430.3; MS (ESI) m/z 452.3;
30		1H-indol-2-carboxilato de ({ [2- (benciloxi) -2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 439.1; HRMS: calculado para C24H26N2O6 + Na+, 461.16831; encontrado

Comp. de Ref. No.	Nombre	Espectro
		(ESI+, [M+NA] 1+), 461.168;
31	N-(Terc-butil)-N-({[(difenilacetil)oxi]metoxi}carbonil)glicinato de bencilo	MS (ESI) m/z 490.2;
32	1-naftoato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 450.1;
33	2-naftoato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 450.1;
34	-metil-1H-indol-3-carboxilato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo 1	MS (ESI) m/z 453.3; MS (ESI) m/z 905.6; MS (ESI) m/z 927.5;
35	quinolin-2-carboxilato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 451.2; MS (ESI) m/z 901.4;
36	nicotinato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 401.1;
37	isonicotinato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 401;
38	2,6-difluorobenzoato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 436.2; MS (ESI) m/z 893.4; MS (ESI) m/z 453.2;
39	2-fluorobenzoato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 418.2; MS (ESI) m/z 857.5; MS (ESI) m/z 440.2;
40	2-(trifluorometil)benzoato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 468.1; MS (ESI) m/z 490.2;
41	4-(1H-pirrol-1-il)benzoato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 465.1; MS (ESI) m/z 482.1;
42	1,1'-bifenil-2-carboxilato de ({[2-(benciloxi)-2-oxoetil] (Terc-butil) amino] carbonil} oxi) metilo	MS (ESI) m/z 476.3; MS (ESI) m/z 493.3;

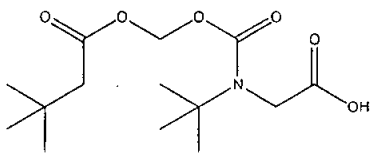
399

Comp. Ref. No.	de	Nombre	Espectro
			MS (ESI) m/z 951.6;
43		2,4,6-trimetilbenzoato de ({[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 442.3; MS (ESI) m/z 459.3;
44		4-isopropoxibenzoato de ({[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 458.3;
45		3,4,5-trimetoxibenzoato de ({[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 490.3; MS (ESI) m/z 996.5; MS (ESI) m/z 979.5;
46		3,5-dimetoxibenzoato de ({[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 460.3; MS (ESI) m/z 936.5; MS (ESI) m/z 919.5;
47		Éster de (benciloxicarbonilmetil-Terc-butil-carbamoiloxi)-metilo de ácido 3-fenil-acrílico	PE agregado cpd
48		3-metil-1-benzofuran-2-carboxilato de ({[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 454.2; MS (ESI) m/z 907.5; HRMS: calculado para C25H27NO7 + Na+, 476.16797; encontrado (ESI, [M+NA]1+), 476.16858;
49		N-{([3,5-bis(trifluorometil)fenil]acetil}oxi)metoxi]carbonil}-N-(Terc-butil)glicinato de bencilo	MS m/z 01-305267LMS; HRMS: calculado para C25H25F6NO6 + Na+, 572.14783; encontrado (ESI+, [M+NA]1+), 572.14702;
50		4-(heptiloxi)benzoato de ({[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 514.3; HRMS: calculado

Comp. Ref. No.	de	Nombre	Espectro
			para C ₂₉ H ₃₉ N ₇ O ₇ + H ⁺ , 514.27993; encontrado (ESI ⁺ , [M+H] ¹⁺), 514.28023;
51		2-(2-feniletíl)benzoato de (benciloxi)-2-oxoetil] (Terc- butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 526.2;
52		4-(dodeciloxi)benzoato de (benciloxi)-2-oxoetil] (Terc- butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 584.3; HRMS: calculado para C ₃₄ H ₄₉ N ₇ O ₇ + H ⁺ , 584.35818; encontrado (ESI ⁺ , [M+H] ¹⁺), 584.3574;
53		4-(acetilamino)benzoato de (benciloxi)-2-oxoetil] (Terc- butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 457.2; MS (ESI) m/z 913.4; HRMS: calculado para C ₂₄ H ₂₈ N ₂ O ₇ + Na ⁺ , 479.17887; encontrado (ESI ⁺ , [M+NA] ¹⁺), 479.17909;
54		antraceno-9-carboxilato de (benciloxi)-2-oxoetil] (Terc- butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 500.2; MS (ESI) m/z 999.5;
55		4-benzoilbenzoato de (benciloxi)-2-oxoetil] (Terc- butil)amino]carbonil}oxi)metilo	MS (ESI) m/z 504.2;

El compuesto de Referencia 56

Éster de (Terc-butil-carboximetil-carbamoiloxi)-metilo de ácido
3,3-Dimetil-butírico.



El producto del Compuesto de Referencia 2, 10% de paladio sobre carbono en acetato de etilo se hidrogena en un agitador Parr a ca. 40 psi durante cerca de una hora. El catalizador se filtra y el solvente se remueve para dar el producto correspondiente de ácido carboxílico del ejemplo MS(ESI) m/z 394.25.

Ejemplos de Referencia 57-108 (Tabla B)

Siguiendo substancialmente el método descrito anteriormente en el Compuesto de Referencia 56 los compuestos de Referencia 57-108 de esta invención se listan abajo en la Tabla B son preparados utilizando los ésteres de bencilo apropiados de los Compuestos de Referencia 3-55.

Tabla B

Cmp. Ref. No.	Nombre	Espectro
57	N-(Terc-butil)-N-({[(4-Terc-butilbenzoil)oxi]metoxi}carbonil)glicina	MS (ESI) m/z 366.18
58	N-(Terc-butil)-N-{[(isobutitriloxi)metoxi]carbonil}glicina	MS (ESI) m/z 274.05; MS (ESI) m/z 549.13; HRMS: calculado para C12H21NO6

Cmp. Ref. No.	Nombre	Espectro
		+ H+, 276.14416; encontrado (ESI+, [M+H] 1+), 276.14314;
59	N-(Terc-butil)-N- ({[(ciclopentilcarbonil)oxi]metoxi}carbonil)glicina	MS (ESI) m/z 300.04; MS (ESI) m/z 601.1; HRMS: calculado para 2 C14H23NO6 - H+, 601.29780; encontrado (ESI-, [2M-H] 1-), 601.29741;
60	N-(Terc-butil)-N-({[(4-metilbenzoil)oxi]metoxi}carbonil)glicina	MS (ESI) m/z 324.19; HRMS: calculado para C16H21NO6 + Na+, 346.12611; encontrado (ESI+, [M+NA] 1+), 346.12625;
61	N-(Terc-butil)-N- {[(heptanoiloxi)metoxi]carbonil}glicina	MS (ESI) m/z 316.25; MS (ESI) m/z 633.54;
62	N-(Terc-butil)-N- {[(propioniloxi)metoxi]carbonil}glicina	MS (ESI) m/z 260.05; MS (ESI) m/z 521.13; HRMS: calculado para C11H19NO6 + Na+, 284.11046; encontrado (ESI, [M+NA] +),

Cmp. Ref. No.	Nombre	Espectro
		284.11017;
63	N- (Terc-butil) -N- ({ [(ciclohexilcarbonil)oxi]metoxi}carbonil)glicina	MS (ESI) m/z 314.06; MS (ESI) m/z 629.14; HRMS: calculado para 2 C15H25NO6 - H+, 629.32910; encontrado (ESI-, [2M-H] 1-), 629.32842;
64	N- (Terc-butil) -N- ({ [(3,5- dimetilbenzoil)oxi]metoxi}carbonil)glicina	MS (ESI) m/z 338.16;
65	N- (Terc-butil) -N- ({ [(4- fluorobenzoil)oxi]metoxi}carbonil)glicina	MS (ESI) m/z 326; MS (ESI) m/z 653; HRMS: calculado para C15H18FNO6 + Na+, 350.10103; encontrado (ESI+, [M+NA] 1+), 350.10131;
66	N- (Terc-butil) -N- ({ [(3- metilbutanoil)oxi]metoxi}carbonil)glicina	HRMS: calculado para C13H23NO6 + Na+, 312.14176; encontrado (ESI+, [M+NA] 1+), 312.14197;
67	N- (Terc-butil) -N- ({ [(ciclopentilacetil)oxi]metoxi}carbonil)glicina	MS (ESI) m/z 314; MS (ESI) m/z 629.1; HRMS: calculado para C15H25NO6 + H+, 316.17546; encontrado

Cmp. Ref. No.	Nombre	Espectro
		(ESI+, [M+H] 1+), 316.17503;
68	N-(Terc-butil)-N-([4-(trifluorometil)benzoil]oxi}metoxi}carbonil}glicina	MS (ESI) m/z 376; MS (ESI) m/z 752.9;
69	N-(Terc-butil)-N-([[(ciclopropilcarbonil)oxi]metoxi}carbonil}glicina	HRMS: calculado para C12H19NO6 + Na+, 296.11046; encontrado (ESI+, [M+NA] 1+), 296.11061;
70	N-([[(1-adamantilcarbonil)oxi]metoxi}carbonil)-N-(Terc-butil)glicina	MS (ESI) m/z 368.21; MS (ESI) m/z 757.37;
71	N-(Terc-butil)-N-([[(pentanoiloxi)metoxi}carbonil}glicina	MS (ESI) m/z 288; MS (ESI) m/z 577.1; HRMS: calculado para C13H23NO6 + H+, 290.15982; encontrado (ESI+, [M+H] 1+), 290.15951;
72	N-(Terc-butil)-N-([[(ciclobutilcarbonil)oxi]metoxi}carbonil}glicina	MS (ESI) m/z 288.1; MS (ESI) m/z 310.1; HRMS: calculado para C13H21NO6 + H+, 288.14416; encontrado (ESI+, [M+H] 1+), 288.14435;
73	N-(Terc-butil)-N-([[(3-ciclohexilpropanoil)oxi]metoxi}carbonil}glicina	MS (ESI) m/z 344.2; MS (ESI)

Cmp. Ref. No.	Nombre	Espectro
		m/z 709.4; HRMS: calculado para C17H29NO6 + Na+, 366.18871; encontrado (ESI+, [M+NA] 1+), 366.18863;
74	N- (Terc-butyl) -N- ([(4-fluorofenoxi) acetil] oxi) metoxi) carbonil) glicina	MS (ESI) m/z 356.1;
75	N- (Terc-butyl) -N- ([(ciclohexilacetil) oxi] metoxi) carbonil) glicina	MS (ESI) m/z 328; MS (ESI) m/z 657.1;
76	N- (Terc-butyl) -N- ([(2,6-dimetilbenzoil) oxi] metoxi) carbonil) glicina	MS (ESI) m/z 338.2;
77	N- (Terc-butyl) -N- ([(fenilacetil) oxi] metoxi) carbonil) glicina	MS (ESI) m/z 322.1; MS (ESI) m/z 645.2; HRMS: calculado para C16H21NO6 + H+, 324.14416; encontrado (ESI+, [M+H] 1+), 324.14351;
78	N- (Terc-butyl) -N- ([(2,2-dimetilpropanoil) oxi] metoxi) carbonil) glicina	MS (ESI) m/z 288.1; MS (ESI) m/z 577.1; HRMS: calculado para C13H23NO6 + H+, 290.15982; encontrado (ESI+, [M+H] 1+), 290.15965;
79	N- ([(1-benzofuran-2-ilcarbonil) oxi] metoxi) carbonil) -N- (Terc-butyl) glicina	MS (ESI) m/z 350; MS (ESI) m/z 721;

Cmp. Ref. No.	Nombre	Espectro
		HRMS: calculado para C17H19NO7 + H+, 350.12343; encontrado (ESI+, [M+H] 1+), 350.12327;
80	N-(Terc-butyl)-N-([[(1-metil-1H-pirrol-2-il)carbonil]oxi]metoxi)carbonil]glicina	MS (ESI) m/z 313; MS (ESI) m/z 647.1;
81	N-([[(1,1'-bifenil-4-ilcarbonil)oxi]metoxi]carbonil)-N-(Terc-butyl)glicina	MS (ESI) m/z 386.2; HRMS: calculado para C21H23NO6 + Na+, 408.14176; encontrado (ESI+, [M+NA] 1+), 408.14195;
82	N-(Terc-butyl)-N-([[(4-metoxibenzoil)oxi]metoxi]carbonil)glicina	MS (ESI) m/z 338.1; MS (ESI) m/z 677.3; HRMS: calculado para C16H21NO7 + Na+, 362.12102; encontrado (ESI+, [M+NA] 1+), 362.12095;
83	N-(Terc-butyl)-N-([[(1H-indol-2-ilcarbonil)oxi]metoxi]carbonil)glicina	MS (ESI) m/z 349.2; HRMS: calculado para C17H20N2O6 + Na+, 371.12136; encontrado (ESI+, [M+NA] 1+), 371.12148;

Cmp. Ref. No.	Nombre	Espectro
84	N-(Terc-butil)-N- ([{(difenilacetil)oxi]metoxi}carbonil)glicina	MS (ESI) m/z 298.2;
85	N-(Terc-butil)-N-{{(1- naftoiloxi)metoxi}carbonil}glicina	MS (ESI) m/z 358.2; MS (ESI) m/z 717.4; MS (ESI) m/z 1076.6;
Cmp Ref No.	Nombre	Espectro
86	N-(Terc-butil)-N-{{(2- naftoiloxi)metoxi}carbonil}glicina	MS (ESI) m/z 360.1; MS (ESI) m/z 472.1;
87	N-(Terc-butil)-N-[[{[(1-metil-1H-indol-3- il)carbonil]oxi]metoxi}carbonil]glicina	MS (ESI) m/z 361.2; MS (ESI) m/z 1085.7; MS (ESI) m/z 723.5; HRMS: calculado para C18H22N2O6 + H+, 363.15506; encontrado (ESI+, [M+H]1+), 363.15556;
88	N-(Terc-butil)-N-({[(quinolin-2- ilcarbonil)oxi]metoxi}carbonil)glicina	MS (ESI) m/z 359.2; MS (ESI) m/z 1079.7; MS (ESI) m/z 719.4;
89	N-(Terc-butil)-N-({[(piridin-3- ilcarbonil)oxi]metoxi}carbonil)glicina	MS (ESI) m/z 309.2; MS (ESI) m/z 929.5; MS (ESI) m/z 619.3;
90	N-(Terc-butil)-N- [{(isonicotinoiloxi)metoxi}carbonil}glicina	MS (ESI) m/z 311.1;

Cmp. Ref. No.	Nombre	Espectro
		MS (ESI) m/z 333.1;
91	N-(Terc-butil)-N-([(2,6-difluorobenzoyl)oxi]metoxi}carbonil)glicina	MS (ESI) m/z 390.2; MS (ESI) m/z 689.3;
92	N-(Terc-butil)-N-([(2-fluorobenzoyl)oxi]metoxi}carbonil)glicina	MS (ESI) m/z 326.2; MS (ESI) m/z 980.6; MS (ESI) m/z 653.3;
93	N-(Terc-butil)-N-([(2-(trifluorometil)benzoyl)oxi]metoxi}carbonil]glicina	MS (ESI) m/z 422.1; MS (ESI) m/z 753;
94	N-(Terc-butil)-N-([(4-pirrolidin-1-ilbenzoyl)oxi]metoxi}carbonil)glicina	MS (ESI) m/z 379.2;
95	N-([(1,1'-bifenil-2-ilcarbonil)oxi]metoxi}carbonil)-N-(Terc-butil)glicina	MS (ESI) m/z 384.3; MS (ESI) m/z 1154.7; MS (ESI) m/z 769.5;
96	N-(Terc-butil)-N-([(mesitilcarbonil)oxi]metoxi}carbonil)glicina	MS (ESI) m/z 701.5; MS (ESI) m/z 386.2; MS (ESI) m/z 1052.8;
97	N-(Terc-butil)-N-([(4-isopropoxibenzoil)oxi]metoxi}carbonil)glicina	MS (ESI) m/z 733.3; MS (ESI) m/z 1100.3; MS (ESI) m/z 412.2; HRMS: calculado para C18H25NO7 + H+, 368.17038; encontrado (ESI+, [M+H]1+), 368.17069;
98	N-(Terc-butil)-N-([(3,4,5-trimetoxibenzoil)oxi]metoxi}carbonil)glicina	MS (ESI) m/z 398; MS (ESI)

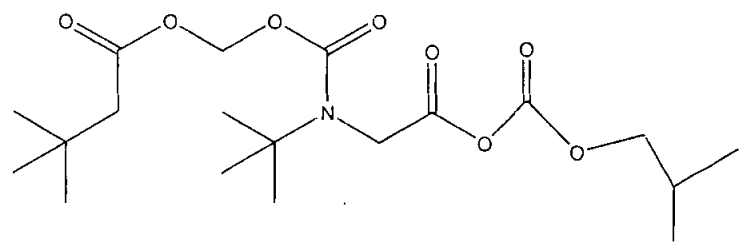
Cmp. Ref. No.	Nombre	Espectro
		m/z 797.2; MS (ESI) m/z 1195.9; HRMS: calculado para C18H25NO9 + H+, 400.16021; encontrado (ESI+, [M+H] 1+), 400.1610
99	N-(Terc-butil)-N-({[(3,5-dimetoxibenzoil)oxi]metoxi}carbonil)glicina	MS (ESI) m/z 368.1; MS (ESI) m/z 737.1; MS (ESI) m/z 414; HRMS: calculado para C17H23NO8 + H+, 370.14965; encontrado (ESI+, [M+H] 1+), 370.15016;
100	N-(Terc-butil)-N-[({(2E)-3-fenilprop-2-enoil)oxi}metoxi)carbonil]glicina	MS (ESI) m/z 334.2; MS (ESI) m/z 669.4; MS (ESI) m/z 1004.6; HRMS: calculado para C17H21NO6 + Na+, 358.12611; encontrado (ESI+, [M+NA] 1+), 358.12763;
10 1	N-(Terc-butil)-N-[({(3-metil-1-benzofuran-2-il)carbonil)oxi}metoxi)carbonil]glicina	MS (ESI) m/z 725.4; MS (ESI) m/z 1088.6; MS (ESI) m/z 398.2;

Cmp. Ref. No.	Nombre	Espectro
		HRMS: calculado para C ₁₈ H ₂₁ NO ₇ + H ⁺ , 364.13908; encontrado (ESI, [M+H] ¹⁺), 364.13956;
10 2	N-{[{[3,5-bis(trifluorometil)fenil]acetil}oxi]metoxi]carbonil}-N-(Terc-butil)glicina	MS (ESI) m/z 458.1; MS (ESI) m/z 917.1; HRMS: calculado para C ₁₈ H ₁₉ F ₆ NO 6 + H ⁺ , 460.11893; encontrado (ESI+, [M+H] ¹⁺), 460.11854;
10 3	N-(Terc-butil)-N-[[{[4-(heptiloxi)benzoil]oxi}metoxi]carbonil]glicina	MS (ESI) m/z 422.2; MS (ESI) m/z 468.3; MS (ESI) m/z 845.3; HRMS: calculado para C ₂₂ H ₃₃ NO ₇ + H ⁺ , 424.23298; encontrado (ESI+, [M+H] ¹⁺), 424.23295;
10 4	N-(Terc-butil)-N-[[{[2-(2-feniletal)benzoil]oxi}metoxi]carbonil]glicina	MS (ESI+) m/z 414.19088; MS (ESI+) m/z 414.19112; HRMS: calculado para C ₂₃ H ₂₇ NO ₆ + H ⁺ , 414.19112; encontrado

Cmp. Ref. No.	Nombre	Espectro
		(ESI+, [M+H] 1+), 414.19088;
105	N-(Terc-butil)-N-[(4-(dodeciloxi)benzoil)oxi]metoxi)carbonil]glicina	MS (ESI+) m/z 494.31095; MS (ESI+) m/z 494.31123; HRMS: calculado para C27H43NO7 + H+, 494.31123; encontrado (ESI+, [M+H] 1+), 494.31095;
106	N-[(4-(acetilamino)benzoil)oxi]metoxi)carbonil]-N-(Terc-butil)glicina	MS (ESI) m/z 367.1; MS (ESI) m/z 733.1;
107	N-[(9-antrilcarbonil)oxi]metoxi)carbonil)-N-(Terc-butil)glicina	MS (ESI) m/z 408.3; MS (ESI) m/z 1226.7; MS (ESI) m/z 817.5;
108	N-[(4-benzoilbenzoil)oxi]metoxi)carbonil)-N-(Terc-butil)glicina	MS (ESI) m/z 414.2;

El compuesto de Referencia 109

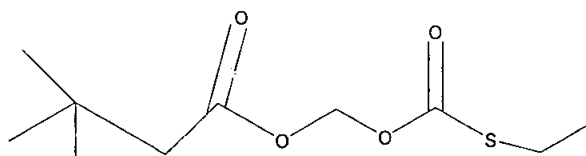
Éster de [Terc-butil-(2-isobutoxicarboniloxi-2-oxo-etil)-carbamoiloxi]-metilo ácido 3,3-Dimetil-butírico



A una solución del Compuesto de Referencia 56 en diclorometano a temperatura ambiente se agrega 1.2 equivalente de [1,8-bis(dimetilamino)naftaleno, N,N,N',N'-tetrametil-1,8-naftalenodiamina] y 0.95 equivalente de iso-butilcloroformato. La reacción se agita durante 24 horas, se diluye con diclorometano, se lava con HCl diluido, solución salina, y luego con agua. Esta se seca con sulfato de sodio. El solvente se remueve y el producto se utiliza en la próxima etapa sin purificación adicional.

El compuesto de Referencia 110

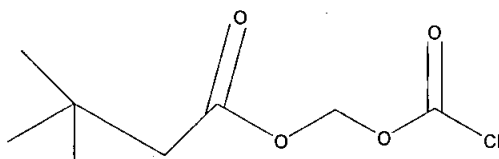
Éster de etilsulfanilcarboniloximetilo de ácido 3,3-Dimetilbutírico



A una solución de ácido t-butilacético (0.025 mol, 3 g) en metanol se agrega hidróxido de tetrabutilamonio (1M/metanol, 25 ml). La mezcla se agita durante 1 h y el solvente se remueve con un residuo. El residuo se disuelve en 150 ml de cloruro de metileno y 150 ml de agua y una solución de carbonotioato de O-clorometilo S-etilo (0.025 mol, 3.85 f) se agrega en 50 ml de cloruro de metileno. La mezcla se agita a temperatura ambiente durante 24 h. La capa separada de cloruro de metileno, se lava con agua, solución salina y se seca sobre sulfato de sodio. El solvente se remueve bajo vacío y el residuo se agita en 300 ml de éter durante 24 h. El sólido blanco resultante se filtra, el

sólido se desecha y el solvente se remueve del filtrado para dar 6 g de un aceite crudo.

El compuesto de Referencia 111

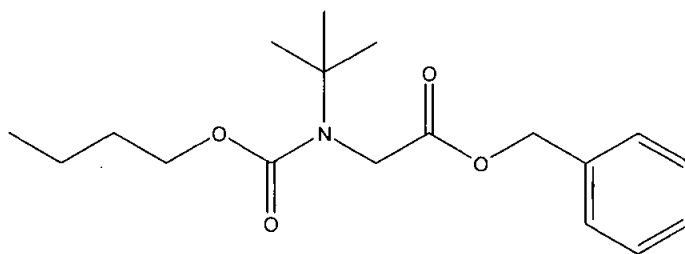


A una solución agitada de éster de etilsulfanilcarboniloximetilo de ácido 3,3-dimetilbutírico (Compuesto de Referencia 110) (0.025 ml, 6 g) en cloruro de metileno a -20° C (hielo seco/tetracloruro de carbono) se agrega cloruro de sulfurilo (0.025 mol, 3.5 g). Después de 10 min, se agrega 0.1 ml de etereato de trifluoruro de boro. La mezcla se agita a 0° C durante 1 h, a temperatura ambiente durante 30 min. Los volátiles se remueven mediante destilación para producir 4.9 g del cloruro de ácido deseado.

Siguiendo el procedimiento del Compuesto de Referencia 111 el cloruro de ácido correspondiente que se utiliza en el Ejemplos 112 a 120 se prepara.

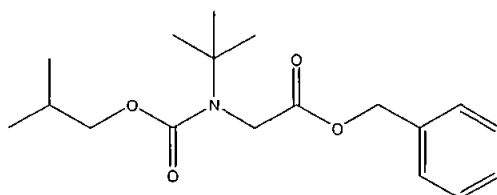
El compuesto de Referencia 112

N-(butoxicarbonil)-N-(Terc-butil)glicinato de bencilo



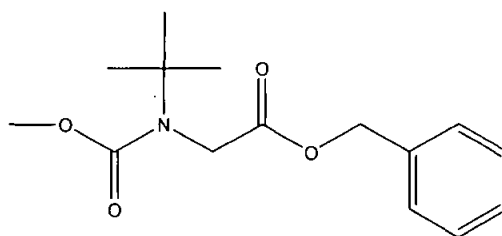
El compuesto de Referencia 113

N-(Terc-butil)-N-(isobutoxicarbonil)glicinato de bencilo



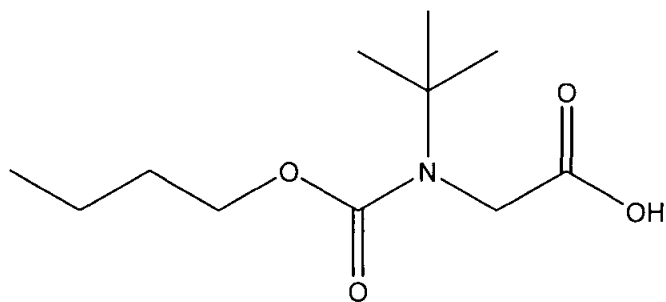
El compuesto de Referencia 114

N-(Terc-butil)-N-(metoxycarbonil)glicinato de bencilo



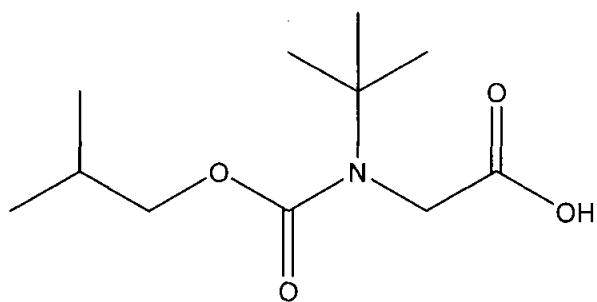
El compuesto de Referencia 115

N-(butoxicarbonil)-N-(Terc-butil)glicina



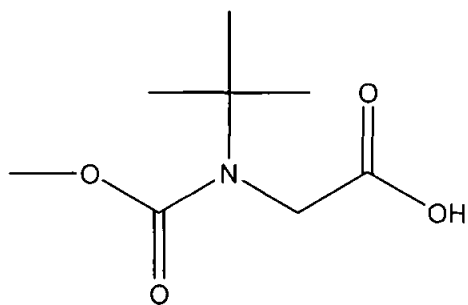
El compuesto de Referencia 116

N-(Terc-butil)-N-(isobutoxicarbonil)glicina



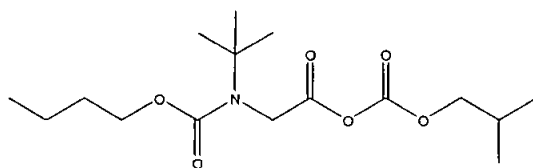
El compuesto de Referencia 117

N-(Terc-butil)-N-(metoxycarbonil)glicina



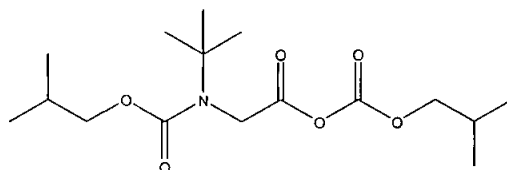
El compuesto de Referencia 118

isobutoxicarbonilo N-(butoxicarbonil)-N-(Terc-butil)glicinato



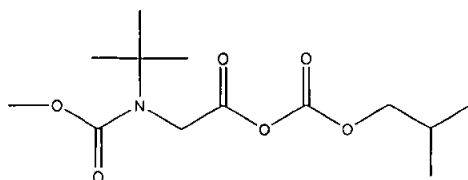
El compuesto de Referencia 119

isobutoxycarbonyl N-(tert-butyl)-N-(isobutoxycarbonyl)glycinate



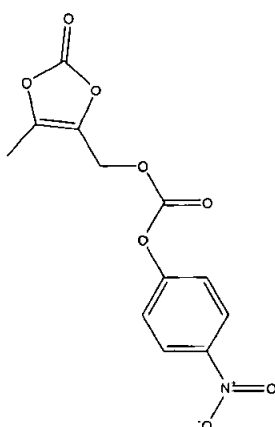
El compuesto de Referencia 120

isobutoxycarbonyl N-(tert-butyl)-N-(methoxycarbonyl)glycinate



El compuesto de Referencia 121

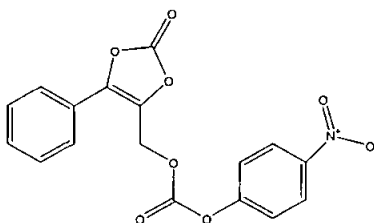
4-nitrophenylcarbonato de (5-metil-2-oxo-1,3-dioxol-4-il)metilo



El producto del ejemplo de Referencia se prepara utilizando las condiciones descritas por R. Sakamoto et al, Chem. Pharm. Bull. 32(6), 2241-2248(1984).

El compuesto de Referencia 122

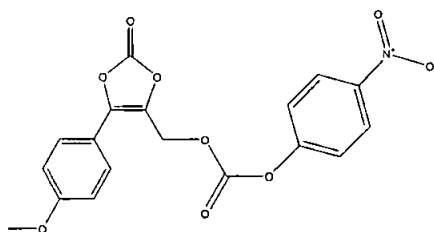
Carbonato de 4-nitrofenil(2-oxo-5-fenil-1,3-dioxol-4-il)metilo



El producto del Ejemplo de Referencia se prepara utilizando las condiciones descritas por R. Sakamoto et al, Chem. Pharm. Bull. 32(6), 2241-2248(1984).

El compuesto de Referencia 123

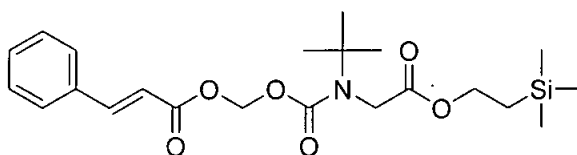
[5-(4-metoxifenil)-2-oxo-1,3-dioxol-4-il]metilo 4-nitrofenil
carbonato



El producto del Ejemplo de Referencia se prepara utilizando las condiciones descritas por R. Sakamoto et al, Chem. Pharm. Bull. 32(6), 2241-2248(1984).

El compuesto de Referencia 124

(2E)-3-fenilacrilato de 4-Terc-butil-10,10-dimetil-3,6-dioxo-2,7-dioxa-4-aza-10-silaundec-1-il

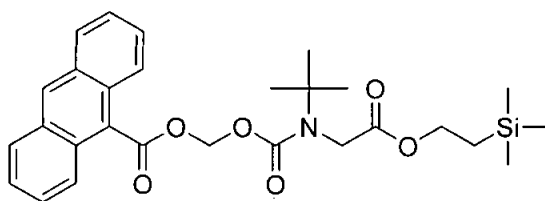


Ácido trans-cinnámico (23.1 mmol) e hidróxido de tetrabutylamonio 1.0 M (22.2 mmol) en metanol se agita durante una hora, y el metanol se remueve. Se agrega THF. A esta solución se agrega 2-(Terc-butil((clorometoxi)carbonil)amino)-acetato de 2-(trimetilsilyl)etilo (18.5 mmol) y la mezcla se agita a temperatura ambiente durante 24 hr. El solvente se remueve y el residuo se diluye con éter. La solución resultante se lava con agua y solución salina. La capa orgánica se seca sobre sulfato de magnesio, se filtra y se concentra bajo presión reducida para producir 5.01 g (61%) MS (ESI) m/z 436.3.

Utilizando substancialmente el mismo procedimiento como se describió anteriormente para el Compuesto de Referencia 124 los siguiente compuestos de Referencia se preparan del ácido carboxílico apropiado:

El compuesto de Referencia 125

antraceno-9-carboxilato de 4-Terc-butil-10,10-dimetil-3,6-dioxo-2,7-dioxa-4-aza-10-silaundec-1-il



MS (ESI) m/z 510.3

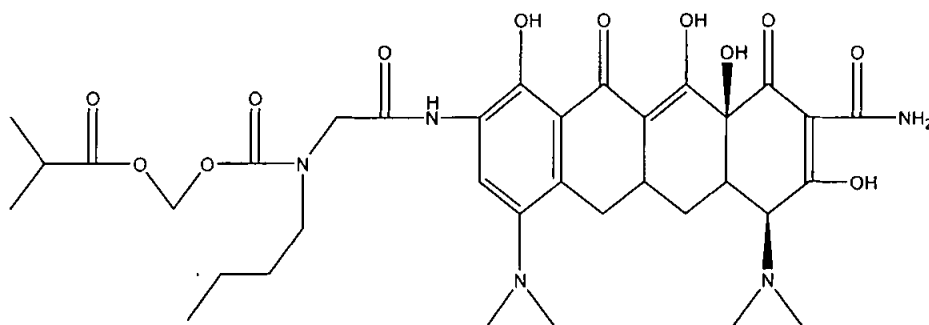
El compuesto de Referencia 126

4-benzoilbenzoato de 4-Terc-butil-10,10-dimetil-3,6-dioxo-2,7-dioxa-4-aza-10-silaundecil

MS (ESI) m/z 536.2

Ejemplo 1

2-metilpropanoato de (((2-(((7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil)oxi)metilo



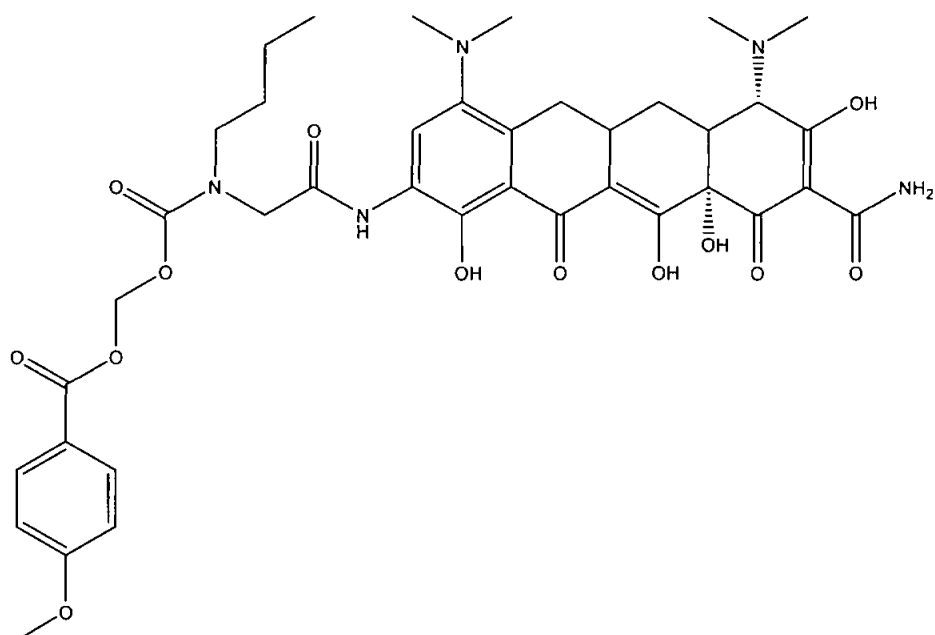
A una solución de n-Butilglicilciclina en acetonitrilo/DMPA (1:5), se agrega carbonato de sodio. La mezcla de reacción se agita durante 5 min y se agrega éster de 2-metil-[(clorocarbonil)oxi]metilo de ácido propanoico y se prepara de acuerdo a los métodos descritos en M. Folkmann y F.J. Lund,

Synthesis, Diciembre 1990, 1159-1166. La agitación se continúa durante cerca de 30 a 45 minutos (o se monitorea por MS (ES)). Sobre la terminación de la reacción, 0.5 mL de metanol se agrega y la mezcla se vierte suavemente en una mezcla de isopropanol y éter. Se agrega HCl 1.0M en éter y el sólido se filtra. El sólido se disuelve en agua y se extrae con cloruro de metileno para dar el producto del ejemplo. MS (ESI) m/z 730.28 (M+H);

El siguiente procedimiento del Ejemplo 1, y el cloruro de ácido correspondiente se preparan por los métodos descritos en M. Folkmann y F.J. Lund, Synthesis, Diciembre 1990, 1159-1166 y N-butilglicilciclina o N-propilglicilciclina en los siguientes Ejemplos 2-41 se preparan

Ejemplo 2

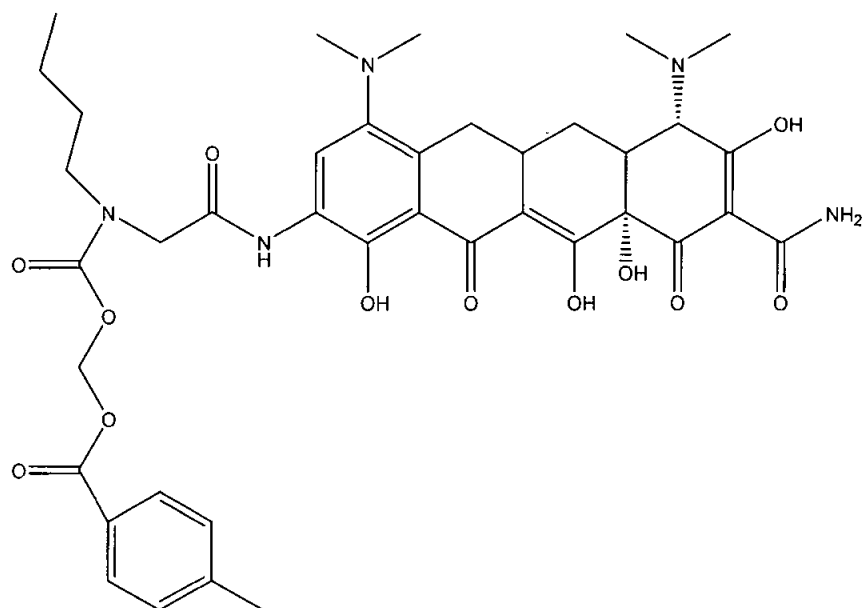
4-metoxibenzoato de (((2-(((7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil)oxi)metilo



El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando 4-metoxibenzoato de [(clorocarbonil)oxi]metilo y N-butilglicilciclina para dar el producto del ejemplo.

Ejemplo 3

4-metilbenzoato de ({[(2-{{[(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(butil)amino]carbonil}oxi)metilo

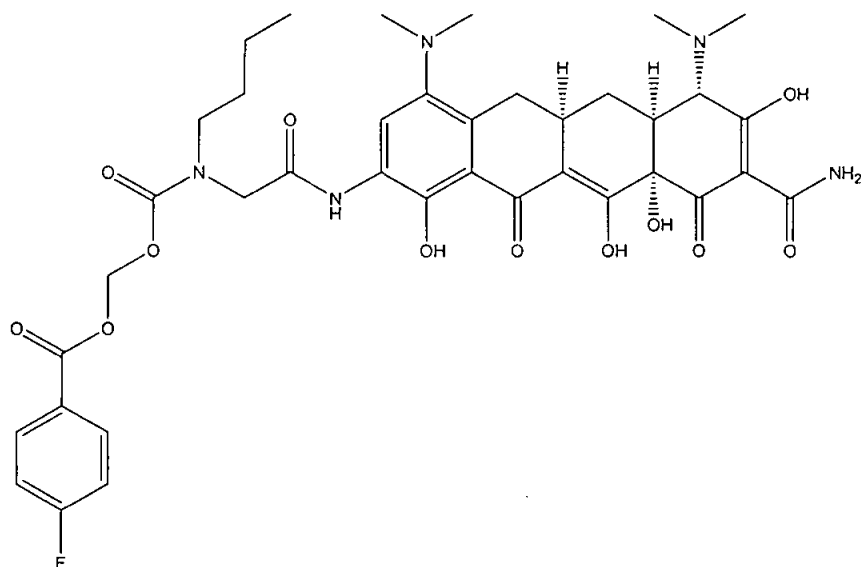


El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando 4-metilbenzoato de [(clorocarbonil)oxi]metilo y N-butilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 778.3 ((M+H)+);

Ejemplo 4

4-fluorobenzoato de ({[(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(butil)amino]carbonil}oxi)metilo

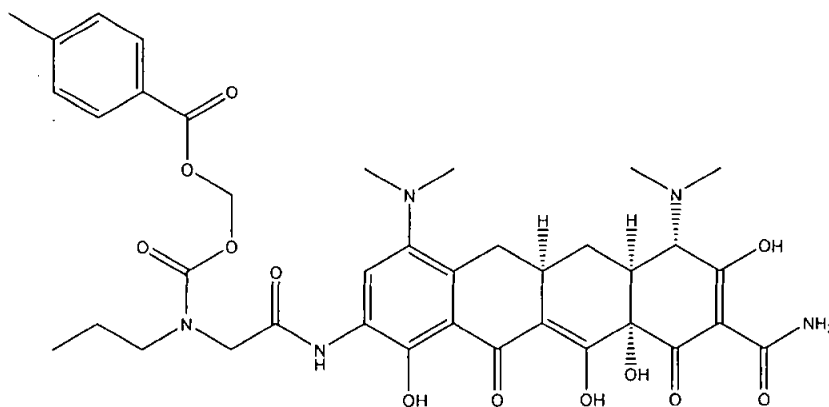


El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando 4-fluorobenzoato de [(clorocarbonil)oxi]metilo y N-butilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 782.3 ((M+H)+);

Ejemplo 5

4-metilbenzoato de ({[(2-{{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil}(propil)amino]carbonil}oxi)metilo

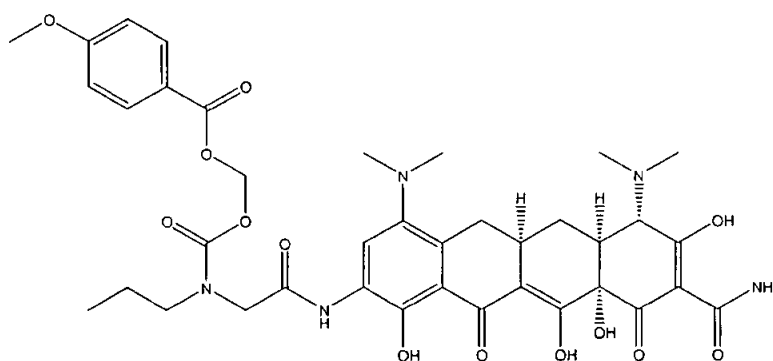


El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando 4-metilbenzoato de [(clorocarbonil)oxi]metilo y N-propilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 764.3 ((M+H)+);

Ejemplo 6

4-metoxibenzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(propil)amino]carbonil)oxi)metilo

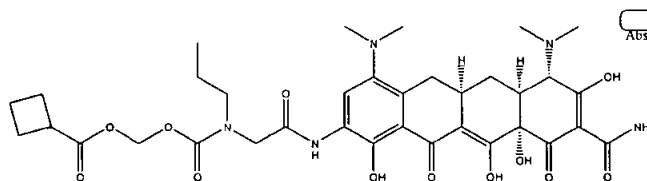


El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando 4-metoxibenzoato de [(clorocarbonil)oxi]metilo y N-propilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 780.3 ((M+H)+);

Ejemplo 7

Ciclobutanocarboxilato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(propil)amino]carbonil}oxi)metilo

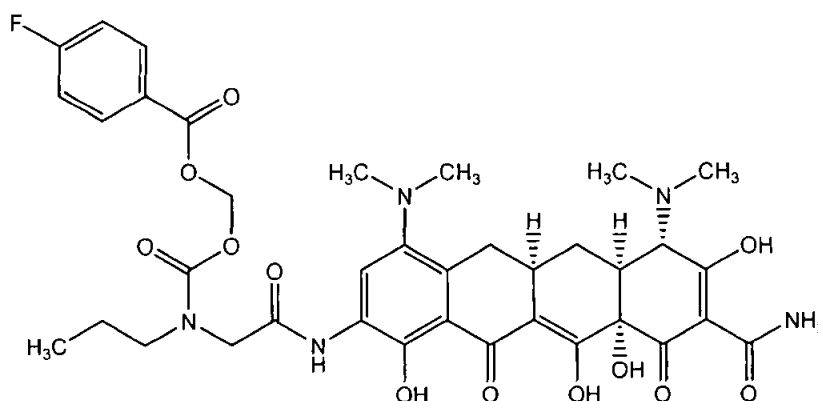


El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando ciclobutanocarboxilato de [(clorocarbonil)oxi]metilo y N-propilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 728.3 ((M+H)+);

Ejemplo 8

4-fluorobenzoato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(propil)amino]carbonil}oxi)metilo

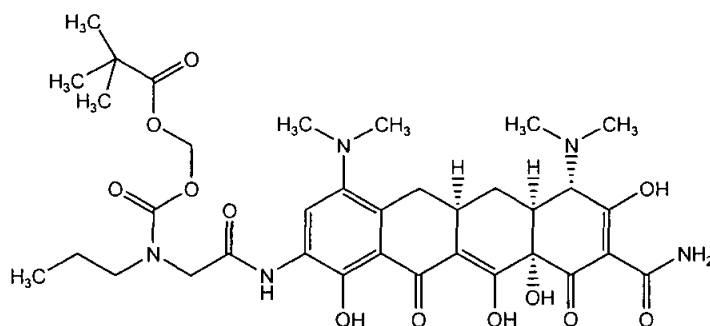


El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando 4-fluorobenzoato de [(clorocarbonil)oxi]metilo y N-propilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 768.3 ((M+H)+);

Ejemplo 9

Pivalato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(propil)amino]carbonil}oxi)metilo

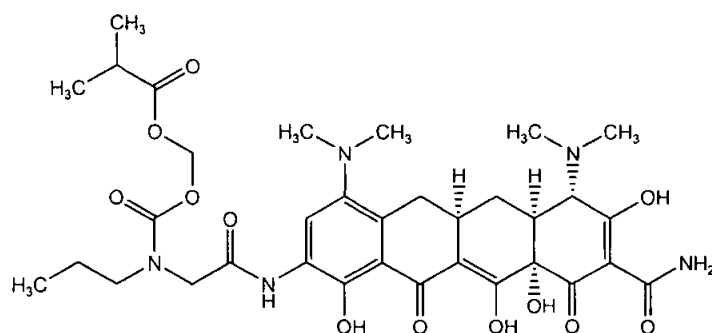


El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando ácido propanoico, éster de 2,2-dimetil-, [(clorocarbonil)oxi]metilo y N-propilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 730.3 ((M+H)+);

Ejemplo 10

2-metilpropanoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(propil)amino]carbonil}oxi)metilo

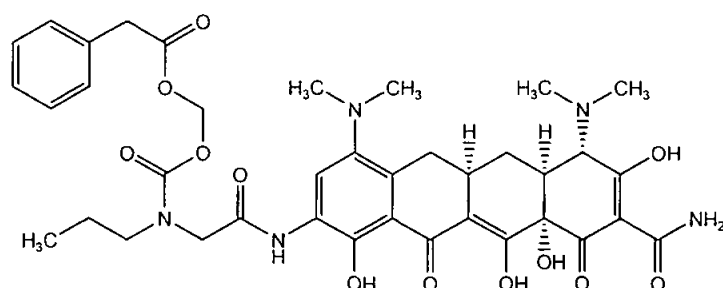


El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando ácido propanoico, éster de 2-metil-, [(clorocarbonil)oxi]metilo y N-propilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 716.3 ((M+H)+);

Ejemplo 11

Fenilacetato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(propil)amino]carbonil}oxi)metilo

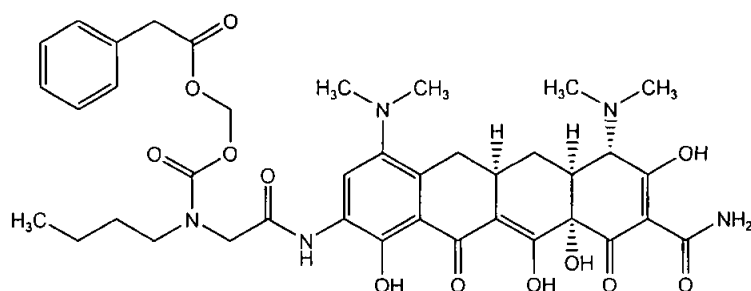


El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando ácido bencenoacético, éster de [(clorocarbonil)oxi]metilo y N-propilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 764.3 ((M+H)+

Ejemplo 12

Fenilacetato de ({[(2-({[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil)oxi]metilo

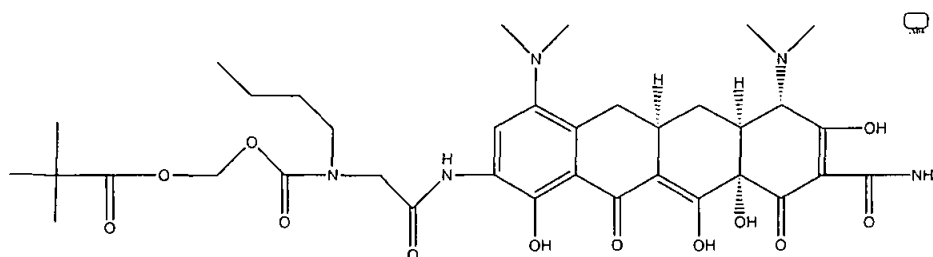


El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando ácido bencenoacético, éster de [(clorocarbonil)oxi]metilo y N-butilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 778.3 ((M+H)+);

Ejemplo 13

Pivalato de ([[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(butil)amino]carbonil}oxi)metilo

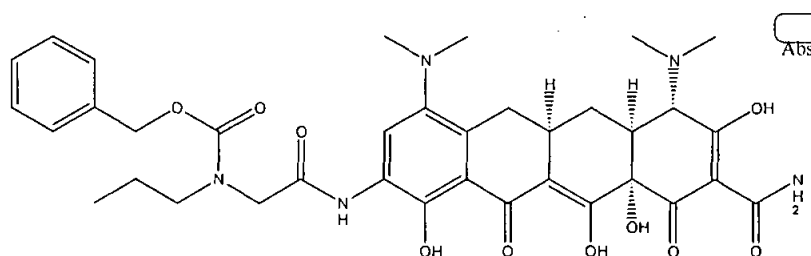


El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando ácido propanoico, éster de 2,2-dimetil-, [(clorocarbonil)oxi]metilo y N-butilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 744.3 ((M+H)+);

Ejemplo 14

2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(propil)carbamato de bencilo

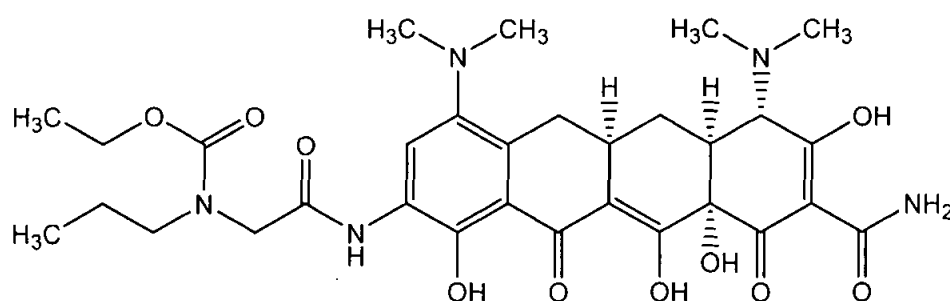


El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando cloroformato de bencilo y N-propilglicilciclina en la presencia de carbonato de sodio y DMPU en acetonitrilo para dar el producto del ejemplo.

MS (ESI) m/z 706.3 ((M+H)+); HRMS: calculado para $C_{36}H_{43}N_5O_{10}$ HCl, 741.2777; encontrado (ESI), 706.31133;

Ejemplo 15

2-([(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil(propil)carbamato de etilo

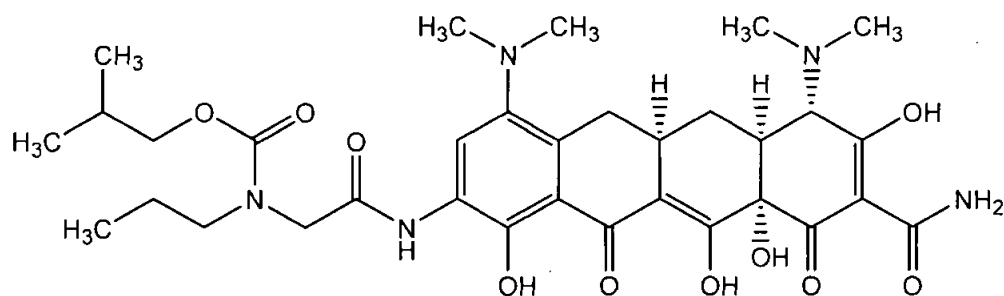


El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando cloroformato de etilo y N-propilglicilciclina en la presencia de carbonato de sodio y DMPU en acetonitrilo para dar el producto del ejemplo.

MS (ESI) m/z 644.3 ((M+H)+);
HRMS: calculado para $C_{31}H_{41}N_5O_{10} \cdot HCl$, 679.2620; encontrado (ESI+), 644.29398;

Ejemplo 16

2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(propil)carbamato de isobutilo



El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando cloroformato de isobutilo y N-propilglicilciclina en la presencia de carbonato de sodio y DMPU en acetonitrilo para dar el producto del ejemplo.

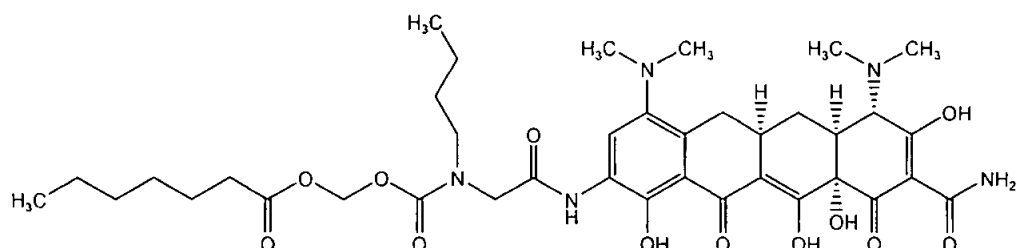
MS (ESI) m/z 672.3 ((M+H)+);

MS (ESI) m/z 336.9 ((M+2H)2+);

HRMS: calculado para $C_{33}H_{45}N_5O_{10} \cdot HCl$, 707.2933; encontrado (ESI+), 672.32618

Ejemplo 17

Heptanoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil}oxi)metilo

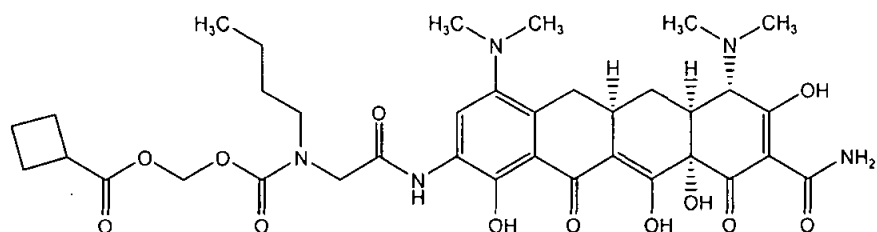


El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando ácido heptanoico, éster de [(clorocarbonil)oxi]metilo y N-butilglicilciclina para dar el producto del ejemplo.

MS (ESI+) m/z 772.2 (M+H); HRMS: calculado para $C_{38}H_{53}N_5O_{12} \cdot 2.00$ HCl, 843.3224; encontrado (ESI+), 772.37696;

Ejemplo 18

Ciclobutanocarboxilato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil}oxi)metilo

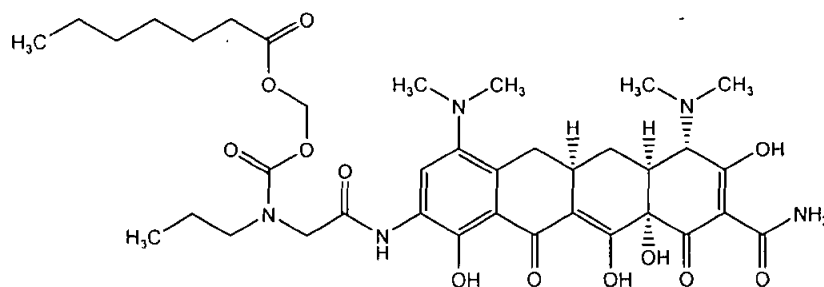


El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando ciclobutanocarboxilato de [(clorocarbonil)oxi]metilo y N-butilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 742.3 ((M+H)+); HRMS: calculado para $C_{36}H_{47}N_5O_{12}$ · 2.00 HCl, 813.2755; encontrado (ESI+), 742.32898;

Ejemplo 19

Heptanoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(propil)amino]carbonil}oxi)metilo



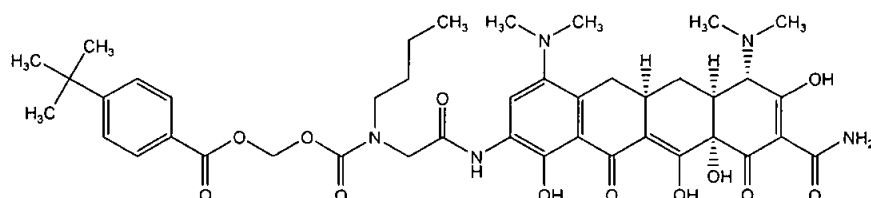
El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando Ácido heptanoico, éster de [(clorocarbonil)oxi]metilo y N-propilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 758.4 ((M+H)+);

HRMS: calculado para $C_{37}H_{51}N_5O_{12}$ · HCl, 793.3301; encontrado (ESI+), 758.36175;

Ejemplo 20

4-Terc-butilbenzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil}oxi)metilo



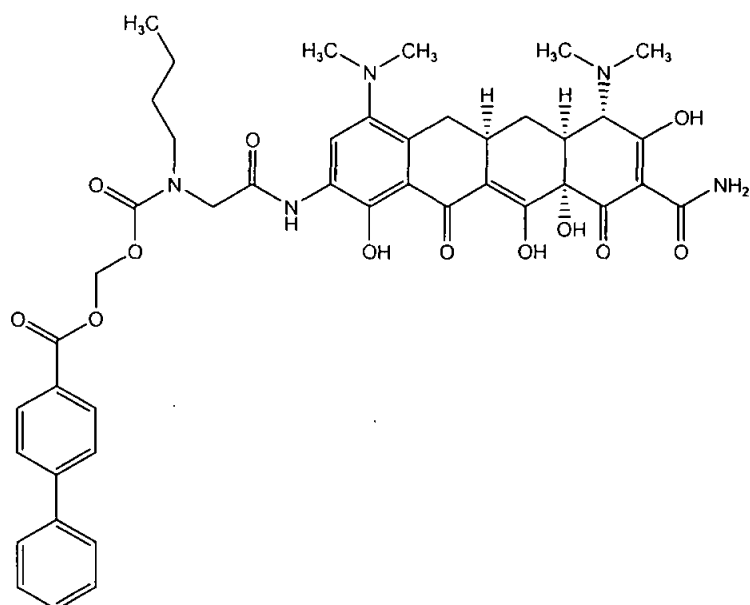
El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando 4-Terc-butilbenzoato de [(clorocarbonil)oxi]metilo y N-butilglicilciclina para dar el producto del ejemplo.

MS (ESI+) m/z 820.2 (M+H);

HRMS: calculado para $C_{42}H_{53}N_5O_{12} \cdot HCl$, 855.3458; encontrado (ESI+), 820.37684;

Ejemplo 21

1,1'-bifenil-4-carboxilato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil}oxi)metilo



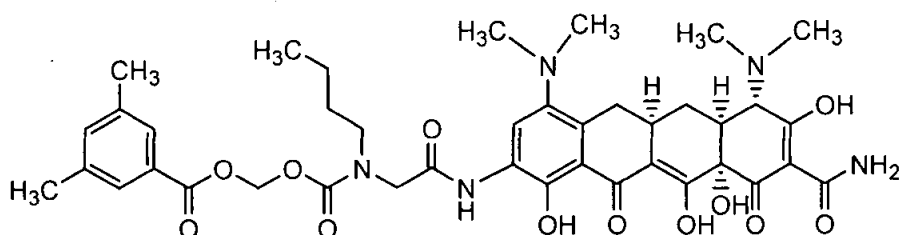
El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando bifenil-4-carboxilato de [(clorocarbonil)oxi]metilo y N-butilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 840.3 ((M+H)+);

HRMS: calculado para $C_{44}H_{49}N_5O_{12} \cdot HCl$, 875.3145; encontrado (ESI+), 840.34337;

Ejemplo 22

3,5-dimetilbenzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil}oxi)metilo



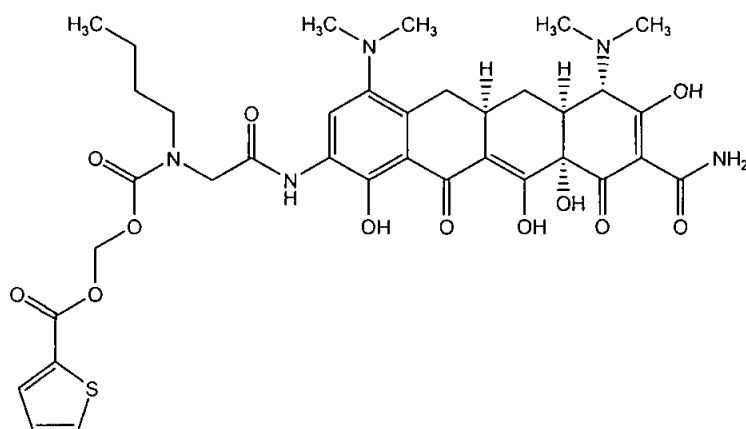
El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando 3,5-dimetilbenzoato de [(clorocarbonil)oxi]metilo y N-butilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 792.3 ((M+H)+);

HRMS: calculado para $C_{40}H_{49}N_5O_{12} \cdot 2.00 \text{ HCl}$, 863.2911; encontrado (ESI+), 792.34378;

Ejemplo 23

tiofen-2-carboxilato de ([[(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(butil)amino]carbonil}oxi)metilo



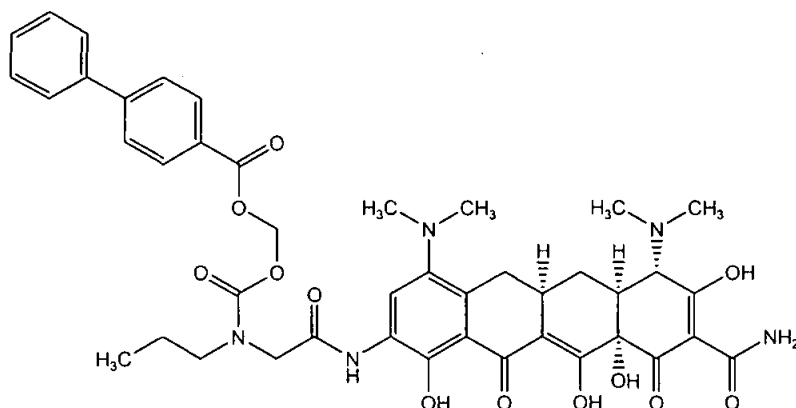
El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando tiofen-2-carboxilato de [(clorocarbonil)oxi]metilo y N-butilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 770.1 ((M+H)+);

HRMS: calculado para $C_{36}H_{43}N_5O_{12}S \cdot HCl$, 805.2396; encontrado (ESI+), 770.27084;

Ejemplo 24

1,1'-bifenil-4-carboxilato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(propil)amino]carbonil}oxi)metilo



El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando bifenil-4-carboxilato de [(clorocarbonil)oxi]metilo y N-propilglicilciclina para dar el producto del ejemplo.

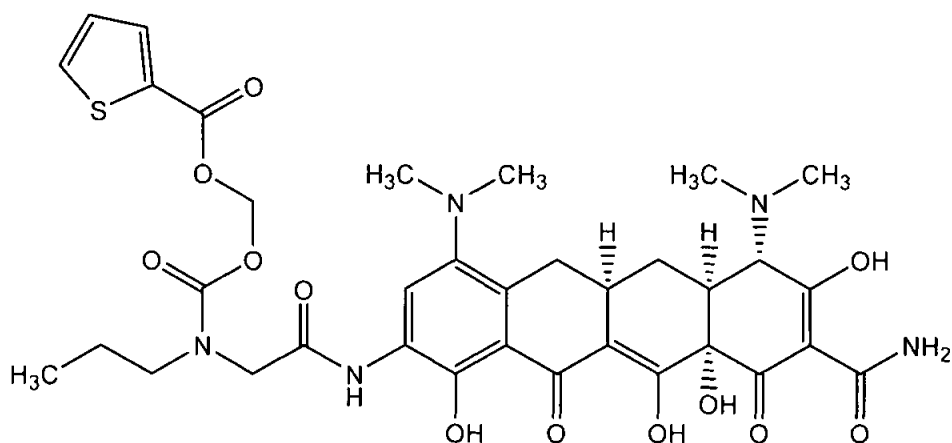
MS (ESI) m/z 826.4 ((M+H)+);

MS (ESI) m/z 414 ((M+2H)2+);

HRMS: calculado para $C_{43}H_{47}N_5O_{12} \cdot HCl$, 861.2988; encontrado (ESI+), 826.32782;

Ejemplo 25

tiofen-2-carboxilato de ([[(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino]-2-oxoetil)(propil)amino]carbonil)oxi)metilo



El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando tiofen-2-carboxilato de [(clorocarbonil)oxi]metilo y N-propilglicilciclina para dar el producto del ejemplo.

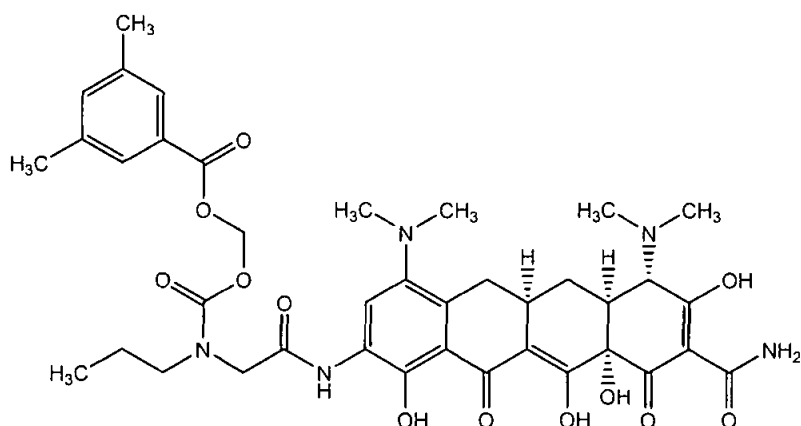
MS (ESI) m/z 756.3 ((M+H)+);

MS (ESI) m/z 378.9 ((M+2H)2+);

HRMS: calculado para $C_{35}H_{41}N_5O_{12}S \cdot HCl$, 791.2239; encontrado (ESI+), 756.2532;

Ejemplo 26

3,5-dimetilbenzoato de ([[(2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino]-2-oxoetil)(propil)amino]carbonil)oxi)metilo



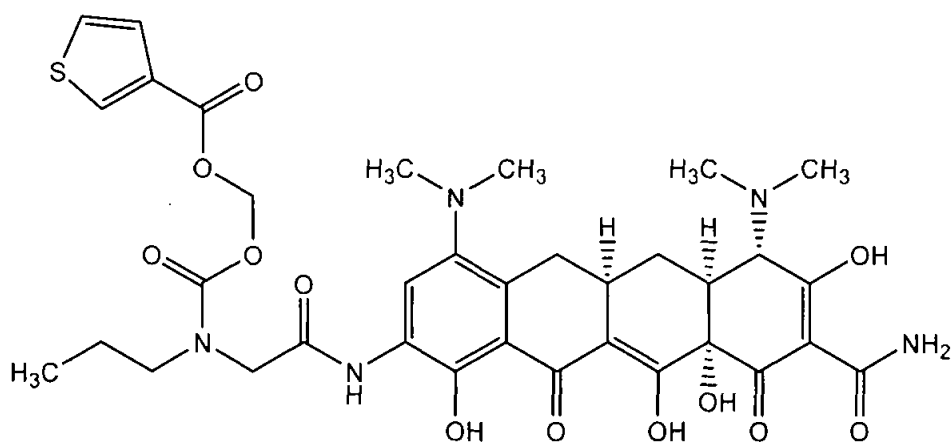
El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando 3,5-dimetilbenzoato de [(clorocarbonil)oxi]metilo y N-propilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 778.3 ((M+H)+);

HRMS: calculado para $C_{39}H_{47}N_5O_{12} \cdot HCl$, 813.2988; encontrado (ESI+), 778.32984;

Ejemplo 27

tiofen-3-carboxilto de ({[(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(propil)amino]carbonil}oxi)metilo



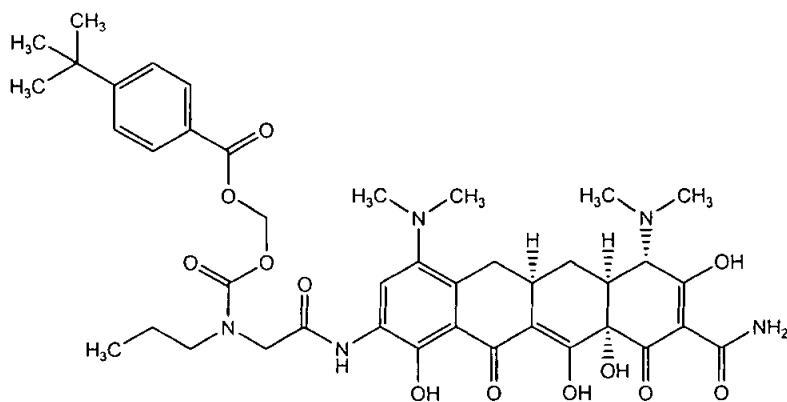
El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando tiofen-3-carboxilato de [(clorocarbonil)oxi]metilo y N-propilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 756.3 ((M+H)+);

HRMS: calculado para C₃₅H₄₁N₅O₁₂S · HCl, 791.2239; encontrado (ESI+), 756.2547;

Ejemplo 28

4-Terc-butilbenzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(propil)amino]carbonil}oxi)metilo



El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando 4-Terc-butilbenzoato de [(clorocarbonil)oxi]metilo y N-propilglicilciclina para dar el producto del ejemplo.

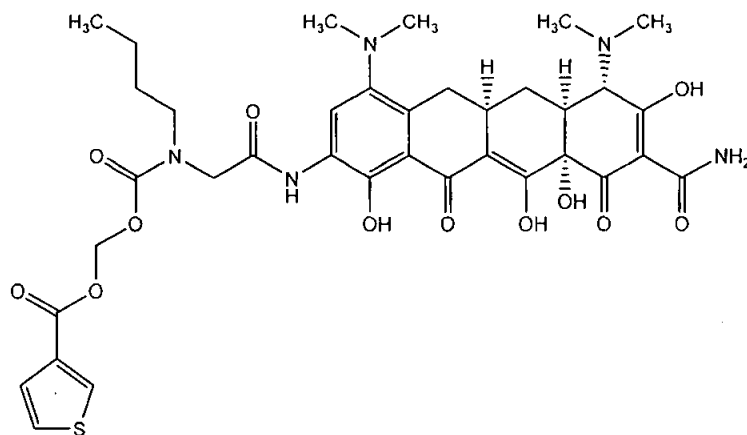
MS (ESI) m/z 806.4 ((M+H)+);

MS (ESI) m/z 403.9 ((M+2H)2+);

HRMS: calculado para $C_{41}H_{51}N_5O_{12} \cdot HCl$, 841.3301; encontrado (ESI+), 806.36024;

Ejemplo 29

tiofen-3-carboxilato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil)oxi)metilo



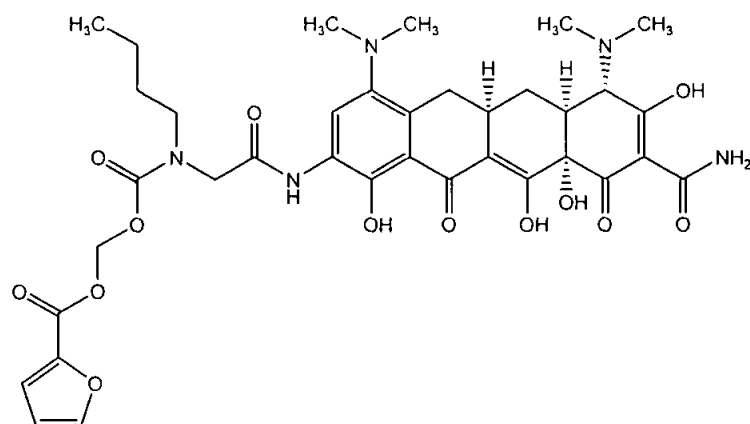
El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando tiofen-3-carboxilato de [(clorocarbonil)oxi]metilo y N-butilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 770.3 ((M+H)+);

HRMS: calculado para $C_{36}H_{43}N_5O_{12}S \cdot HCl$, 805.2396; encontrado (ESI+), 770.27028;

Ejemplo 30

2-furoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil)oxi)metilo



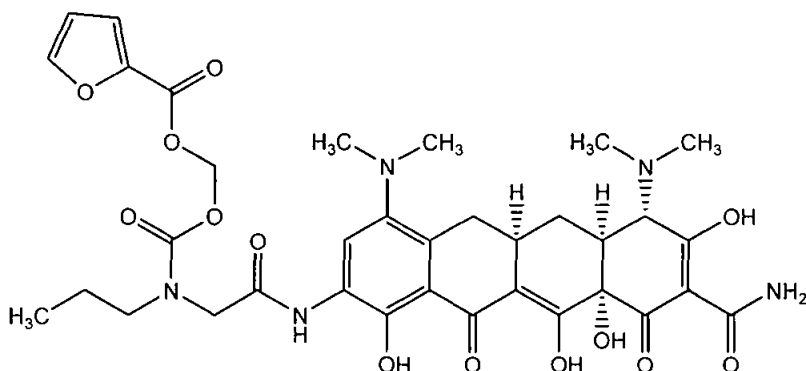
El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando 2-furoato de [(clorocarbonil)oxi]metilo y N-butilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 752.2 ((M-H)-);

HRMS: calculado para $C_{36}H_{43}N_5O_{13} \cdot HCl$, 789.2624; encontrado (ESI+), 754.29242;

Ejemplo 31

2-furoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(propil)amino]carbonil}oxi)metilo

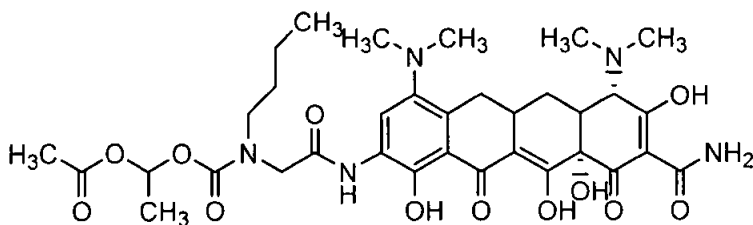


El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando 2-furoato de [(clorocarbonil)oxi]metilo y N-propilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 740.19 (M+H);

Ejemplo 32

Acetato de 1-(((2-(((7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil}oxi)etilo



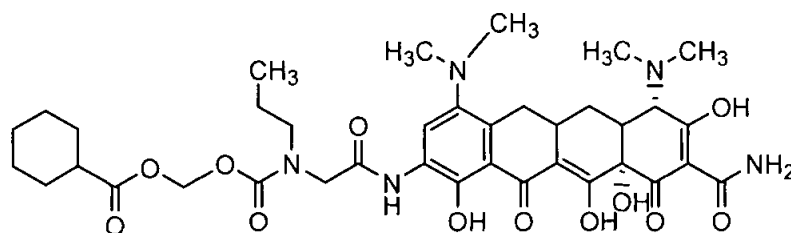
El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando acetato de 1-[(clorocarbonil)oxi]etilo y N-butilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 716.14 (M+H);

HRMS: calculado para $C_{34}H_{45}N_5O_{12}$, 715.3065; encontrado (ESI+), 716.31469;

Ejemplo 33

Ciclohexanocarboxilato de (((2-(((7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(propil)amino]carbonil)oxi)metilo



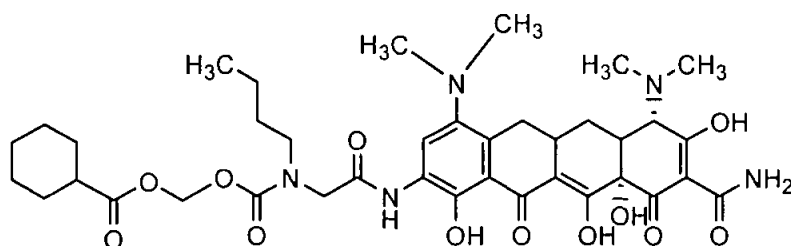
El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando ácido ciclohexanocarboxílico, éster de [(clorocarbonil)oxi]metilo y N-propilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 756.08 (M+H);

HRMS: calculado para $C_{37}H_{49}N_5O_{12}$, 755.3378; encontrado (ESI+), 756.34507;

Ejemplo 34

Ciclohexanocarboxilato de (((2-(((7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil)oxi)metilo



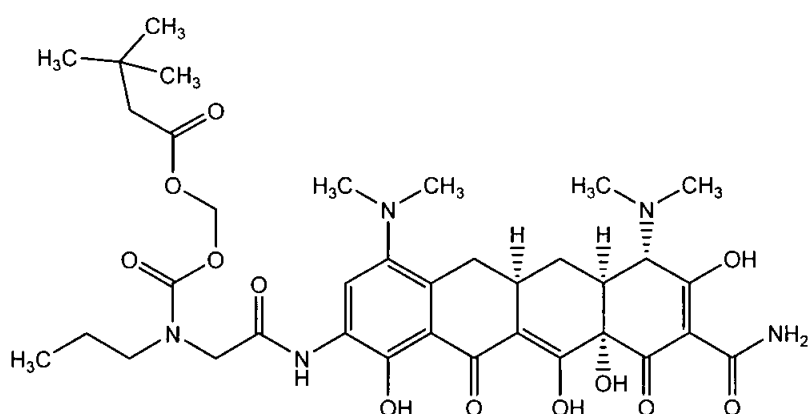
El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando ácido ciclohexanocarboxílico, éster de [(clorocarbonil)oxi]metilo y N-butilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 70.64 (M+H);

HRMS: calculado para $C_{38}H_{51}N_5O_{12} \cdot HCl$, 805.3301; encontrado (ESI+), 770.36093;

Ejemplo 35

3,3-dimetilbutanoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(propil)amino]carbonil)oxi)metilo



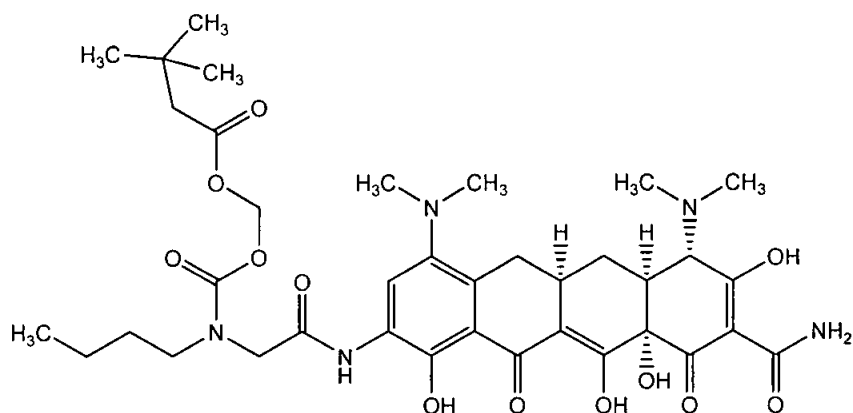
El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando ácido butanoico, 3,3-dimetil-, éster de [(clorocarbonil)oxi]metilo y N-propilglicilciclina para dar el producto del ejemplo.

MS m/z 00-304761LMS;

HRMS: calculado para $C_{36}H_{49}N_5O_{12} \cdot HCl$, 779.3145; encontrado (ESI+), 744.34539;

Ejemplo 36

3,3-dimetilbutanoato de {{{(2-{{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil}(butil)amino]carbonil}oxi)metilo



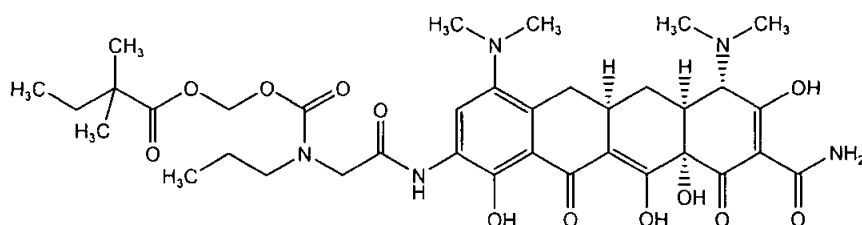
El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando Ácido butanoico, 3,3-dimetil-, éster de [(clorocarbonil)oxi]metilo y N-butilglicilciclina para dar el producto del ejemplo.

MS m/z 00-304762LMS;

HRMS: calculado para $C_{37}H_{51}N_5O_{12} \cdot HCl$, 793.3301; encontrado (ESI+), 758.36071;

Ejemplo 37

2,2-dimetilbutanoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](propil)amino]carbonil}oxi)metilo



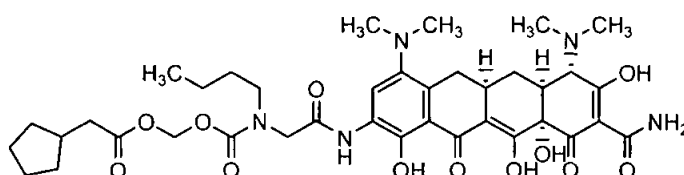
El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando 2,2-dimetilbutanoato de [(clorocarbonil)oxi]metilo y N-propilglicilciclina para dar el producto del ejemplo.

MS m/z 00-304763LMS;

HRMS: calculado para $C_{36}H_{49}N_5O_{12} \cdot HCl$, 779.3145; encontrado (ESI+), 744.3452;

Ejemplo 38

Ciclopentilacetato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](butil)amino]carbonil}oxi)metilo



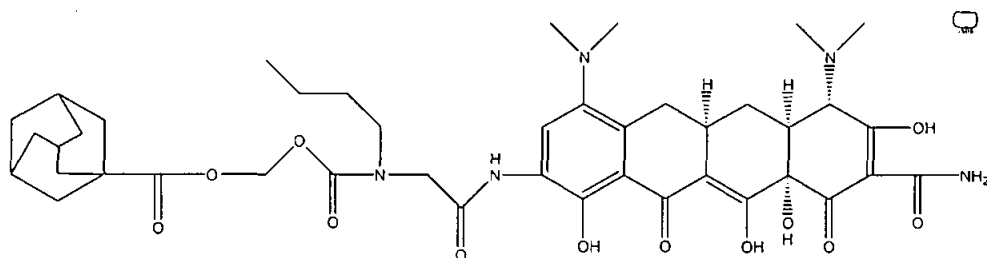
El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando ciclopentilacetato de [(clorocarbonil)oxi]metilo y N-butilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 770.7 (M+H);

HRMS: calculado para $C_{38}H_{51}N_5O_{12} \cdot HCl$, 805.3301; encontrado ESI+), 770.36062;

Ejemplo 39

adamantan-1-carboxilato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](butil)amino]carbonil}oxi)metilo



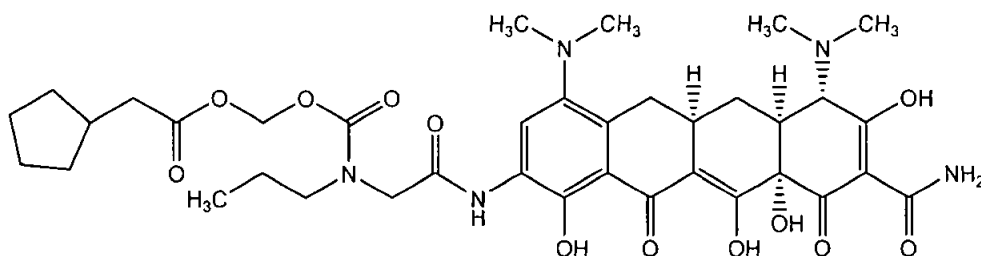
El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando adamantan-1-carboxilato [(clorocarbonil)oxi]metilo y N-butilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 822.9 (M+H);

HRMS: calculado para $C_{42}H_{55}N_5O_{12} \cdot HCl$, 857.3614; encontrado ESI+), 822.39184;

Ejemplo 40

Ciclopentilacetato de ([[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(propil)amino]carbonil}oxi)metilo



El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando ciclopentilacetato de

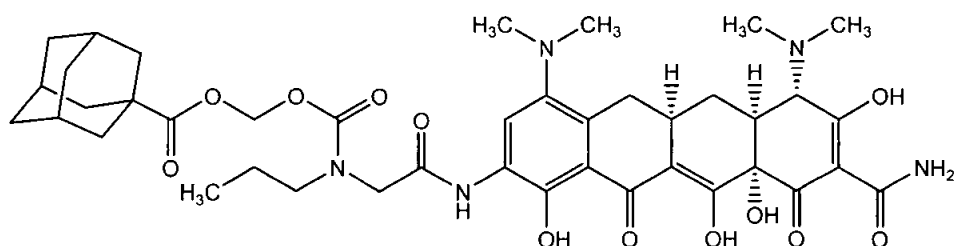
[(clorocarbonil)oxi]metilo y N-propilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 754.2 ((M-H)-);

HRMS: calculado para $C_{37}H_{49}N_5O_{12} \cdot HCl$, 791.3145; encontrado (ESI+), 756.34433;

Ejemplo 41

adamantan-1-carboxilato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(propil)amino]carbonil)oxi)metilo



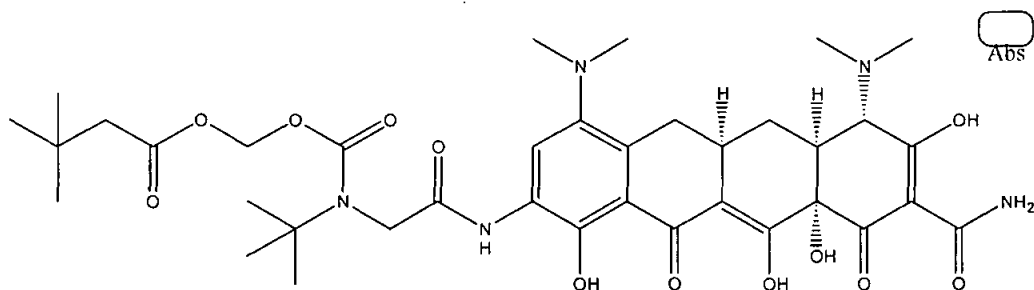
El compuesto del título se prepara mediante el procedimiento del Ejemplo 1, utilizando adamantan-1-carboxilato de [(clorocarbonil)oxi]metilo y N-propilglicilciclina para dar el producto del ejemplo.

MS (ESI) m/z 808.8 (M+H);

HRMS: calculado para $C_{41}H_{53}N_5O_{12} \cdot HCl$, 843.3458; encontrado (ESI+), 808.37604;

Ejemplo 42

3,3-dimetilbutanoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



A una solución de monosulfato de 9-amino-minociclina (0.0055 mol, 3.135g, 1 equivalente) en una mezcla de 12 ml de acetonitrilo y 50 ml de DMPU se agrega 1.66 g (3 equivalentes) de trietilamina y Compuesto de Referencia 109 (0.012 mole, 4.88g), éster de [Terc-butil-(2-isobutoxicarboniloxi-2-oxo-etil)-carbamoiloxi)-metilo de ácido 3,3-Dimetil-butírico. La reacción se agita a temperatura ambiente durante 2 horas, se agrega 1 mL metanol, se agita durante 5 min. y la mezcla se vierte en una mezcla de 500 ml de éter y 100 ml de isopropanol. El sólido se recolecta y se purifica mediante extracción para dar 1.5 g del producto del ejemplo.

MS (ESI) m/z 758.55 (M+H);

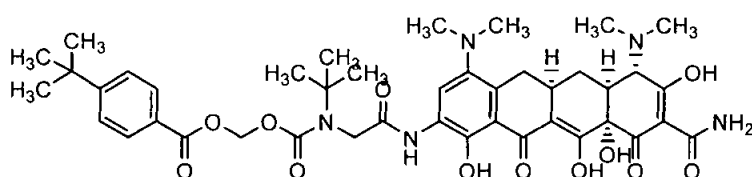
HRMS: calculado para $C_{37}H_{51}N_5O_{12} \cdot HCl$, 793.3301; encontrado (ESI+), 758.36201;

Ejemplo 43

453

Preparado de acuerdo al Esquema II

4-Terc-butilbenzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil)oxi)metilo



El compuesto de Referencia 57 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominciclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

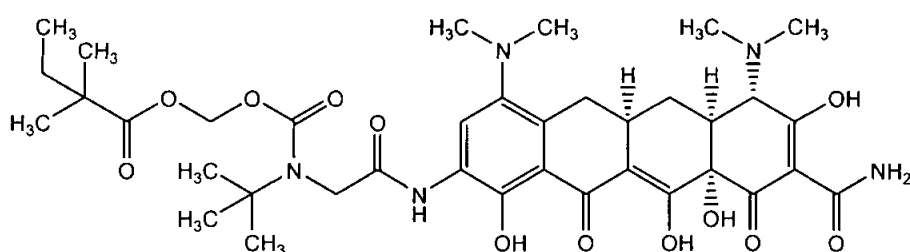
MS (ESI) m/z 820.37 (M+H);

HRMS: calculado para $C_{42}H_{53}N_5O_{12} \cdot HCl$, 855.3458; encontrado (ESI+), 820.37574;

Ejemplo 44

2,2-dimetilbutanoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil)oxi)metilo

454



El compuesto del título se prepara al hacer reaccionar el producto de la reacción de N-(Terc-butil)-N-(((2,2-dimetilbutanoil)oxi]metoxi}carbonil)glicina utilizando las condiciones del Compuesto de Referencia 109 con 9-aminociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

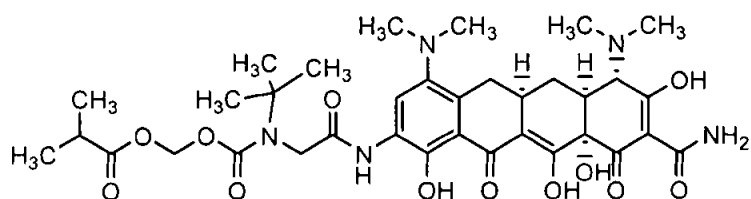
MS (ESI) m/z 758.63 (M+H);

HRMS: calculado para $C_{37}H_{51}N_5O_{12} \cdot HCl$, 793.3301; encontrado (ESI+), 758.36119;

Ejemplo 45

Preparado de acuerdo al Esquema 2

2-metilpropanoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil) (Terc-butil)amino]carbonil}oxi)metilo

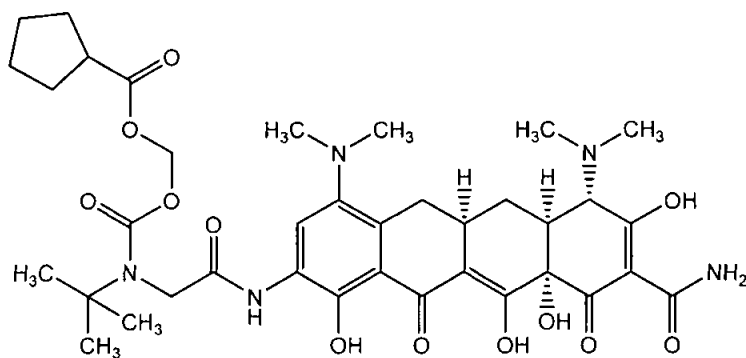


El compuesto de Referencia 58 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 730.38 (M+H); HRMS: calculado para $C_{35}H_{47}N_5O_{12} \cdot HCl$, 765.2988; encontrado (ESI+), 730.33002;

Ejemplo 46

ciclopentanocarboxilato de {[(2- { [(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il] amino }-2-oxoetil) (Terc-butil) amino] carbonil} oxi) metilo



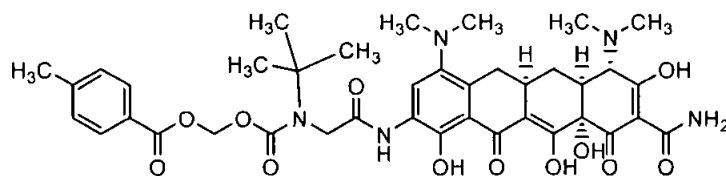
El compuesto de Referencia 59 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 754.09 ((M-H)-);

HRMS: calculado para $C_{37}H_{49}N_5O_{12}$ HCl, 791.3145; encontrado (ESI+), 378.67644;

Ejemplo 47

4-metilbenzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil)oxi)metilo



El compuesto de Referencia 60 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 778.34 (M+H);

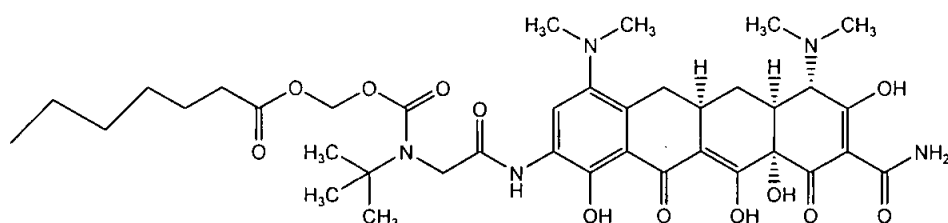
HRMS: calculado para $C_{39}H_{47}N_5O_{12}$, 777.3221; encontrado (ESI+), 778.33065;

Ejemplo 48

Preparado de acuerdo al Esquema II

heptanoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-

5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil) (Terc-butil)amino]carbonil}oxi)metilo



El compuesto de Referencia 61 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminonociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

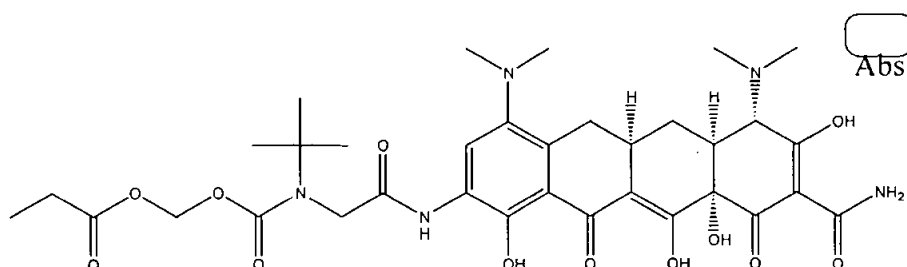
MS (ESI) m/z 772.45 (M+H);

HRMS: calculado para $C_{38}H_{53}N_5O_{12} \cdot HCl$, 807.3458; encontrado (ESI+), 772.37695;

Ejemplo 49

Preparado de acuerdo al Esquema II

propionato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil) (Terc-butil)amino]carbonil}oxi)metilo



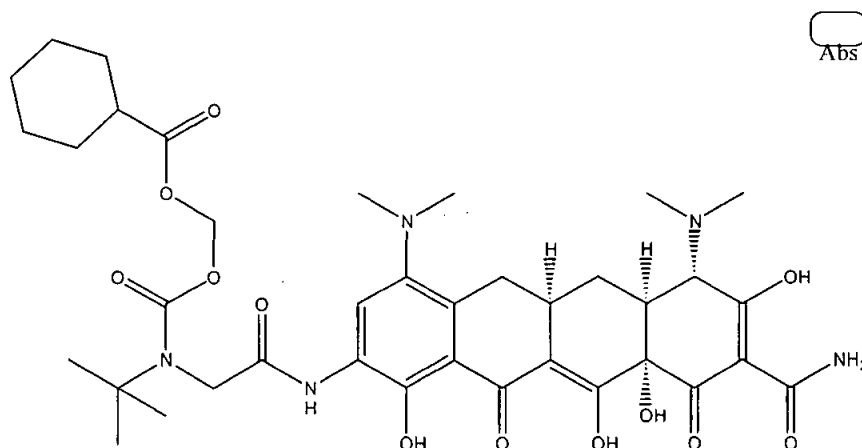
El compuesto de Referencia 62 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 716.3 (M+H);

HRMS: calculado para $C_{34}H_{45}N_5O_{12} \cdot HCl$, 751.2832; encontrado (ESI+), 716.31461;

Ejemplo 50

ciclohexanocarboxilato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil)oxi)metilo



El compuesto de Referencia 63 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-

aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

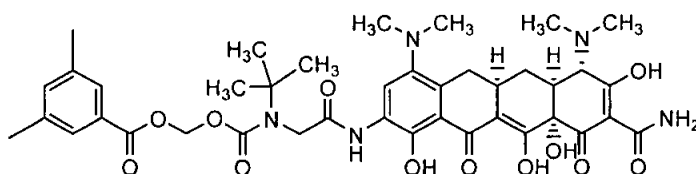
MS (ESI) m/z 770.36 (M+H);

HRMS: calculado para $C_{38}H_{51}N_5O_{12} \cdot HCl$, 805.3301; encontrado (ESI-), 768.34546;

Ejemplo 51

Preparado de acuerdo al Esquema 2

3,5-dimetilbenzoato de {{{(2-{{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



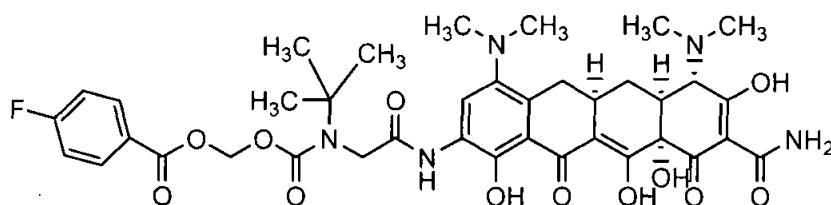
El compuesto de Referencia 64 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 792.32 (M+H);

HRMS: calculado para $C_{40}H_{49}N_5O_{12} \cdot HCl$, 827.3145; encontrado (ESI+), 792.34613;

Ejemplo 52

4-fluorobenzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



El compuesto de Referencia 65 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

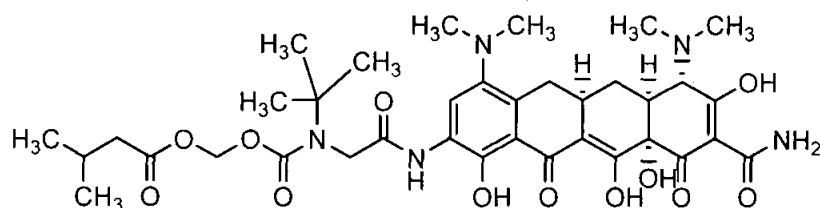
MS (ESI) m/z 782.3 (M+H);

HRMS: calculado para $C_{38}H_{44}FN_5O_{12} \cdot HCl$, 817.2737; encontrado (ESI+), 782.30406

Ejemplo 53

Preparado de acuerdo al Esquema 2

3-metilbutanoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



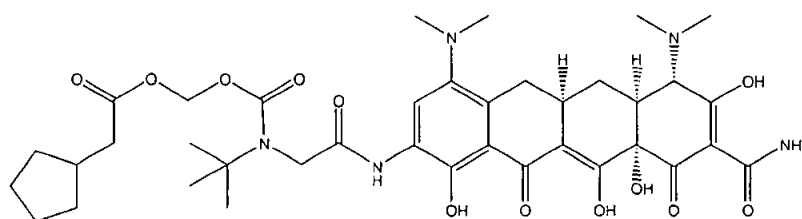
El compuesto de Referencia 66 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 744.37 (M+H);

HRMS: calculado para $C_{36}H_{49}N_5O_{12} \cdot HCl$, 779.3145; encontrado (ESI+), 744.34481;

Ejemplo 54

Ciclopentilacetato de ([[(2-[[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil) (Terc-butil) amino]carbonil)oxi)metilo



El compuesto de Referencia 67 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-

aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

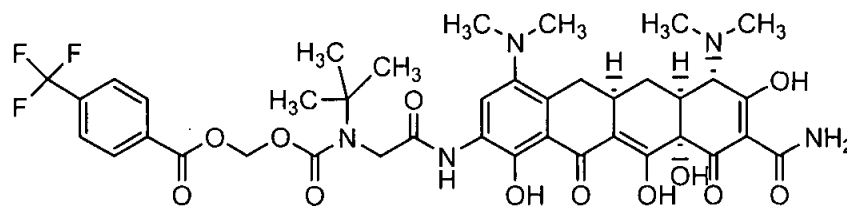
MS (ESI) m/z 770.4 (M+H);

HRMS: calculado para $C_{38}H_{51}N_5O_{12} \cdot HCl$, 805.3301; encontrado (ESI+), 770.35888;

Ejemplo 55

Preparado de acuerdo al Esquema 2

4-(trifluorometil)benzoato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino})-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo



El compuesto de Referencia 68 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

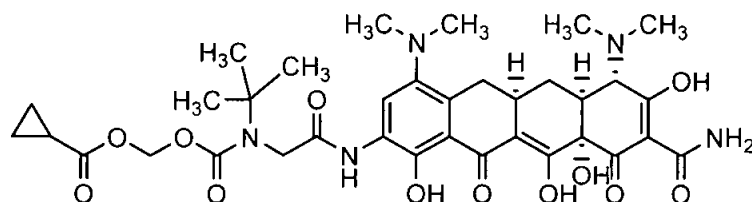
MS (ESI) m/z 832.2 (M+H);

MS (ESI) m/z 416.6 (M+2H);

HRMS: calculado para $C_{39}H_{44}F_3N_5O_{12} \cdot HCl$, 867.2705; encontrado (ESI+), 832.30055;

Ejemplo 56

ciclopropanocarboxilato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



El compuesto de Referencia 69 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

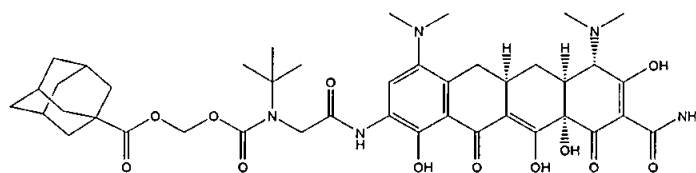
MS (ESI) m/z 728.34 (M^+_H);

HRMS: calculado para $C_{35}H_{45}N_5O_{12} \cdot HCl$, 763.2832; encontrado (ESI+), 728.31289;

Ejemplo 57

Preparado de acuerdo al Esquema 2

adamantan-1-carboxilato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



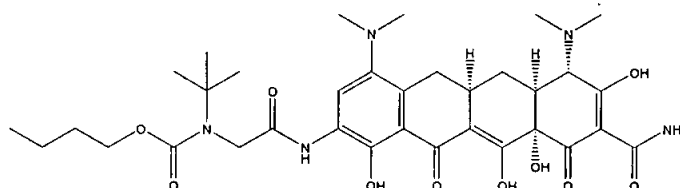
El compuesto de Referencia 70 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominciclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 822.5 (M+H);

HRMS: calculado para $C_{42}H_{55}N_5O_{12} \cdot HCl$, 857.3614; encontrado (ESI+), 822.39237

Ejemplo 58

2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(Terc-butyl)carbamato de butilo



El compuesto del título se prepara mediante el procedimiento del Ejemplo 42, utilizando 1 equivalente de 9-amino-minociclina y 2 equivalentes de isobutoxicarbonilo N-(butoxicarbonil)-N-(Terc-

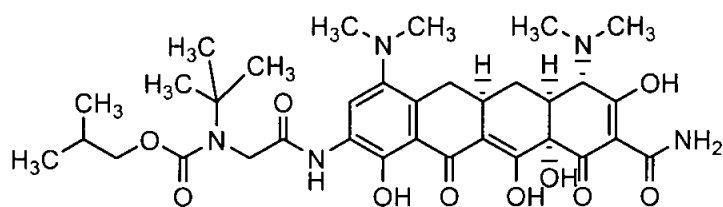
butil)glicinato Ejemplo de Referencia 118 para dar el producto del ejemplo.

MS (ESI) m/z 686.4 (M+H);

HRMS: calculado para $C_{34}H_{47}N_5O_{10} \cdot HCl$, 721.3090; encontrado (ESI+), 686.34079;

Ejemplo 59

2-[[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(Terc-butil)carbamato de isobutilo



El compuesto del título se prepara mediante el procedimiento del Ejemplo 42, utilizando 1 equivalente de 9-amino-minociclina y 2 equivalentes de isobutoxicarbonilo N-(Terc-butil)-N-(isobutoxicarbonil)glicinato, Ejemplo de Referencia 119 para dar el producto del ejemplo.

MS (ESI) m/z 686.3 (M+H);

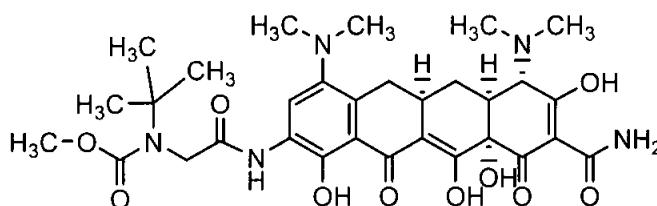
MS (ESI) m/z 1371.7 (2M+H);

HRMS: calculado para $C_{34}H_{47}N_5O_{10} \cdot HCl$, 721.3090; encontrado (ESI-), 684.32433;

Ejemplo 60

466

2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(Terc-butil)carbamato de isobutilo



El compuesto del título se prepara mediante el procedimiento del Ejemplo 42, utilizando 1 equivalente de 9-amino-minociclina y 2 equivalentes de isobutoxicarbonilo N-(Terc-butil)-N-(metoxicarbonil)glicinato Ejemplo de Referencia 120 para dar el producto del ejemplo.

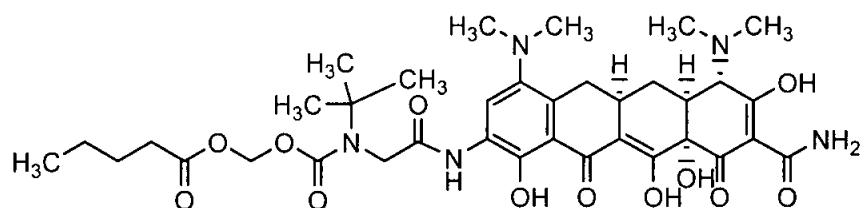
MS (ESI) m/z 644.3 (M+H);

MS (ESI) m/z 322.6 (M+2H);

HRMS: calculado para $C_{31}H_{41}N_5O_{10} \cdot HCl$, 679.2620; encontrado (ESI-), 642.27736;

Ejemplo 61

pentanoato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



El compuesto de Referencia 71 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominciclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

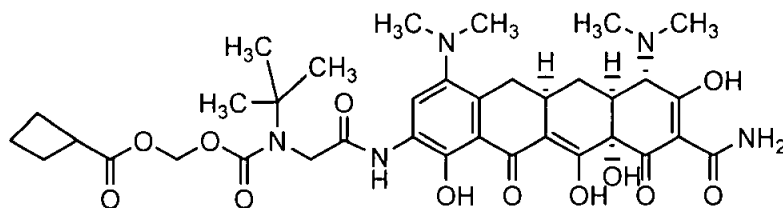
MS (ESI) m/z 742 (M-H);

HRMS: calculado para $C_{36}H_{49}N_5O_{12} \cdot HCl$, 779.3145; encontrado (ESI+), 744.34613;

Ejemplo 62

Preparado de acuerdo al Esquema II

ciclobutanocarboxilato de ({[(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butyl)amino]carbónil}oxi)metilo



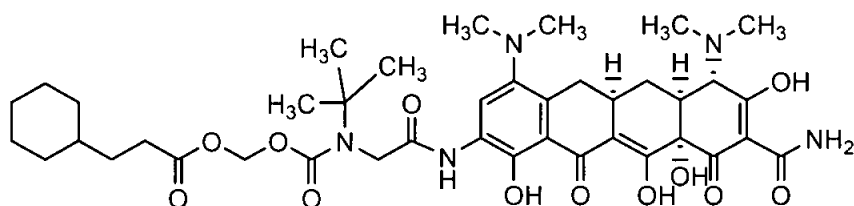
El compuesto de Referencia 72 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de

dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 742.4 (M+H);

Ejemplo 63

3-ciclohexilpropanoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



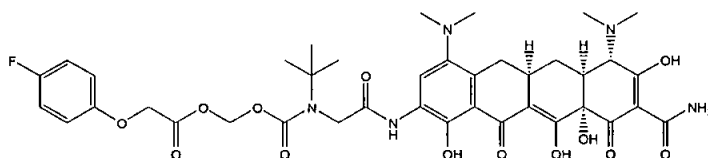
El compuesto de Referencia 73 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 796.4 (M-H);

Ejemplo 64

(4-fluorofenoxi)acetato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-

10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-
2-oxoetil) (Terc-butil)amino]carbonil}oxi)metilo



El compuesto de Referencia 74 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

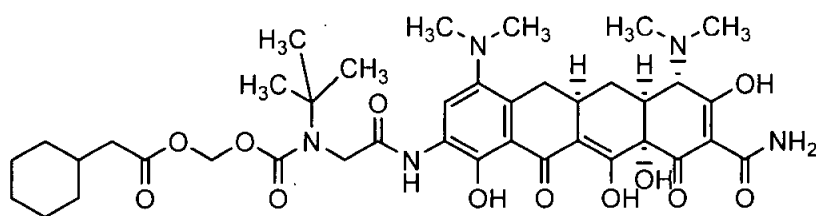
MS (ESI) m/z 812.4 (M+H);

MS (ESI) m/z 406.7 (M+2H);

HRMS: calculado para $C_{39}H_{46}FN_5O_{13} \cdot HCl$, 847.2843; encontrado ESI+), 812.31518;

Ejemplo 65

ciclohexilacetato de ({[(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-
4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-
5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-
oxoetil) (Terc-butil)amino]carbonil}oxi)metilo



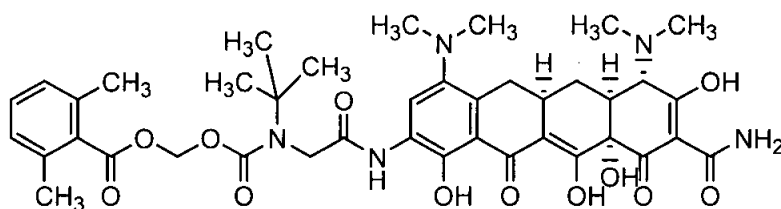
El compuesto de Referencia 75 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 782.2 (M-H);

HRMS: calculado para $C_{39}H_{53}N_5O_{12} \cdot HCl$, 819.3458; encontrado (ESI+), 784.37621;

Ejemplo 66

2,6-dimetilbenzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil)oxi)metilo



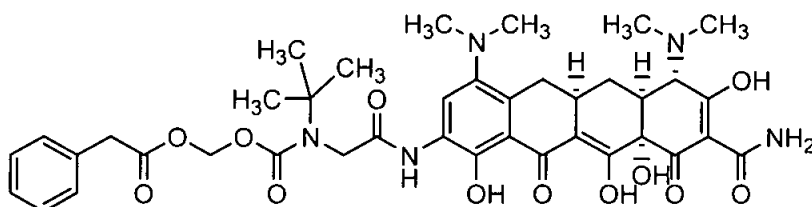
El compuesto de Referencia 76 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 790.4 (M-H);

HRMS: calculado para $C_{40}H_{49}N_5O_{12} \cdot HCl$, 827.3145; encontrado (ESI+), 792.34423;

Ejemplo 67

fenilacetato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



El compuesto de Referencia 77 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

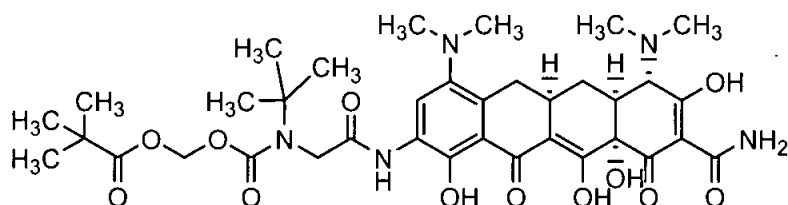
MS (ESI) m/z 778.3 (M+H);

HRMS: calculado para $C_{39}H_{47}N_5O_{12} \cdot HCl$, 813.2988; encontrado (ESI+), 778.3299;

Ejemplo 68

pivalato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-

5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil) (Terc-butil) amino]carbonil}oxi)metilo



El compuesto de Referencia 78 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminonociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

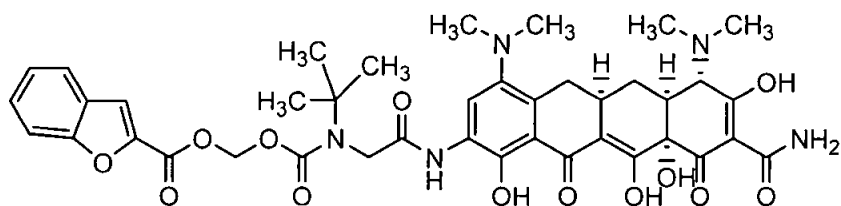
MS (ESI) m/z 744.5 (M+H);

HRMS: calculado para $C_{36}H_{49}N_5O_{12} \cdot HCl$, 779.3145; encontrado (ESI+), 744.34434;

Ejemplo 69

Preparado de acuerdo al Esquema II

1-benzofuran-2-carboxilato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil) (Terc-butil) amino]carbonil}oxi)metilo



El compuesto de Referencia 79 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

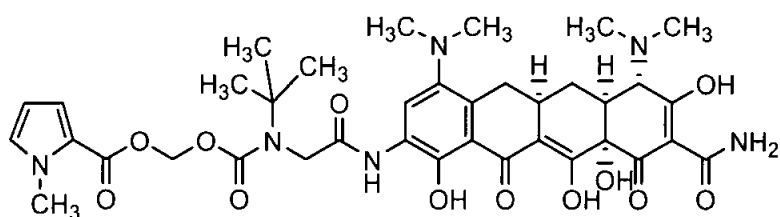
MS (ESI) m/z 804.4 (M+H);

MS (ESI) m/z 402.7 (M+2H);

HRMS: calculado para $C_{40}H_{45}N_5O_{13} \cdot HCl$, 839.2781; encontrado (ESI+), 804.30779;

Ejemplo 70

1-benzofuran-2-carboxilato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butyl)amino]carbonil)oxi)metilo



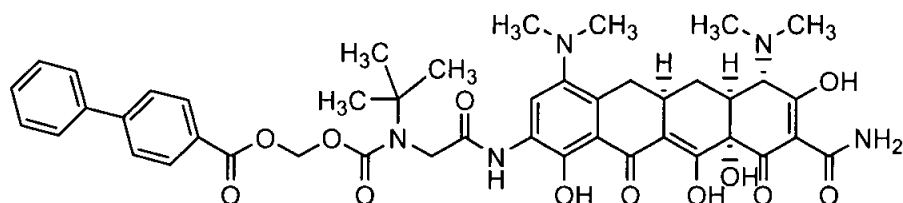
El compuesto de Referencia 80 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 767.4 (M+H);

HRMS: calculado para $C_{37}H_{46}N_6O_{12}$, 766.3174; encontrado (ESI+), 767.32406;

Ejemplo 71

1,1'-bifenil-4-carboxilato de ({[(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



El compuesto de Referencia 81 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

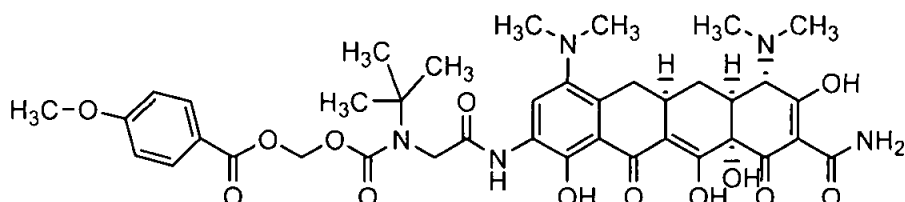
MS (ESI) m/z 838.2 (M-H);

MS (ESI) m/z 113 (TFA-H);

HRMS: calculado para $C_{44}H_{49}N_5O_{12} \cdot HCl$, 875.3145; encontrado (ESI+), 840.34496;

Ejemplo 72

4-metoxibenzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil)oxi)metilo



El compuesto de Referencia 82 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

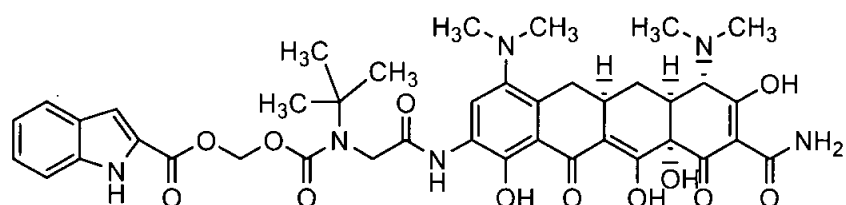
MS (ESI) m/z 792.3 (M-H);

HRMS: calculado para $C_{39}H_{47}N_5O_{13} \cdot HCl$, 829.2937; encontrado (ESI+), 794.32511;

Ejemplo 73

Preparado de acuerdo al Esquema II

1H-indol-2-carboxilato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil)oxi)metilo

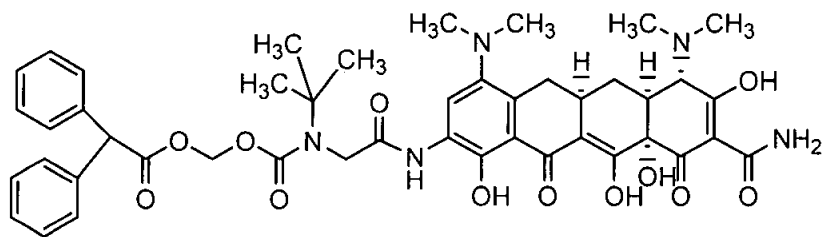


El compuesto de Referencia 83 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminocicliclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 803.4 (M+H); HRMS: calculado para $C_{40}H_{46}N_6O_{12} \cdot HCl$, 838.2941; encontrado (ESI+), 803.32375;

Ejemplo 74

difenilacetato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil) (Terc-butil)amino]carbonil}oxi)metilo



El compuesto de Referencia 84 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-

aminominciclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

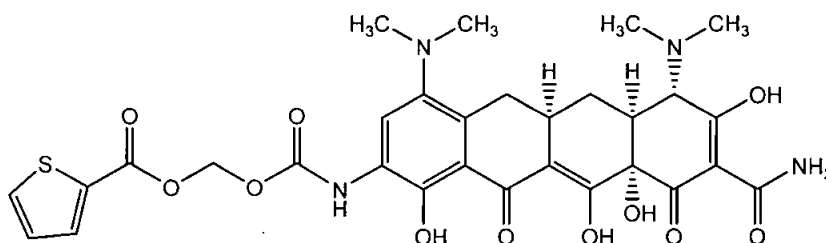
MS (ESI) m/z 852.4 (M-H);

HRMS: calculado para $C_{45}H_{51}N_5O_{12} \cdot HCl$, 889.3301; encontrado (ESI-), 852.3463;

Ejemplo 75

Preparado de acuerdo al Esquema 6

tiofen-2-carboxilato de [({[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}carbonil)oxi]metilo



El compuesto del título se prepara mediante el procedimiento del Ejemplo 42, utilizando tiofen-2-carboxilato de [(clorocarbonil)oxi]metilo en lugar del Compuesto de Referencia 109 para dar el producto del ejemplo.

MS (ESI) m/z 655.2 (M-H);

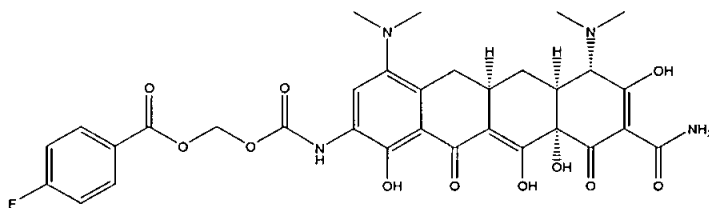
HRMS: calculado para $C_{30}H_{32}N_4O_{11}S \cdot HCl$, 692.1555; encontrado (ESI+), 657.18613;

424

Ejemplo 76

Preparado de acuerdo al Esquema 6

4-fluorobenzoato de [(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}carbonil)oxi]metilo



El compuesto del título se prepara mediante el procedimiento del Ejemplo 42, utilizando 4-fluorobenzoato de [(clorocarbonil)oxi]metilo en lugar del Compuesto de Referencia 109 para dar el producto del ejemplo.

MS (ESI) m/z 667.2 (M-H);

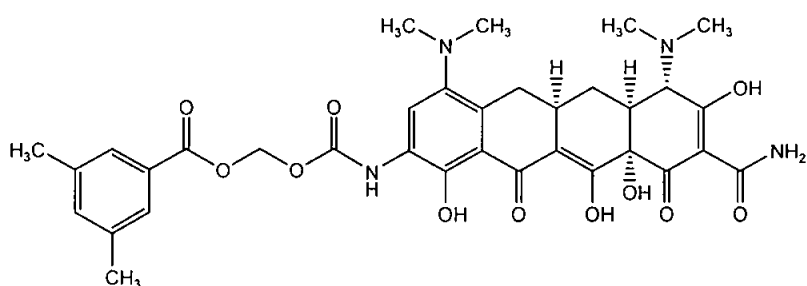
HRMS: calculado para $C_{32}H_{33}FN_4O_{11} \cdot HCl$, 704.1897; encontrado (ESI+), 669.22024;

Ejemplo 77

Preparado de acuerdo al Esquema 6

3,5-dimetilbenzoato de [(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}carbonil)oxi]metilo

479



El compuesto del título se prepara mediante el procedimiento del Ejemplo 42, utilizando 3,5-dimetilbenzoato de [(clorocarbonil)oxi]metilo en lugar del Compuesto de Referencia 109 para dar el producto del ejemplo.

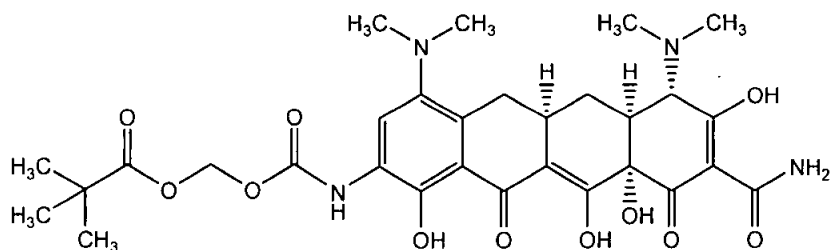
MS (ESI) m/z 679.2 (M+H);

HRMS: calculado para $C_{34}H_{38}N_4O_{11} \cdot HCl$, 714.2304; encontrado (ESI+), 679.26076;

Ejemplo 78

Preparado de acuerdo al Esquema 6

pivalato de [(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}carbonil)oxi]metilo



El compuesto del título se prepara mediante el procedimiento del Ejemplo 42, utilizando pivalato de [(clorocarbonil)oxi]metilo

en lugar del Compuesto de Referencia 109 para dar el producto del ejemplo.

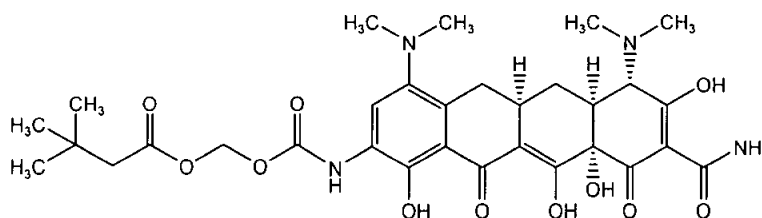
MS (ESI) m/z 631.2 (M+H);

HRMS: calculado para $C_{30}H_{38}N_4O_{11} \cdot HCl$, 666.2304; encontrado (ESI+), 631.26094;

Ejemplo 79

Preparado de acuerdo al Esquema 6

3,3-dimetilbutanoato de [(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)carbonil)oxi]metilo



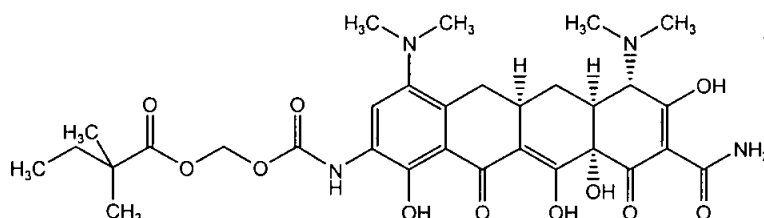
El compuesto del título se prepara mediante el procedimiento del Ejemplo 42, utilizando 3,3-dimetilbutanoato de [(clorocarbonil)oxi]metilo en lugar del Compuesto de Referencia 109 para dar el producto del ejemplo.

MS (ESI) m/z 643.3 (M-H); HRMS: calculado para $C_{31}H_{40}N_4O_{11} \cdot HCl$, 680.2460; encontrado (ESI+), 645.27632;

Ejemplo 80

Preparado de acuerdo al Esquema 6

2,2-dimetilbutanoato de [(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)carbonil)oxi]metilo



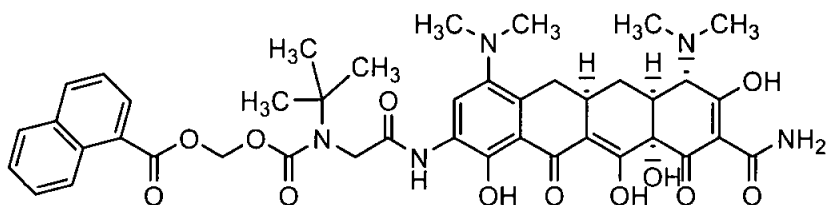
El compuesto del título se prepara mediante el procedimiento del Ejemplo 42, utilizando 2,2-dimetilbutanoato de [(clorocarbonil)oxi]metilo en lugar del Compuesto de Referencia 109 para dar el producto del ejemplo.

MS (ESI) m/z 645.2 (M+H);

HRMS: calculado para $C_{31}H_{40}N_4O_{11} \cdot HCl$, 680.2460; encontrado (ESI+), 645.27637;

Ejemplo 81

1-naftoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butyl)amino)carbonil)oxi)metilo



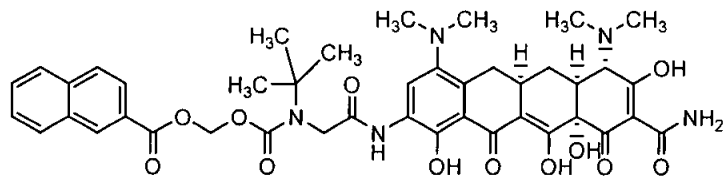
El compuesto de Referencia 85 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminocicliclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 812.5 (M-H);

HRMS: calculado para $C_{42}H_{47}N_5O_{12} \cdot HCl$, 849.2988; encontrado (ESI+), 814.33029;

Ejemplo 82

2-naftoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil)oxi)metilo



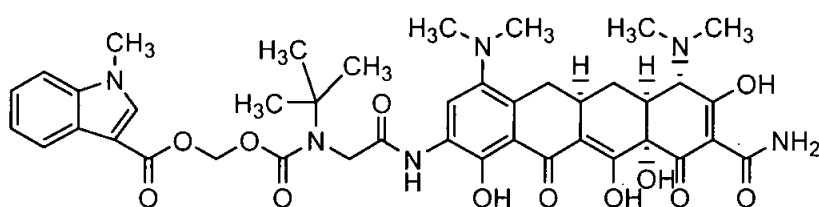
El compuesto de Referencia 86 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-

aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 812.5 (M-H); HRMS: calculado para $C_{42}H_{47}N_5O_{12} \cdot HCl$, 849.2988; encontrado (ESI+), 814.33004;

Ejemplo 83

1-metil-1H-indol-3-carboxilato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil)oxi)metilo



El compuesto de Referencia 87 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

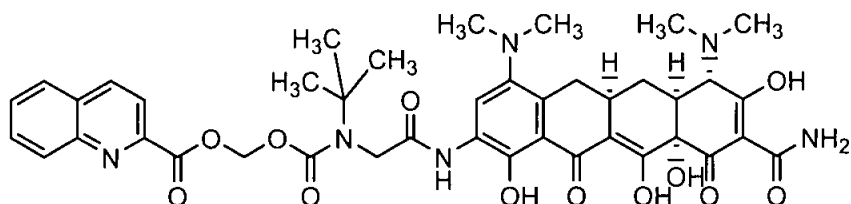
MS (ESI) m/z 815.5 (M-H);

HRMS: calculado para $C_{41}H_{48}N_6O_{12} \cdot HCl$, 852.3097; encontrado (ESI-), 815.32484;

Ejemplo 84

484

quinolin-2-carboxilato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butyl)amino]carbonil)oxi)metilo



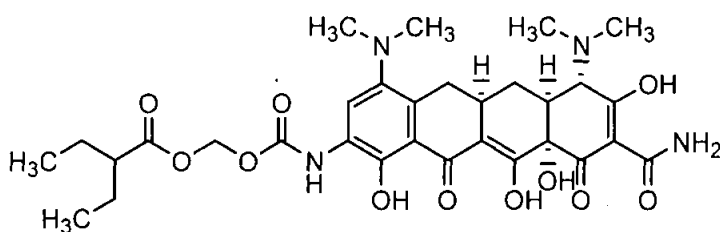
El compuesto de Referencia 88 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 813.5 (M-H); HRMS: calculado para $C_{41}H_{46}N_6O_{12} \cdot HCl$, 850.2941; encontrado (ESI+), 815.32509;

Ejemplo 85

Preparado de acuerdo al Esquema 6

2-etilbutanoato de (((((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}carbonil)oxi]metilo



El compuesto del título se prepara mediante el procedimiento del Ejemplo 42, utilizando 2-etilbutanoato de [(clorocarbonil)oxi]metilo en lugar del Compuesto de Referencia 109 para dar el producto del ejemplo.

MS (ESI) m/z 643.4 (M-H);

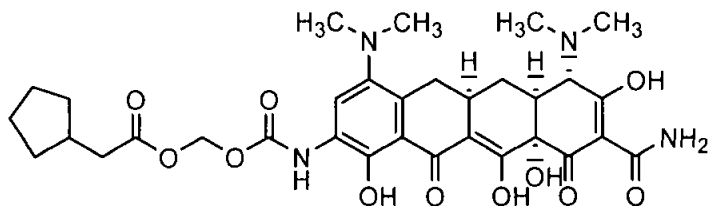
MS (ESI) m/z 1287.7 (2M-H);

HRMS: calculado para $C_{31}H_{40}N_4O_{11} \cdot HCl$, 680.2460; encontrado (ESI+), 645.27618;

Ejemplo 86

Preparado de acuerdo al Esquema 6

ciclopentilacetato de [(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)carbonil)oxi]metilo



El compuesto del título se prepara mediante el procedimiento del Ejemplo 42, utilizando ciclopentilacetato de

[(clorocarbonil)oxi]metilo en lugar del Compuesto de Referencia 109 para dar el producto del ejemplo.

MS (ESI) m/z 655.3 (M-H);

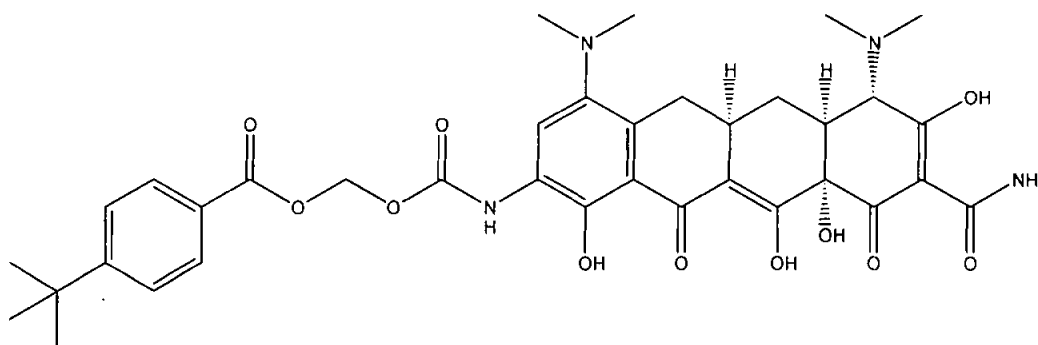
MS (ESI) m/z 1311.7 (2M-H);

HRMS: calculado para $C_{32}H_{40}N_4O_{11} \cdot HCl$, 692.2460; encontrado (ESI+), 657.27572;

Ejemplo 87

Preparado de acuerdo al Esquema 6

4-Terc-butilbenzoato de [({[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}carbonil)oxi]metilo



El compuesto del título se prepara mediante el procedimiento del Ejemplo 42, utilizando 4-Terc-butilbenzoato de [(clorocarbonil)oxi]metilo en lugar del Compuesto de Referencia 109 para dar el producto del ejemplo.

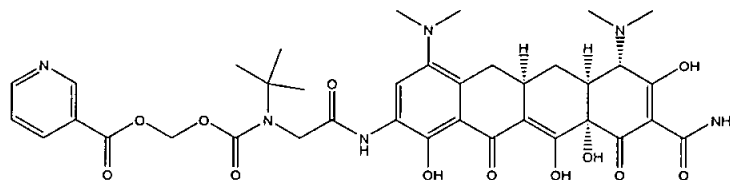
MS (ESI) m/z 705.1 (M-H);

MS (ESI) m/z 1410.9 (2M-H);

HRMS: calculado para $C_{36}H_{42}N_4O_{11} \cdot HCl$, 742.2617; encontrado (ESI+), 707.29336;

Ejemplo 88

nicotinato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butyl)amino]carbonil)oxi)metilo



El compuesto de Referencia 89 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

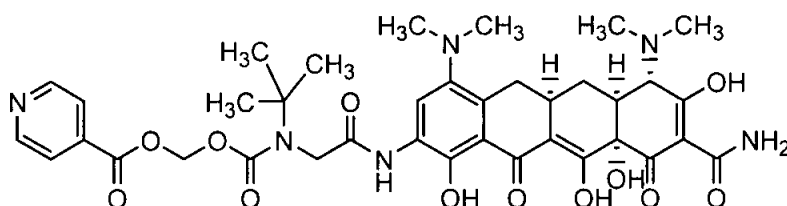
MS (ESI) m/z 763.5 (M-H);

HRMS: calculado para $C_{37}H_{44}N_6O_{12} \cdot HCl$, 800.2784; encontrado (ESI+), 765.30896;

Ejemplo 89

isonicotinato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-

5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil) (Terc-butil) amino]carbonil}oxi)metilo

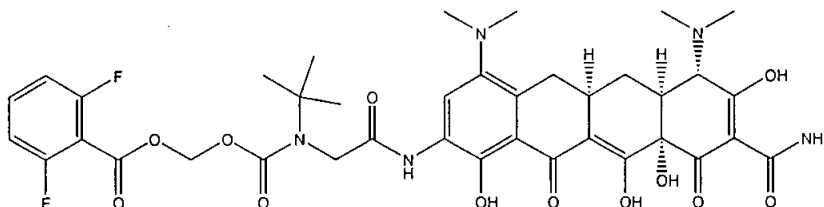


El compuesto de Referencia 90 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminociclinolona utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

HRMS: calculado para $C_{37}H_{44}N_6O_{12} \cdot HCl$, 800.2784; encontrado (ESI+), 765.3117;

Ejemplo 90

2,6-difluorobenzoato de {{{(2-{{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil) (Terc-butil) amino]carbonil}oxi)metilo



El compuesto de Referencia 91 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de

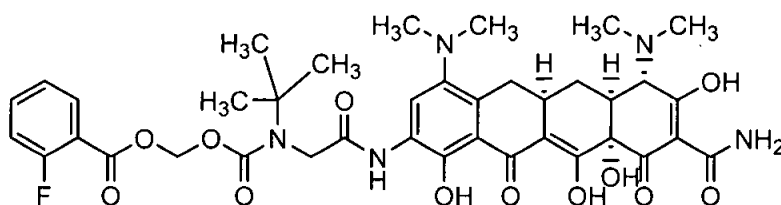
dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 798.2 (M-H);

HRMS: calculado para $C_{38}H_{43}F_2N_5O_{12} \cdot HCl$, 835.2643; encontrado (ESI+), 800.29464;

Ejemplo 91

2-fluorobenzoato de ({[(2-{{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



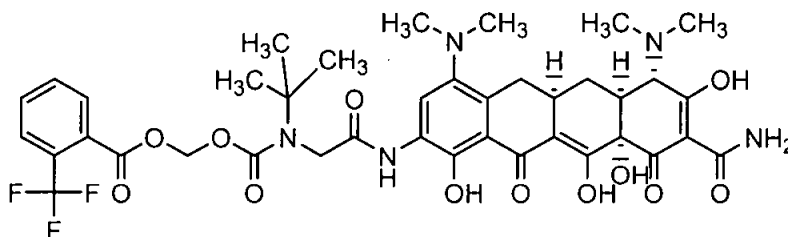
El compuesto de Referencia 92 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 780 (M-H);

HRMS: calculado para $C_{38}H_{44}FN_5O_{12} \cdot HCl$, 817.2737; encontrado (ESI+), 782.30558;

Ejemplo 92

2-(trifluorometil)benzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil)oxi)metilo

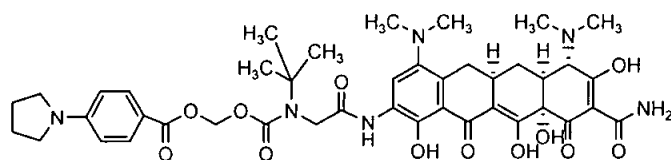


El compuesto de Referencia 93 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

HRMS: calculado para $C_{39}H_{44}F_3N_5O_{12} \cdot HCl$, 867.2705; encontrado (ESI+), 832.30026;

Ejemplo 93

4-pirrolidin-1-ilbenzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil)oxi)metilo



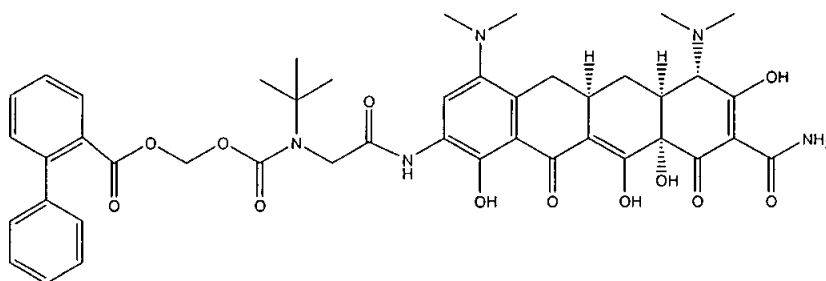
El compuesto de Referencia 94 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminocicliclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 833.4 (M+H);

HRMS: calculado para $C_{42}H_{52}N_6O_{12} \cdot HCl$, 868.3410; encontrado (ESI-), 831.3565;

Ejemplo 94

1,1'-bifenil-2-carboxilato de {{{(2-{{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



El compuesto de Referencia 95 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-

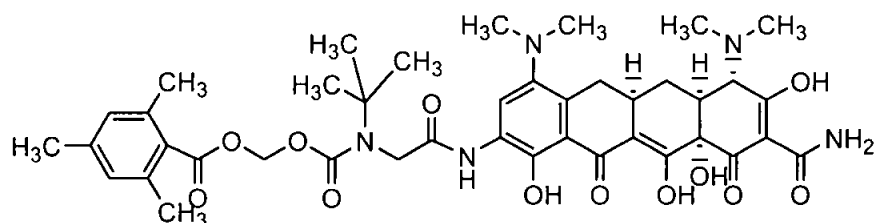
aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 838.4 (M-H);

HRMS: calculado para $C_{44}H_{49}N_5O_{12} \cdot HCl$, 875.3145; encontrado (ESI+), 840.34553;

Ejemplo 95

2,4,6-trimetilbenzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



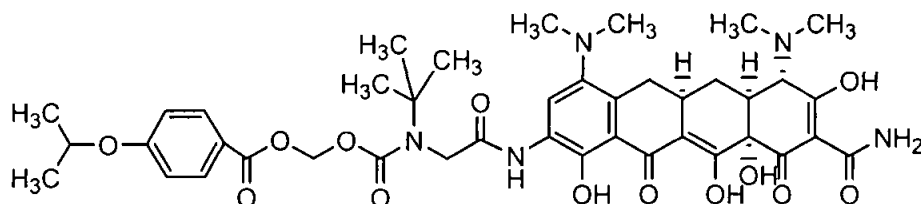
El compuesto de Referencia 96 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 804.5 (M-H);

HRMS: calculado para $C_{41}H_{51}N_5O_{12} \cdot HCl$, 841.3301; encontrado (ESI+), 806.36101;

Ejemplo 96

4-isopropoxibenzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



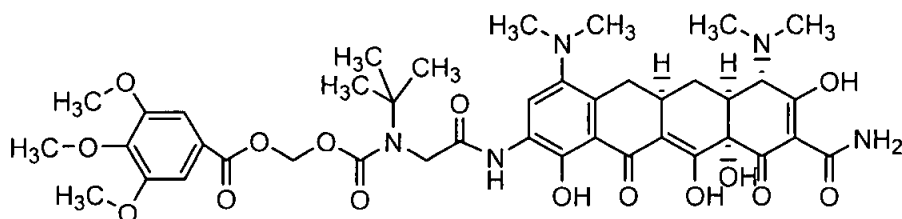
El compuesto de Referencia 97 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 820.2 (M-H);

HRMS: calculado para $C_{41}H_{51}N_5O_{13} \cdot HCl$, 857.3250; encontrado (ESI-), 820.34117;

Ejemplo 97

3,4,5-trimetoxibenzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



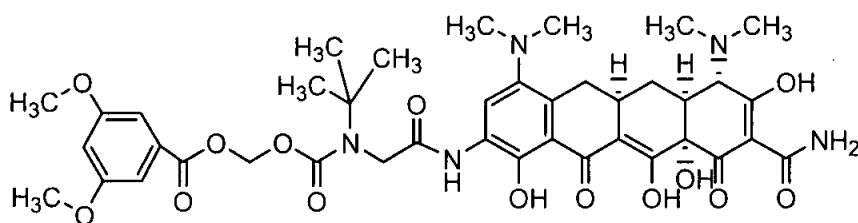
El compuesto de Referencia 98 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 852.2 (M-H);

HRMS: calculado para $C_{41}H_{51}N_5O_{15} \cdot HCl$, 889.3148; encontrado (ESI+), 854.34728;

Ejemplo 98

3,5-dimetoxibenzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



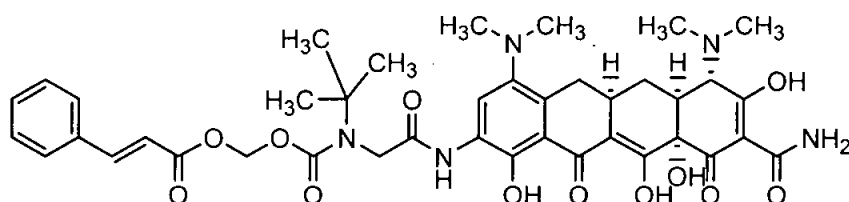
El compuesto de Referencia 99 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 822.1 (M-H);

HRMS: calculado para $C_{40}H_{49}N_5O_{14}$, 824.3349; encontrado (ESI+), 824.3351;

Ejemplo 99

(2E)-3-fenilprop-2-enoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



El compuesto de Referencia 100 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminociclotetrasileno utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

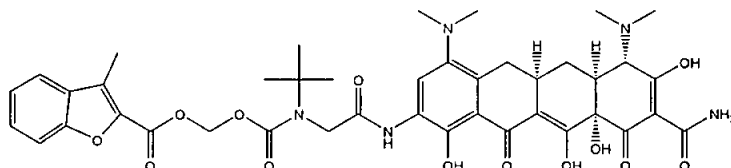
MS (ESI) m/z 788.3 (M-H);

HRMS: calculado para $C_{40}H_{47}N_5O_{12} \cdot HCl$, 825.2988; encontrado (ESI+), 790.33068;

Ejemplo 100

3-metil-1-benzofuran-2-carboxilato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-

10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-
2-oxoetil) (Terc-butil) amino] carbonil} oxi) metilo



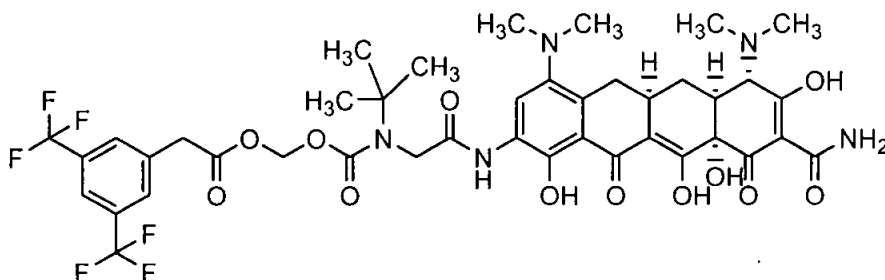
El compuesto de Referencia 101 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 816.5 (M-H);

HRMS: calculado para $C_{41}H_{47}N_5O_{13} \cdot HCl$, 853.2937; encontrado (ESI+), 818.3234;

Ejemplo 101

[3,5-bis(trifluorometil)fenil]acetato de (((2-
{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-
1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-
octahidrotetracen-2-il]amino}-2-oxoetil) (Terc-
butil) amino] carbonil} oxi) metilo



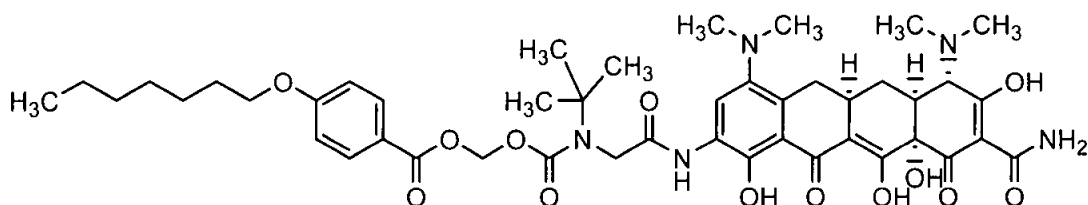
El compuesto de Referencia 102 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo..

MS (ESI) m/z 912 (M-H);

HRMS: calculado para $C_{41}H_{45}F_6N_5O_{12} \cdot HCl$, 949.2736; encontrado (ESI+), 914.30367;

Ejemplo 102

4-(heptiloxi)benzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino))-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



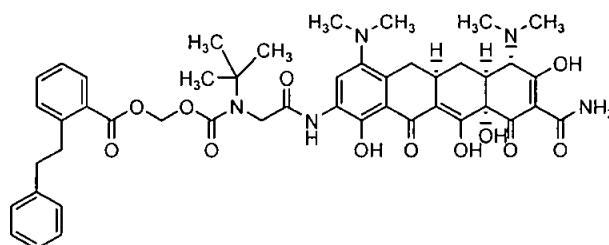
El compuesto de Referencia 103 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 876.1 (M-H);

HRMS: calculado para $C_{45}H_{59}N_5O_{13} \cdot HCl$, 913.3876; encontrado (ESI+), 878.41791;

Ejemplo 103

2-(2-feniletil)benzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



El compuesto de Referencia 104 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

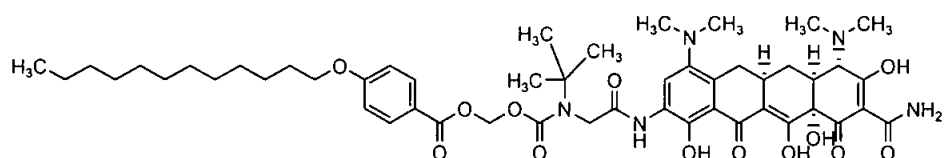
MS (ESI) m/z 866.5 (M-H);

HRMS: calculado para $C_{46}H_{53}N_5O_{12} \cdot HCl$, 903.3458; encontrado (ESI), 868.37357;

Ejemplo 104

4-(dodeciloxi)benzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-

10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-
2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



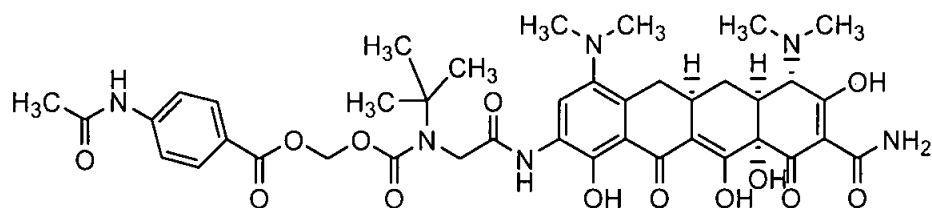
El compuesto de Referencia 105 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 946.7 (M-H);

HRMS: calculado para $C_{50}H_{69}N_5O_{13} \cdot HCl$, 983.4659; encontrado (ESI-), 946.48106;

Ejemplo 105

4-(acetilamino)benzoato de ({[(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



El compuesto de Referencia 106 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de

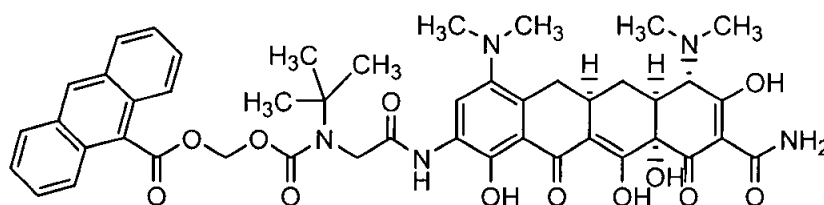
dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 819.1 (M-H);

HRMS: calculado para $C_{40}H_{48}N_6O_{13} \cdot HCl$, 856.3046; encontrado (ESI-), 819.32051;

Ejemplo 106

antraceno-9-carboxilato de ([[(2-[[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil) (Terc-butyl)amino]carbonil)oxi)metilo



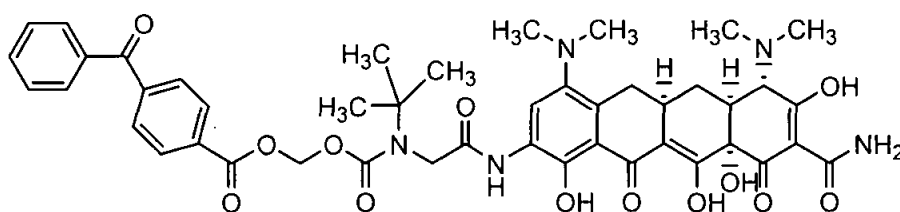
El compuesto de Referencia 107 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminominociclina utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 864.3 (M+H);

HRMS: calculado para $C_{46}H_{49}N_5O_{12} \cdot HCl$, 899.3145; encontrado (ESI-), 862.32855;

Ejemplo 107

4-benzoilbenzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo



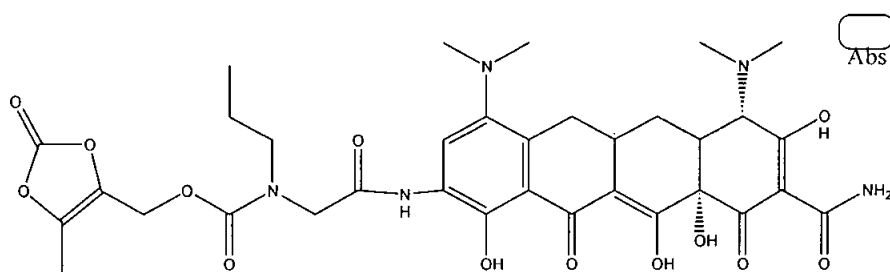
El compuesto de Referencia 108 se hace reaccionar bajo las condiciones del Compuesto de Referencia 109 y el producto de dicha reacción adicionalmente entra en contacto con 9-aminociclinol utilizando las condiciones del Ejemplo 42 para dar el producto del ejemplo.

MS (ESI) m/z 866.3 (M-H);

HRMS: calculado para $C_{45}H_{49}N_5O_{13} \cdot HCl$, 903.3094; encontrado (ESI-), 866.32405;

Ejemplo 108

2-(((7S,10aR)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil(propil)carbamato de (5-metil-2-oxo-1,3-dioxol-4-il)metilo



A una solución de 107 mg (0.166 mmol) de N-propilglicilciclina (N-prop-glicil) en DMPU (2 ml) se agrega 5 equivalentes de carbonato de sodio (95 mg, 0.9 mmol) seguido por 2 equivalentes de 4-nitrofenil carbonato de (5-metil-2-oxo-1,3-dioxol-4-il)metilo (95 mg, 0.33 mmol) el compuesto de Referencia 121 y agitado durante 2 hr a temperatura ambiente. La mezcla de reacción se filtra a través de tierra de diatomáceas y el filtrado se agrega a una mezcla de (1:4) (20 ml) éter: alcohol de isopropilo y HCl (1M en éter) se agrega y el sólido formado se filtra, se redicuelve en agua, el pH se ajusta a aproximadamente 2 y se extrae con cloruro de metileno para dar 15 mg of el producto del ejempl

MS (ESI) m/z 728.5 (M+H);

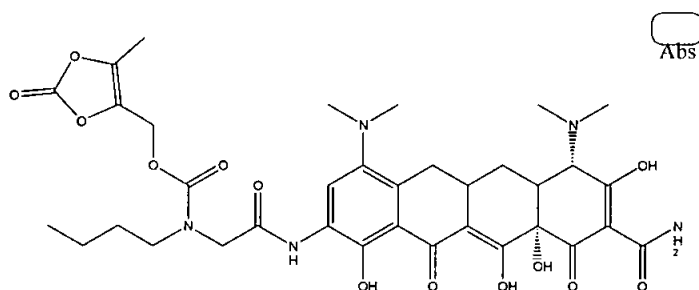
MS (ESI) m/z 364.8 (M+2H);

HRMS: calculado para $C_{34}H_{41}N_5O_{13}$, 727.2701; encontrado (ESI+), 728.27606;

Ejemplo 109

2-{[(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(butil)carbamato de (5-metil-2-oxo-1,3-dioxol-4-il)metilo

503

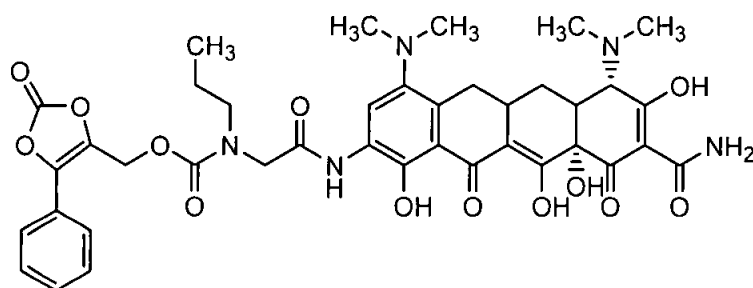


El compuesto del título se prepara mediante el procedimiento del Ejemplo 108, utilizando N-butil-glicilciclina (N-bu-glicil) y 4-nitrofenil carbonato de (5-metil-2-oxo-1,3-dioxol-4-il)metilo del Compuesto de Referencia 121 para dar el producto del ejemplo.

MS (ESI) m/z 742.3 ((M+H)+);

Ejemplo 110

2-([(7R,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil(propil)carbamato (2-oxo-5-fenil-1,3-dioxol-4-il)metilo



El compuesto del título se prepara mediante el procedimiento del Ejemplo 108, utilizando N-propil-glicilciclina (N-prop-glicil) y 4-nitrofenil carbonato de (2-oxo-5-fenil-1,3-dioxol-4-

304

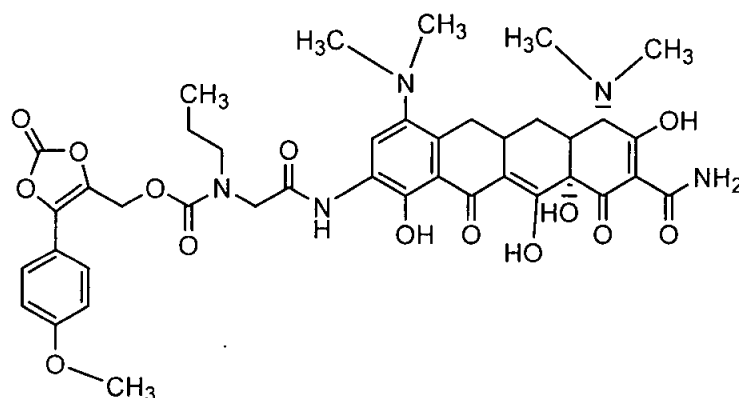
il)metilo del Compuesto de Referencia 122 para dar el producto del ejemplo.

MS (ESI) m/z 790.3 ((M+H)+);

HRMS: calculado para $C_{39}H_{43}N_5O_{13}$, 789.2857; encontrado (ESI+), 790.29243;

Ejemplo 111

2-{[(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(propil)carbamato de [5-(4-metoxifenil)-2-oxo-1,3-dioxol-4-il]metilo

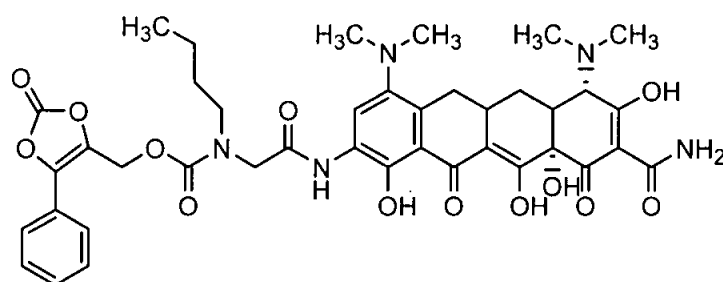


El compuesto del título se prepara mediante el procedimiento del Ejemplo 108, utilizando N-propil-glicilciclina (N-prop-glicil) y 4-nitrofenil carbonato de [5-(4-metoxifenil)-2-oxo-1,3-dioxol-4-il]metilo del Compuesto de Referencia 123 para dar el producto del ejemplo.

MS (ESI) m/z 820.3 ((M+H)+);

Ejemplo 112

2-{[(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(butil)carbamato de (2-oxo-5-fenil-1,3-dioxol-4-il)metilo



El compuesto del título se prepara mediante el procedimiento del Ejemplo 108, utilizando N-butil-glicilciclina (N-bu-glicil) y 4-nitrofenil carbonato de (2-oxo-5-fenil-1,3-dioxol-4-il)metilo del Compuesto de Referencia 122 para dar el producto del ejemplo.

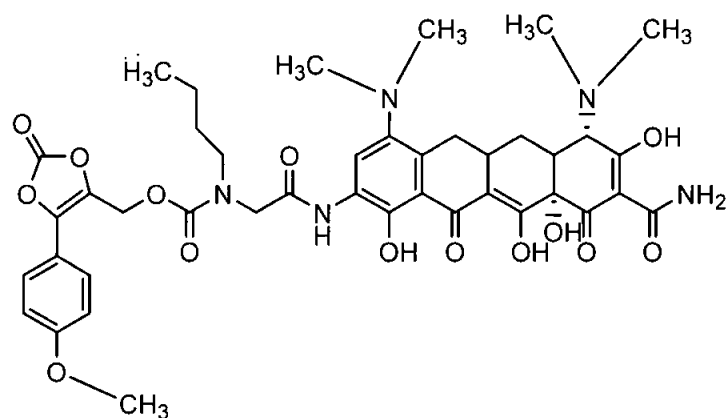
MS (ESI) m/z 804.12 (M+H);

MS (ESI) m/z 402.58 (M+2H);

HRMS: calculado para $C_{40}H_{45}N_5O_{13}$, 803.3014; encontrado (ESI+), 804.30946;

Ejemplo 113

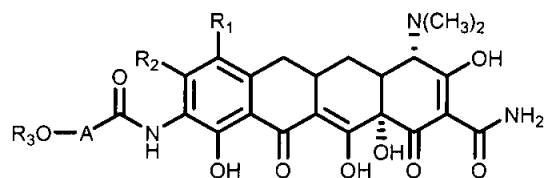
2-{[(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(butil)carbamato de [5-(4-metoxifenil)-2-oxo-1,3-dioxol-4-il]metilo



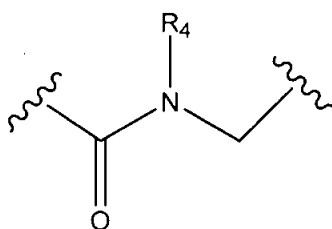
El compuesto del título se prepara mediante el procedimiento del Ejemplo 108, utilizando N-butil-glicilciclina (N-bu-glicil) y 4-nitrofenil carbonato de [5-(4-metoxifenil)-2-oxo-1,3-dioxol-4-il]metilo del Compuesto de Referencia 123 para dar el producto del ejemplo.

REIVINDICACIONES

1. Un compuesto representado por la Fórmula (I);

 $\langle 1 \rangle$

en donde:



A es una parte $\emptyset$ o está ausente;

R₁ se selecciona de hidrógeno, -OH, amino, -NR₇R₈, halógeno, alquilo de 1 a 12 átomos de carbono, opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de halógeno, amino, ciano, cicloalquilo de 3 a 6 átomos de carbono, alquilo de 1 a 12 átomos de carbono, fenilo, hidroxilo, alcoxi de 1 a 12 átomos de carbono, N-alquilo de 1 a 12 átomos de carbono, N-cicloalquilo de 3 a 6 átomos de carbono, heterociclilo de 3 a 8 átomos en anillo, arilo, ariloxi y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo, ariloxi y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alquenilo,

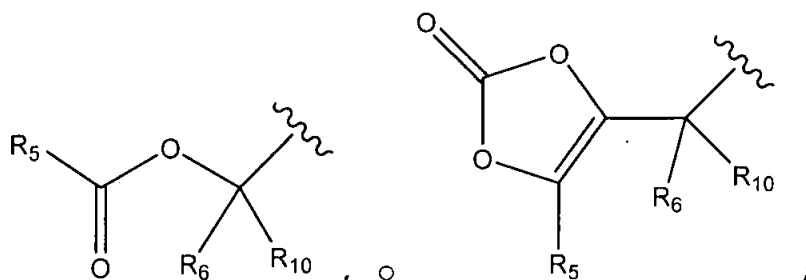
hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, alquénilo de 2 a 12 átomos de carbono opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de fenilo, heteroarilo, halógeno, amino, ciano, alquilo, hidroxilo, alcoxi, arilo, alquínilo y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo y arilo de N-(alquilo de 1 a 12 átomos de carbono)-arilo puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alquénilo, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, ariloxi, heterociclilo y fenilo, y alquínilo de 2 a 12 átomos de carbono opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados del grupo halógeno, amino, ciano, alquilo, hidroxilo, y alcoxi;

R₂ se selecciona de hidrógeno, halógeno, alquilo de 1 a 12 átomos de carbono, opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de halógeno, amino, ciano, cicloalquilo de 3 a 6 átomos de carbono, alquilo de 1 a 12 átomos de carbono, fenilo, hidroxilo, alcoxi de 1 a 12 átomos de carbono, N-alquilo de 1 a 12 átomos de carbono, N-cicloalquilo de 3 a 6 átomos de carbono, heterociclilo de 3 a 8 átomos en anillo, arilo, ariloxi y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo, ariloxi y arilo del N-(alquilo de 1 a 12

átomos de carbono)-arilo puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alqueno, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, alqueno de 2 a 12 átomos de carbono opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de fenilo, heteroarilo, halógeno, amino, ciano, alquilo, hidroxilo, alcoxi, arilo, alquino y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alqueno, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, y

alquino de 2 a 12 átomos de carbono opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados del grupo halógeno, amino, ciano, alquilo, hidroxilo, y alcoxi;

R₃ es una parte de R₉,



R₄ se selecciona de hidrógeno, alquilo de 1 a 12 átomos de carbono, opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de halógeno, amino, ciano, cicloalquilo de 3 a 6 átomos de carbono, alquilo de 1 a 12 átomos de carbono, fenilo, hidroxilo, alcoxi de 1 a 12 átomos de carbono, N-alquilo de 1 a 12 átomos de carbono, N-cicloalquilo de 3 a 6 átomos de carbono, heterociclilo de 3 a 8 átomos en anillo, arilo, ariloxi y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo, ariloxi y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alquenilo, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, alquenilo de 2 a 12 átomos de carbono opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de fenilo, heteroarilo, halógeno, amino, ciano, alquilo, hidroxilo, alcoxi, arilo, alquinilo y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alquenilo, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, alquinilo de 2 a 12 átomos de carbono opcionalmente sustituido con 1 a 3 sustituyentes

independientemente seleccionados del grupo halógeno, amino, ciano, alquilo, hidroxilo, y alcoxi, arilo de 6, 10 o 14 átomos de carbono dicho arilo es opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados entre halógeno, nitro, ciano, alqueno, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, N-(alquilo de 1 a 12 átomos de carbono)-arilo, dicho arilo es opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados entre halógeno, nitro, ciano, alqueno, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, aralquilo de 7 a 16 átomos de carbono opcionalmente sustituido, aroilo de 7 a 13 átomos de carbono opcionalmente sustituidos, SR³, heteroarilo opcionalmente sustituido y heteroarilcarbonilo opcionalmente sustituido;

R₅ se selecciona de alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de halógeno, amino, ciano, cicloalquilo de 3 a 6 átomos de carbono, alquilo de 1 a 12 átomos de carbono, fenilo, hidroxilo, alcoxi de 1 a 12 átomos de carbono, N-alquilo de 1 a 12 átomos de carbono, N-cicloalquilo de 3 a 6 átomos de carbono, heterociclilo de 3 a 8 átomos en anillo, arilo de 6, 10 o 14 átomos de carbono, ariloxi y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en donde dicho arilo, ariloxi y

arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo, puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados entre halógeno, nitro, ciano, alquenilo, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, aralquilo de 7 a 16 átomos de carbono opcionalmente sustituido, aroilo, -CH₂(CO)OCH₂arilo, dicho arilo es opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados entre halógeno, nitro, ciano, alquenilo, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, ariloxi y fenilo, alquenilo de 2 a 12 átomos de carbono opcionalmente sustituido, heteroarilo opcionalmente sustituido, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituido, alquinilo de 2 a 12 átomos de carbono opcionalmente sustituido, cicloalquilo de 3 a 6 átomos en anillo, aril-CH=CH-, cicloalquil-alquilo; y adamantly;

R₆ se selecciona de hidrógeno, alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de halógeno, amino, ciano, cicloalquilo de 3 a 6 átomos de carbono, alquilo de 1 a 12 átomos de carbono, fenilo, hidroxilo, alcoxi de 1 a 12 átomos de carbono, N-alquilo de 1 a 12 átomos de carbono, N-cicloalquilo de 3 a 6 átomos de carbono, heterociclilo de 3 a 8 átomos en anillo, arilo, ariloxi y N-(alquilo de 1 a 12 átomos de carbono)-arilo, en

donde dicho arilo, ariloxi y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alquenilo, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcoxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, y cicloalquilo de 3 a 6 átomos de carbono;

R₇ y R₈ son cada uno independientemente H o alquilo de 1 a 12 átomos de carbono o R₇ y R₈ cuando son opcionalmente tomados juntos con el átomo de nitrógeno al cual cada uno está sujeto forman un anillo heterociclilo de 3 a 8 miembros;

R₉ es aralquilo de 7 a 16 átomos de carbono opcionalmente sustituido o alquilo de 1 a 12 átomos de carbono;

R₁₀ es H o alquilo de 1 a 12 átomos de carbono;

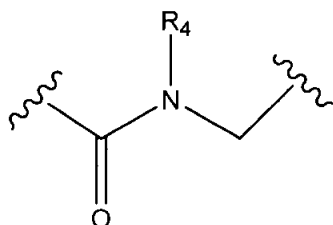
o una sal farmacéuticamente aceptable de estos.

2. Un compuesto de acuerdo a la reivindicación 1, en donde R₁ es -NR₇R₈, R₇ es hidrógeno, R₈ es metilo, etilo, n-propilo, n-butilo, 1-metiletilo, 1-metilpropilo, 2-metilpropilo o 1,1-dimetiletilo o una sal farmacéuticamente aceptable de estos.

3. Un compuesto de acuerdo a la reivindicación 1, en donde R₁ es -NR₇R₈, R₇ es metilo o etilo, R₈ es metilo, etilo, n-propilo, 1-metiletilo, n-propilo, 1-metilpropilo, o 2-

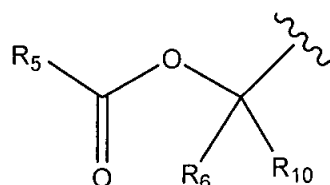
metilpropilo o una sal farmacéuticamente aceptable de estos.

4. Un compuesto de acuerdo a la reivindicación 1, en donde R_1 es $-NR_7R_8$, R_7 y R_8 son tomados juntos con el átomo de nitrógeno al cual cada uno está sujeto forman un anillo heterociclilo de 3 a 8 miembros o una sal farmacéuticamente aceptable de estos.
5. Un compuesto de acuerdo a una cualquiera de las reivindicaciones 1 a 5, en donde R_2 es H o una sal farmacéuticamente aceptable de estos.
6. Un compuesto de acuerdo a una cualquiera de las reivindicaciones 1 a 5, en donde A es una parte



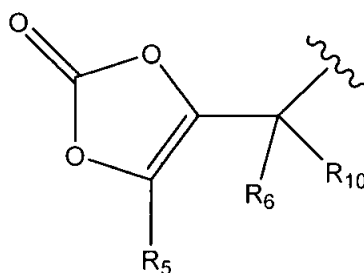
o una sal farmacéuticamente aceptable de estos.

7. Un compuesto de acuerdo a una cualquiera de las reivindicaciones 1 a 5, en donde A está ausente o una sal farmacéuticamente aceptable de estos.
8. Un compuesto de acuerdo a una cualquiera de las reivindicaciones 1 a 7, en donde R_3 es una parte



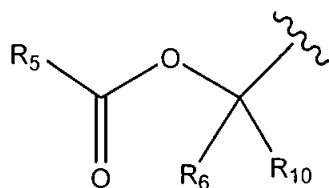
o una sal farmacéuticamente aceptable de estos.

9. Un compuesto de acuerdo a una cualquiera de las reivindicaciones 1 a 7, en donde R₃ es una parte



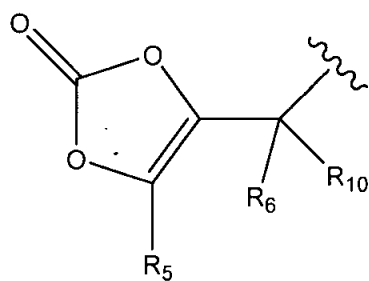
o una sal farmacéuticamente aceptable de estos.

10. Un compuesto de acuerdo a una cualquiera de las reivindicaciones 1 a 7, en donde R₃ es una parte



y R₆ y R₁₀ son H o una sal farmacéuticamente aceptable de estos.

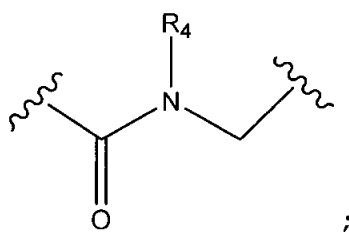
11. Un compuesto de acuerdo a una cualquiera de las reivindicaciones 1 a 7, en donde R₃ es una parte



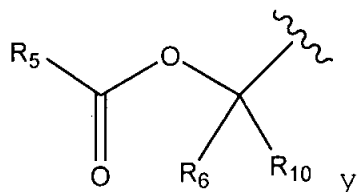
y R_6 y R_{10} son H o una sal farmacéuticamente aceptable de estos.

12. Un compuesto de acuerdo a una cualquiera de las reivindicaciones 1 a 7, en donde R_3 es R_9 o una sal farmacéuticamente aceptable de estos.

13. Un compuesto de acuerdo a la reivindicación 1, en donde A es una parte de,

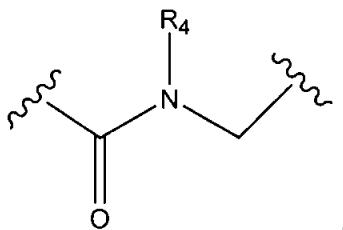


R_3 es una parte de

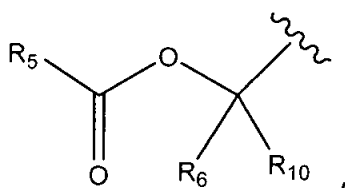


R_5 es arilo de 6 átomos de carbono o una sal farmacéuticamente aceptable de estos.

14. Un compuesto de acuerdo a la reivindicación 1, en donde A es una parte de



R₃ es una parte de,

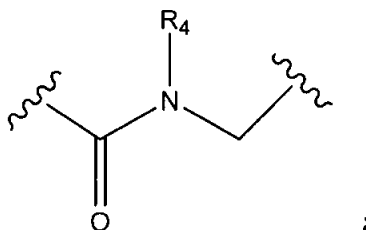


R₄ es 1,1-dimetiletilo y

R₅ es arilo de 6 átomos de carbono o una sal farmacéuticamente aceptable de estos.

15. Un compuesto de acuerdo a la reivindicación 1, en donde

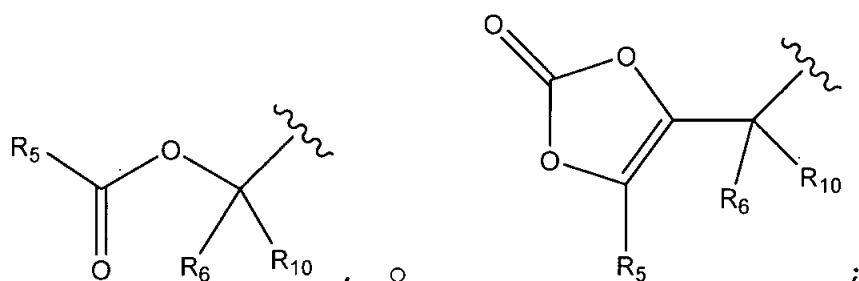
A es una parte



R₁ es -NR₇R₈;

R₂ es hidrógeno;

R₃ es una parte de



R₄ se selecciona de alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de halógeno, amino, ciano, cicloalquilo de 3 a 6 átomos de carbono, alquilo de 1 a 12 átomos de carbono, fenilo, hidroxilo, alcoxi de 1 a 12 átomos de carbono, N-alquilo de 1 a 12 átomos de carbono, N-cicloalquilo de 3 a 6 átomos de carbono, heterociclilo de 3 a 8 átomos en anillo, arilo, y ariloxi en donde dicho arilo y ariloxi es opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados de halógeno, nitro, ciano, alqueno, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcoxicarbonilo, ariloxi y fenilo;

R₅ se selecciona de alquilo de 1 a 12 átomos de carbono opcionalmente sustituidos con 1 a 3 sustituyentes independientemente seleccionados del grupo de halógeno, amino, ciano, cicloalquilo de 3 a 6 átomos de carbono, alquilo de 1 a 12 átomos de carbono, fenilo, hidroxilo, alcoxi de 1 a 12 átomos de carbono, N-alquilo de 1 a 12 átomos de carbono, N-cicloalquilo de 3 a 6 átomos de carbono, heterociclilo de 3 a 8 átomos en anillo, arilo de

6, 10 o 14 átomos de carbono, y ariloxi en donde dicho arilo, ariloxi y arilo del N-(alquilo de 1 a 12 átomos de carbono)-arilo, puede ser opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados entre halógeno, nitro, ciano, alqueno, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, aril-C(O)-, CH₃-C(O)-NH-, aralquilo, ariloxi, heterociclilo y fenilo, aralquilo de 7 a 16 átomos de carbono opcionalmente sustituido, aroilo, -CH₂(CO)OCH₂arilo, dicho arilo es opcionalmente sustituido con 1 a 3 sustituyentes independientemente seleccionados entre halógeno, nitro, ciano, alqueno, hidroxilo, alquilo, haloalquilo, alcoxi, amino, alquilamino, dialquilamino, carboxilo, alcóxicarbonilo, ariloxi y fenilo, heteroarilo opcionalmente sustituido, arilo de 6, 10 o 14 átomos de carbono opcionalmente sustituido, cicloalquilo de 3 a 6 átomos en anillo, aril-CH=CH-, cicloalquil-alquilo; y adamantilo;

R₆ es hidrógeno;

R₇ y R₈ son cada uno independientemente H o alquilo de 1 a 12 átomos de carbono;

R₉ es aralquilo de 7 a 16 átomos de carbono opcionalmente sustituido o alquilo de 1 a 12 átomos de carbono;

R₁₀ es H;

o una sal farmacéuticamente aceptable de estos.

16. Un compuesto de acuerdo a la reivindicación 1, seleccionados de los grupos o sales farmacéuticamente aceptables de estos:

2-metilpropanoato de ([[(2-[(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil)oxi)metilo,

4-metoxibenzoato de ([[(2-[(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil)oxi)metilo,

4-metilbenzoato de ([[(2-[(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil)oxi)metilo,

4-fluorobenzoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil)oxi)metilo,

4-metilbenzoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-

octahidrotetracen-2-il]amino}-2-
oxoetil) (propil) amino] carbonil}oxi) metilo,

4-metoxibenzoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil) (propil) amino] carbonil}oxi) metilo,

ciclobutanocarboxilato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil) (propil) amino] carbonil}oxi) metilo,

4-fluorobenzoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil) (propil) amino] carbonil}oxi) metilo,

Pivalato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil) (propil) amino] carbonil}oxi) metilo,

2-metilpropanoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-

octahidrotetracen-2-il]amino}-2-
oxoetil) (propil)amino]carbonil}oxi)metilo,

fenilacetato de ({[(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-
4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-
dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-
il]amino}-2-oxoetil) (propil)amino]carbonil}oxi)metilo,

fenilacetato de ({[(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-
4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-
dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-
il]amino}-2-oxoetil) (butil)amino]carbonil}oxi)metilo,

pivalato de ({[(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-
bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-
5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-
oxoetil) (butil)amino]carbonil}oxi)metilo

heptanoato de ({[(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-
4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-
dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-
il]amino}-2-oxoetil) (butil)amino]carbonil}oxi)metilo,

ciclobutanocarboxilato de ({[(2-{{(5aR,6aS,7S,10aS)-9-
(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-
tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-
octahidrotetracen-2-il]amino}-2-
oxoetil) (butil)amino]carbonil}oxi)metilo,

523

heptanoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](propil)amino]carbonil)oxi)metilo,

4-Terc-butilbenzoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](butil)amino]carbonil)oxi)metilo,

1,1'-bifenil-4-carboxilato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](butil)amino]carbonil)oxi)metilo,

3,5-dimetilbenzoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](butil)amino]carbonil)oxi)metilo,

1,1'-bifenil-4-carboxilato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](propil)amino]carbonil)oxi)metilo,

3,5-dimetilbenzoato de ([[(2-[[(5aR, 6aS, 7S, 10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil) (propil)amino]carbonil}oxi)metilo,

4-Terc-butilbenzoato de ([[(2-[[(5aR, 6aS, 7S, 10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil) (propil)amino]carbonil}oxi)metilo,

acetato de 1-([[(2-[[(7S, 10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil) (butil)amino]carbonil}oxi)etilo,

ciclohexanocarboxilato de ([[(2-[[(7S, 10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil) (propil)amino]carbonil}oxi)metilo,

ciclohexanocarboxilato de ([[(2-[[(7S, 10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil) (butil)amino]carbonil}oxi)metilo,

3,3-dimetilbutanoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(propil)amino]carbonil}oxi)metilo,

3,3-dimetilbutanoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil}oxi)metilo,

2,2-dimetilbutanoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(propil)amino]carbonil}oxi)metilo,

ciclopentilacetato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil}oxi)metilo,

adamantan-1-carboxilato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-

octahidrotetracen-2-il]amino}-2-
oxoetil) (butil) amino] carbonil}oxi) metilo,

ciclopentilacetato de ([[(2-{[(5aR, 6aS, 7S, 10aS)-9-
(aminocarbonil)-4, 7-bis(dimetilamino)-1, 8, 10a, 11-
tetrahidroxi-10, 12-dioxo-5, 5a, 6, 6a, 7, 10, 10a, 12-
octahidrotetracen-2-il]amino}-2-
oxoetil) (propil) amino] carbonil}oxi) metilo,

adamantan-1-carboxilato de ([[(2-{[(5aR, 6aS, 7S, 10aS)-9-
(aminocarbonil)-4, 7-bis(dimetilamino)-1, 8, 10a, 11-
tetrahidroxi-10, 12-dioxo-5, 5a, 6, 6a, 7, 10, 10a, 12-
octahidrotetracen-2-il]amino}-2-
oxoetil) (propil) amino] carbonil}oxi) metilo,

3, 3-dimetilbutanoato de ([[(2-{[(5aR, 6aS, 7S, 10aS)-9-
(aminocarbonil)-4, 7-bis(dimetilamino)-1, 8, 10a, 11-
tetrahidroxi-10, 12-dioxo-5, 5a, 6, 6a, 7, 10, 10a, 12-
octahidrotetracen-2-il]amino}-2-oxoetil) (Terc-
butil) amino] carbonil}oxi) metilo,

4-Terc-butylbenzoato de ([[(2-{[(5aR, 6aS, 7S, 10aS)-9-
(aminocarbonil)-4, 7-bis(dimetilamino)-1, 8, 10a, 11-
tetrahidroxi-10, 12-dioxo-5, 5a, 6, 6a, 7, 10, 10a, 12-
octahidrotetracen-2-il]amino}-2-oxoetil) (Terc-
butil) amino] carbonil}oxi) metilo,

2, 2-dimetilbutanoato de ([[(2-{[(5aR, 6aS, 7S, 10aS)-9-
(aminocarbonil)-4, 7-bis(dimetilamino)-1, 8, 10a, 11-

tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-
octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-
butil)amino]carbonil}oxi)metilo,

2-metilpropanoato de {{{(2-{{{(5aR,6aS,7S,10aS)-9-
(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-
tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-
octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-
butil)amino]carbonil}oxi)metilo,

ciclopentanocarboxilato de {{{(2-{{{(5aR,6aS,7S,10aS)-9-
(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-
tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-
octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-
butil)amino]carbonil}oxi)metilo,

4-metilbenzoato de {{{(2-{{{(5aR,6aS,7S,10aS)-9-
(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-
tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-
octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-
butil)amino]carbonil}oxi)metilo,

heptanoato de {{{(2-{{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-
4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-
dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-
il]amino}-2-oxoetil)(Terc-
butil)amino]carbonil}oxi)metilo, y

4-metoxibenzoato de {{{(2-{{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butyl)amino]carbonil}oxi)metilo.

17. Un compuesto de acuerdo a la reivindicación 1 seleccionado del grupo

2-{{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(propil)carbamato de bencilo,

2-{{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(propil)carbamato de etilo, y

2-{{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(propil)carbamato de isobutilo.

o sales farmacéuticamente aceptables de estos.

18. Un compuesto de acuerdo a la reivindicación 1 seleccionado del grupo

tiofen-2-carboxilato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil]oxi)metilo,

tiofen-2-carboxilato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(propil)amino]carbonil]oxi)metilo,

tiofen-3-carboxilato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(propil)amino]carbonil]oxi)metilo,

tiofen-3-carboxilato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil]oxi)metilo,

2-furoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(butil)amino]carbonil]oxi)metilo, y

2-furoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(propil)amino]carbonil]oxi)metilo.

o sales farmacéuticamente aceptables de estos.

19. Un compuesto de acuerdo a la reivindicación 1 seleccionado del grupo

propionato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil]oxi)metilo,

ciclohexanocarboxilato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil]oxi)metilo,

3,5-dimetilbenzoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil]oxi)metilo,

4-fluorobenzoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](Terc-butyl)amino]carbonil)oxi)metilo,

3-metilbutanoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](Terc-butyl)amino]carbonil)oxi)metilo,

ciclopentilacetato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](Terc-butyl)amino]carbonil)oxi)metilo,

4-(trifluorometil)benzoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](Terc-butyl)amino]carbonil)oxi)metilo,

ciclopropanocarboxilato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](Terc-butyl)amino]carbonil)oxi)metilo,

adamantan-1-carboxilato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butyl)amino]carbonil}oxi)metilo,

2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(Terc-butyl)carbamato de butilo,

2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(Terc-butyl)carbamato de isobutilo,

2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(Terc-butyl)carbamato de metilo,

pentanoato de ({[(2-{[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butyl)amino]carbonil}oxi)metilo,

532

ciclobutanocarboxilato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](Terc-butyl)amino]carbonil)oxi)metilo,

3-ciclohexilpropanoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](Terc-butyl)amino]carbonil)oxi)metilo,

(4-fluorofenoxi)acetato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](Terc-butyl)amino]carbonil)oxi)metilo,

ciclohexilacetato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](Terc-butyl)amino]carbonil)oxi)metilo,

2,6-dimetilbenzoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](Terc-butyl)amino]carbonil)oxi)metilo,

fenilacetato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butyl)amino]carbonil}oxi)metilo,

pivalato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butyl)amino]carbonil}oxi)metilo,

1,1'-bifenil-4-carboxilato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butyl)amino]carbonil}oxi)metilo,

1-naftoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butyl)amino]carbonil}oxi)metilo,

2-naftoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butyl)amino]carbonil}oxi)metilo,

534

2,6-difluorobenzoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

2-fluorobenzoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

2-(trifluorometil)benzoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

1,1'-bifenil-2-carboxilato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

2,4,6-trimetilbenzoato de ([[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-

octahidrotetracen-2-il]amino)-2-oxoetil) (Terc-
butil)amino]carbonil}oxi)metilo,

4-isopropoxibenzoato de ({[(2-{{(5aR,6aS,7S,10aS)-9-
(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-
tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-
octahidrotetracen-2-il]amino)-2-oxoetil) (Terc-
butil)amino]carbonil}oxi)metilo,

3,4,5-trimetoxibenzoato de ({[(2-{{(5aR,6aS,7S,10aS)-9-
(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-
tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-
octahidrotetracen-2-il]amino)-2-oxoetil) (Terc-
butil)amino]carbonil}oxi)metilo,

3,5-dimetoxibenzoato de ({[(2-{{(5aR,6aS,7S,10aS)-9-
(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-
tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-
octahidrotetracen-2-il]amino)-2-oxoetil) (Terc-
butil)amino]carbonil}oxi)metilo,

(2E)-3-fenilprop-2-enoato de ({[(2-{{(5aR,6aS,7S,10aS)-9-
(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-
tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-
octahidrotetracen-2-il]amino)-2-oxoetil) (Terc-
butil)amino]carbonil}oxi)metilo,

[3,5-bis(trifluorometil)fenil]acetato de ({[(2-
{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-

bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

4-(heptiloxi)benzoato de ([[2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

2-(2-feniletel)benzoato de ([[2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

4-(dodeciloxi)benzoato de ([[2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

4-(acetilamino)benzoato de ([[2-[[[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

538

antraceno-9-carboxilato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butyl)amino]carbonil)oxi)metilo,

4-benzoilbenzoato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butyl)amino]carbonil)oxi)metilo, y

difenilacetato de (((2-(((5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butyl)amino]carbonil)oxi)metilo.

20. Un compuesto de acuerdo a la reivindicación 1 seleccionado del grupo

4-fluorobenzoato de ((([(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)carbonil)oxi]metilo,

3,5-dimetilbenzoato de ((([(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-

tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-
octahidrotetracen-2-il]amino}carbonil)oxi]metilo,

pivalato de [({[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-
bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-
5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-
il]amino}carbonil)oxi]metilo,

3,3-dimetilbutanoato de [({[(5aR,6aS,7S,10aS)-9-
(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-
tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-
octahidrotetracen-2-il]amino}carbonil)oxi]metilo,

2,2-dimetilbutanoato de [({[(5aR,6aS,7S,10aS)-9-
(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-
tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-
octahidrotetracen-2-il]amino}carbonil)oxi]metilo,

2-etilbutanoato de [({[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-
4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-
dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-
il]amino}carbonil)oxi]metilo,

tiofen-2-carboxilato de [({[(5aR,6aS,7S,10aS)-9-
(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-
tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-
octahidrotetracen-2-il]amino}carbonil)oxi]metilo,

ciclopentilacetato de [({[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}carbonil)oxi]metilo, y

4-Terc-butilbenzoato de [({[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}carbonil)oxi]metilo.

o sales farmacéuticamente aceptables de estos.

21. Un compuesto de acuerdo a la reivindicación 1 seleccionado del grupo

1H-indol-2-carboxilato de ({[(2-({[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil)oxi)metilo,

nicotinato de ({[(2-({[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil)oxi)metilo,

isonicotinato de ({[(2-({[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-

dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

4-pirrolidin-1-ilbenzoato de ({[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

3-metil-1-benzofuran-2-carboxilato de ({[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

1-metil-1H-indol-3-carboxilato de ({[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

quinolin-2-carboxilato de ({[(2-[(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino)-2-oxoetil)(Terc-butil)amino]carbonil}oxi)metilo,

1-benzofuran-2-carboxilato de ({[(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butyl)amino]carbonil)oxi)metilo, y

{{[(2-{{(5aR,6aS,7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil)(Terc-butyl)amino]carbonil)oxi)metil-1-metil-1H-pirrol-2-carboxilato.

o sales farmacéuticamente aceptables de estos.

22. Un compuesto de acuerdo a la reivindicación 1 seleccionado del grupo

2-{{[(7S,10aR)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(propil)carbamato de (5-metil-2-oxo-1,3-dioxol-4-il)metilo,

2-{{[(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-1,8,10a,11-tetrahidroxi-10,12-dioxo-5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-oxoetil(butil)carbamato de (5-metil-2-oxo-1,3-dioxol-4-il)metilo,

542

2- { [(7R,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-
1,8,10a,11-tetrahidroxi-10,12-dioxo-
5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-
oxoetil(propil)carbamato,

[5-(4-metoxifenil)-2-oxo-1,3-dioxol-4-il]metilo 2-
 { [(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-
1,8,10a,11-tetrahidroxi-10,12-dioxo-
5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-
oxoetil(propil)carbamato de (2-oxo-5-fenil-1,3-dioxol-4-
il)metilo,

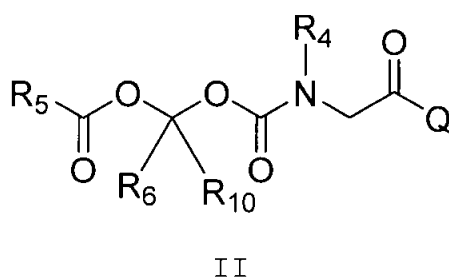
2- { [(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-
1,8,10a,11-tetrahidroxi-10,12-dioxo-
5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-
oxoetil(butil)carbamato de (2-oxo-5-fenil-1,3-dioxol-4-
il)metilo y

2- { [(7S,10aS)-9-(aminocarbonil)-4,7-bis(dimetilamino)-
1,8,10a,11-tetrahidroxi-10,12-dioxo-
5,5a,6,6a,7,10,10a,12-octahidrotetracen-2-il]amino}-2-
oxoetil(butil)carbamato de [5-(4-metoxifenil)-2-oxo-1,3-
dioxol-4-il]metilo.

o sales farmacéuticamente aceptables de estos.

23. Una composición farmacéutica que comprende un compuesto
de acuerdo a una cualquiera de las reivindicaciones 1 a

- 22, en asociación con un portador farmacéuticamente aceptable.
24. Un método para la prevención, tratamiento o control de infecciones bacteriales en animales de sangre caliente que comprende suministrar a dicho animal de sangre caliente una cantidad antibacterial efectiva de acuerdo a una cualquiera de las reivindicaciones 1 a 22, o una sal farmacéuticamente aceptable de estos.
25. Un compuesto de acuerdo a una cualquiera de las reivindicaciones 1 a 22 para la preparación de un medicamento para el tratamiento de infecciones bacteriales.
26. Un compuesto de acuerdo a la Fórmula (II):

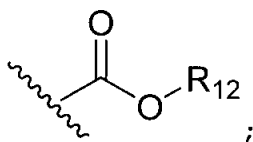


en donde R_4 , R_5 , R_6 , y R_{10} se definen en la reivindicación 1, y

Q es $-OR_{11}$, Cl , Br , o I ;

R_{11} es H , bencilo opcionalmente sustituido con nitro o una parte de la fórmula

544



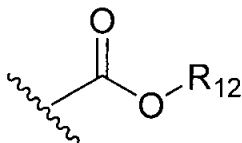
y R₁₂ es alquilo de 1 a 6 átomos de carbono.

27. Un compuesto de acuerdo a la reivindicación 26 en donde R₄ es t-butilo, R₅ es alquilo de 1 a 6 átomos de carbono, y R₁₁ es bencilo opcionalmente sustituido con nitro.

28. Un compuesto de acuerdo a la reivindicación 26 en donde R₄ es alquilo de 1 a 6 átomos de carbono, R₅ es fenilo opcionalmente sustituido y R₁₁ es bencilo opcionalmente sustituido con nitro.

29. Un compuesto de acuerdo a la reivindicación 26 en donde R₅ es alquilo de 1 a 6 átomos de carbono, R₄ es t-butilo y R₁₁ es H.

30. Un compuesto de acuerdo a la reivindicación 26 en donde R₅ es alquilo de 1 a 6 átomos de carbono, R₄ es t-butilo, Q es



y R₁₂ es alquilo de 1 a 6 átomos de carbono.

31. Un compuesto de acuerdo a cualquiera de las reivindicaciones 26 a 30 en donde R_6 y R_{10} son H.

32. Un compuesto de acuerdo a la reivindicación 26 seleccionado del grupo

4-Terc-butilbenzoato de ([2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil)oximetilo,

2,2-dimetilbutanoato de ([2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil)oximetilo,

2-metilpropanoato de ([2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil)oximetilo,

ciclopentanocarboxilato de ([2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil)oximetilo,

4-metilbenzoato de ([2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil)oximetilo,

heptanoato de ([2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil)oximetilo,

propionato de ([2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil)oximetilo,

ciclohexanocarboxilato de ([2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil)oximetilo,

546

3,5-dimetilbenzoato de ([[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

4-fluorobenzoato de ([[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

3-metilbutanoato ([[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

N-(Terc-butyl)-N-
(((ciclopentilacetil)oxi)metoxi)carbonil)glicinato de
bencilo,

4-(trifluorometil)benzoato de ([[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

ciclopropanocarboxilato de ([[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

adamantan-1-carboxilato de ([[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

pentanoato de ([[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

ciclobutanocarboxilato de ([[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

543

(([[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo 3-ciclohexilpropanoato,

N-(Terc-butyl)-N-(((4-fluorofenoxi)acetil}oxi}metoxi)carbonil}glicinato de bencilo,

N-(Terc-butyl)-N-(((ciclohexilacetil)oxi}metoxi}carbonil)glicinato de bencilo,

2,6-dimetilbenzoato de ((([2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

N-(Terc-butyl)-N-(((fenilacetil)oxi}metoxi}carbonil)glicinato de bencilo,

pivalato de ((([2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo

1-benzofuran-2-carboxilato de ((([2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

1-metil-1H-pirrol-2-carboxilato de ((([2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

1,1'-bifenil-4-carboxilato de
(((2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

548

4-metoxibenzoato de ([[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

1H-indol-2-carboxilato de ([[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

N-(Terc-butyl)-N-
([[difenilacetil)oxi]metoxi}carbonil)glicinato de
bencilo,

1-naftoato de ([[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

2-naftoato ([[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

1-metil-1H-indol-3-carboxilato de ([[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

quinolin-2-carboxilato de ([[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

nicotinato de ([[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

isonicotinato de ([[2-(benciloxi)-2-oxoetil](Terc-butyl)amino]carbonil}oxi)metilo,

2,6-difluorobenzoato de [2-(benciloxi)-2-oxoetil] (Terc-butyl)amino]carbonil}oxi)metilo,

2-fluorobenzoato de 2-(benciloxi)-2-oxoetil] (Terc-butyl)amino]carbonil}oxi)metilo,

2-(trifluorometil)benzoato de [2-(benciloxi)-2-oxoetil] (Terc-butyl)amino]carbonil}oxi)metilo,

4-(1H-pirrol-1-il)benzoato de [2-(benciloxi)-2-oxoetil] (Terc-butyl)amino]carbonil}oxi)metilo,

1,1'-bifenil-2-carboxilato de ([2-(benciloxi)-2-oxoetil] (Terc-butyl)amino]carbonil}oxi)metilo,

2,4,6-trimetilbenzoato de [2-(benciloxi)-2-oxoetil] (Terc-butyl)amino]carbonil}oxi)metilo,

4-isopropoxibenzoato de [2-(benciloxi)-2-oxoetil] (Terc-butyl)amino]carbonil}oxi)metilo,

3,4,5-trimetoxibenzoato de 2-(benciloxi)-2-oxoetil] (Terc-butyl)amino]carbonil}oxi)metilo,

3,5-dimetoxibenzoato de 2-(benciloxi)-2-oxoetil] (Terc-butyl)amino]carbonil}oxi)metilo,

Éster de (benciloxicarbonilmetil-Terc-butyl-carbamoiloxi)-metilo de ácido 3-fenil-acrílico,

55°

3-metil-1-benzofuran-2-carboxilato de ([[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo,

N-[[[3,5-bis(trifluorometil)fenil]acetil}oxi)metoxi]carbonil}-N-(Terc-butil)glicinato de bencilo,

4-(heptiloxi)benzoato de ([[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo,

2-(2-feniletil)benzoato de ([[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo,

4-(dodeciloxi)benzoato de ([[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo,

4-(acetilamino)benzoato de ([[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo,

antraceno-9-carboxilato de ([[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo y

4-benzoilbenzoato de ([[2-(benciloxi)-2-oxoetil](Terc-butil)amino]carbonil}oxi)metilo.

N-(Terc-butil)-N-([(4-Terc-butilbenzoil)oxi]metoxi]carbonil)glicina,

N-(Terc-butyl)-N-[[(isobutitriloxi)metoxi]carbonil]glicina,

N-(Terc-butyl)-N-
([[(ciclopentilcarbonil)oxi]metoxi]carbonil)glicina,

N-(Terc-butyl)-N-([[(4-
metilbenzoil)oxi]metoxi]carbonil)glicina,

N-(Terc-butyl)-N-[[(heptanoiloxi)metoxi]carbonil]glicina,

N-(Terc-butyl)-N-[[(propioniloxi)metoxi]carbonil]glicina,

N-(Terc-butyl)-N-
([[(ciclohexilcarbonil)oxi]metoxi]carbonil)glicina,

N-(Terc-butyl)-N-([[(3,5-
dimetilbenzoil)oxi]metoxi]carbonil)glicina,

N-(Terc-butyl)-N-([[(4-
fluorobenzoil)oxi]metoxi]carbonil)glicina,

N-(Terc-butyl)-N-([[(3-
metilbutanoil)oxi]metoxi]carbonil)glicina,

N-(Terc-butyl)-N-
([[(ciclopentilacetil)oxi]metoxi]carbonil)glicina,

N-(Terc-butyl)-N-[[(4-
(trifluorometil)benzoil)oxi]metoxi]carbonil]glicina,

N-(Terc-butyl)-N-

(([(ciclopropilcarbonil)oxi]metoxi)carbonil)glicina,

N-([(1-adamantilcarbonil)oxi]metoxi)carbonil)-N-(Terc-butyl)glicina,

N-(Terc-butyl)-N-([(pentanoiloxi)metoxi]carbonil)glicina,

N-(Terc-butyl)-N-

(([(ciclobutilcarbonil)oxi]metoxi)carbonil)glicina,

N-(Terc-butyl)-N-([(3-

ciclohexilpropanoil)oxi]metoxi)carbonil)glicina,

N-(Terc-butyl)-N-([(4-

fluorofenoxi)acetil]oxi]metoxi)carbonil]glicina

N-(Terc-butyl)-N-

(([(ciclohexilacetil)oxi]metoxi)carbonil)glicina,

N-(Terc-butyl)-N-([(2,6-

dimetilbenzoil)oxi]metoxi)carbonil)glicina,

N-(Terc-butyl)-N-([(fenilacetil)oxi]metoxi)carbonil)glicina,

N-(Terc-butyl)-N-([(2,2-

dimetilpropanoil)oxi]metoxi)carbonil)glicina,

N-([(1-benzofuran-2-ilcarbonil)oxi]metoxi)carbonil)-N-(Terc-butyl)glicina,

N-(Terc-butyl)-N-([(1-metil-1H-pirrol-2-il)carbonil]oxi]metoxi)carbonil]glicina,

N-([(1,1'-bifenil-4-ilcarbonil)oxi]metoxi)carbonil)-N-(Terc-butyl)glicina,

N-(Terc-butyl)-N-([(4-metoxibenzoil)oxi]metoxi)carbonil)glicina,

N-(Terc-butyl)-N-([(1H-indol-2-ilcarbonil)oxi]metoxi)carbonil)glicina,

N-(Terc-butyl)-N-([(difenilacetil)oxi]metoxi)carbonil)glicina,

N-(Terc-butyl)-N-([(1-naftoiloxi)metoxi]carbonil)glicina,

N-(Terc-butyl)-N-([(2-naftoiloxi)metoxi]carbonil)glicina,

N-(Terc-butyl)-N-([(1-metil-1H-indol-3-il)carbonil]oxi]metoxi)carbonil]glicina,

N-(Terc-butyl)-N-([(quinolin-2-ilcarbonil)oxi]metoxi)carbonil)glicina,

55⁴

N-(Terc-butil)-N-([(piridin-3-

ilcarbonil)oxi]metoxi}carbonil)glicina,

N-(Terc-butil)-N-([(isonicotinoiloxi)metoxi]carbonil}glicina,

N-(Terc-butil)-N-([(2,6-

difluorobenzoil)oxi]metoxi}carbonil)glicina,

N-(Terc-butil)-N-([(2-

fluorobenzoil)oxi]metoxi}carbonil)glicina,

N-(Terc-butil)-N-([(2-

(trifluorometil)benzoil]oxi}metoxi}carbonil]glicina,

N-(Terc-butil)-N-([(4-pirrolidin-1-

ilbenzoil)oxi]metoxi}carbonil)glicina,

N-([(1,1'-bifenil-2-ilcarbonil)oxi]metoxi}carbonil)-N-(Terc-

butil)glicina,

N-(Terc-butil)-N-

([(mesitilcarbonil)oxi]metoxi}carbonil)glicina,

N-(Terc-butil)-N-([(4-

isopropoxibenzoil)oxi]metoxi}carbonil)glicina,

N-(Terc-butil)-N-([(3,4,5-

trimetoxibenzoil)oxi]metoxi}carbonil)glicina,

N-(Terc-butyl)-N-([[(3,5-dimetoxibenzoil)oxi]metoxi)carbonil]glicina,

N-(Terc-butyl)-N-([[(2E)-3-fenilprop-2-enoil]oxi]metoxi)carbonil]glicina,

N-(Terc-butyl)-N-([[(3-metil-1-benzofuran-2-il)carbonil]oxi]metoxi)carbonil]glicina,

N-([[(3,5-bis(trifluorometil)fenil]acetil)oxi]metoxi)carbonil]-N-(Terc-butyl)glicina,

N-(Terc-butyl)-N-([[(4-(heptiloxi)benzoil]oxi]metoxi)carbonil]glicina,

N-(Terc-butyl)-N-([[(2-(2-feniletal)benzoil]oxi]metoxi)carbonil]glicina,

N-(Terc-butyl)-N-([[(4-(dodeciloxi)benzoil]oxi]metoxi)carbonil]glicina,

N-([[(4-(acetilamino)benzoil]oxi]metoxi)carbonil]-N-(Terc-butyl)glicina,

N-([[(9-antrilcarbonil)oxi]metoxi)carbonil]-N-(Terc-butyl)glicina y

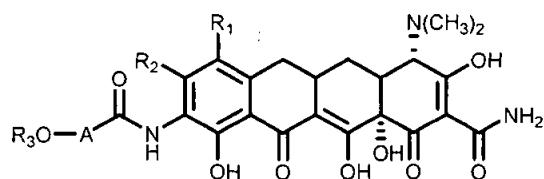
55⁶

N-([(4-benzoilbenzoil)oxi]metoxi)carbonil)-N-(Terc-butyl)glicina

34. Un compuesto de acuerdo a la reivindicación 26 el cual es

Éster de [Terc-butyl-(2-isobutoxicarboniloxi-2-oxo-etil)-carbamoiloxi]-metilo de ácido 3,3-Dimetil-butírico.

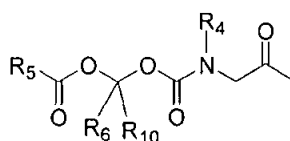
35. Un método para la preparación de compuestos representados por la Fórmula Formula (I);



(I)

en donde:

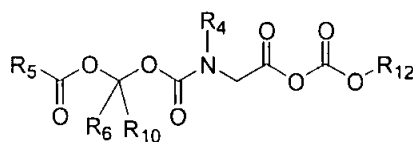
R₃O - A - CO- representa



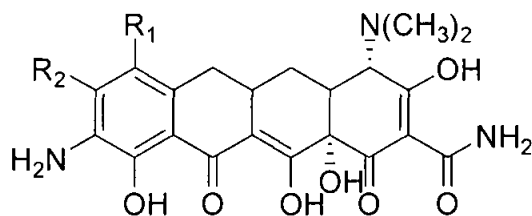
y R₁, R₂, R₄, R₅, R₆, y R₁₀ se definen en la reivindicación 1

o una sal farmacéuticamente aceptable de estos que comprende la etapa de:

- a. hacer reaccionar un intermedio de aciloxicarbamato activado de la fórmula



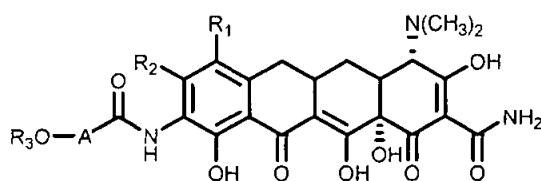
En donde R_4 , R_5 , R_6 , y R_{10} se definen en la reivindicación 1 y R_{12} es como se define en la reivindicación 26 con una 9-aminotetraciclina-7,8-disustituida de la Fórmula



donde R_1 , y R_2 se definen en la reivindicación 1 en la presencia de 1,3-dimetil-3,4,5,6-tetrahidro-2(1H)-pirimidinona y trietilamina para dar un compuesto de Fórmula (I) y, si se desea,

- b. convertir el compuesto de Fórmula (I) en una sal farmacéuticamente aceptable de estos.

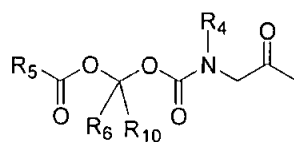
36. Un método para la preparación de compuestos representados por la Fórmula (I);



(I)

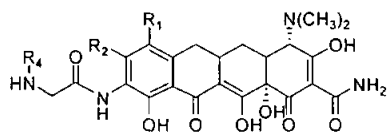
en donde:

R₃O - A - CO- representa

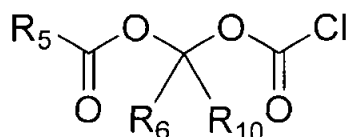


y R₁, R₂, R₄, R₅, R₆, y R₁₀ se definen en la reivindicación 1 o una sal farmacéuticamente aceptable de estos comprende:

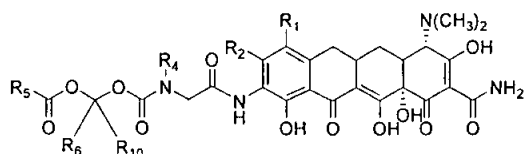
hacer reaccionar una amina de la fórmula



en donde R₁, R₂, R₄, R₅, R₆, y R₁₀ se definen en la reivindicación 1 con un cloro intermedio de la fórmula

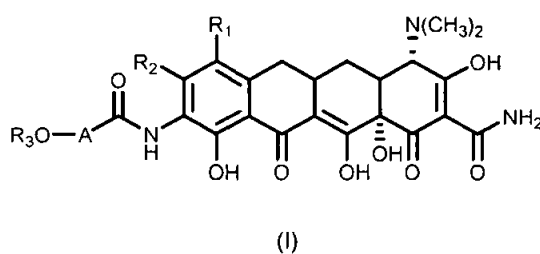


en la presencia de carbonato de metal alcalino, 1,3-dimetil-3,4,5,6-tetrahidro-2(1H)-pirimidinona y acetonitrilo para dar un compuesto de la fórmula



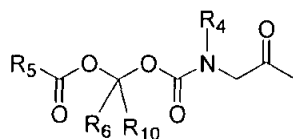
o una sal farmacéuticamente aceptable de estos y, sise desea convertir el compuesto de Fórmula (I) en una sal farmacéuticamente aceptable de estos.

37. Un método para la preparación de compuestos representados por la Fórmula (I);



en donde:

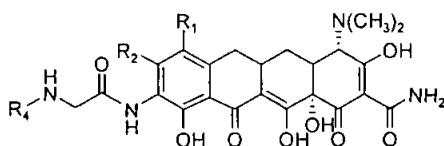
$R_3O - A - CO-$ representa



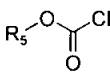
Y

R_1 , R_2 , R_4 , R_5 , R_6 , y R_{10} se definen en la reivindicación 1 o una sal farmacéuticamente aceptable de estos que comprende la etapa de:

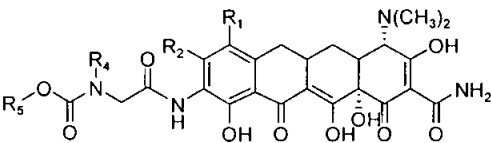
Hacer reaccionar un compuesto de la fórmula



en donde R₁, R₂, y R₄ se definen en la reivindicación 1 con un cloro intermedio de la fórmula

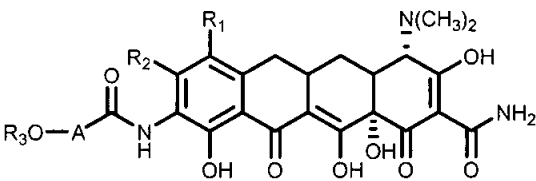


en donde R₅ es como se define en la reivindicación 1 en la presencia de carbonato de metal alcalino, y 1,3-dimetil-3,4,5,6-tetrahidro-2(1H)-pirimidinona en acetonitrilo para dar un compuesto de Fórmula I



y, si se desea, convertir el compuesto de Fórmula (I) en una sal farmacéuticamente aceptable de estos.

38. Un método para la preparación de un compuesto representado por la Fórmula (I);

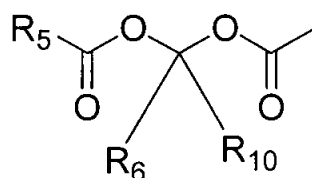


(I)

en donde:

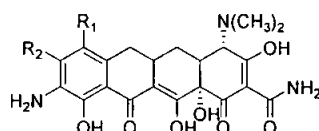
R₃O - A - CO- representa

561

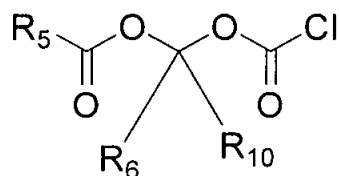


y R_1 , R_2 , R_5 , R_6 , y R_{10} se definen en la reivindicación 1
o una sal farmacéuticamente aceptable de estos que comprende
la etapa de:

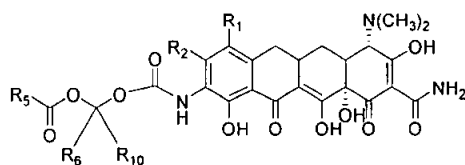
hacer reaccionar una 9-aminotetraciclina-7,8-disustituida de
la fórmula



con un cloro intermedio de la fórmula

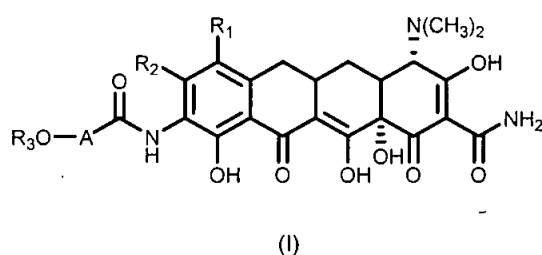


donde R_1 , R_2 , R_5 , R_6 , y R_{10} se definen en la reivindicación en
la presencia de trietilamina y 1,3-dimetil-3,4,5,6-
tetrahidro-2(1H)-pirimidinona para dar un compuesto de la
fórmula



o una sal farmacéuticamente aceptable de estos y, si se desea, convertir el compuesto de Fórmula (I) en una sal farmacéuticamente aceptable de estos.

39. Un método para la preparación de un compuesto representado por la Fórmula (I);

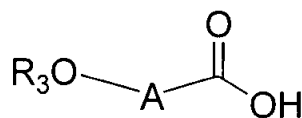


en donde:

A, R₁, R₂, y R₃ se definen en la reivindicación 1

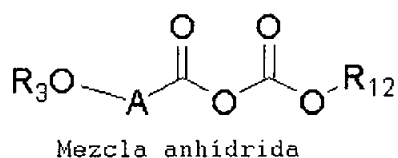
o una sal farmacéuticamente aceptable de estos comprende:

hacer reaccionar un ácido carboxílico de la fórmula

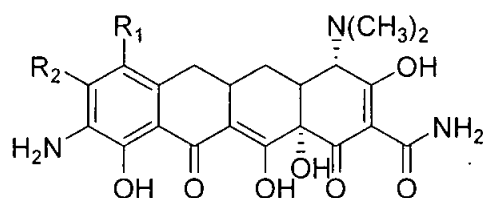


en donde A, y R₃ son como se definió anteriormente

con un cloroformato ClCO₂R₁₂ en donde R₁₂ es alquilo de 1 a 6 átomos de carbono en la presencia de 1,8-bis(dimetilamino)naftaleno en cloruro de metileno para dar una mezcla anhídrida de fórmula

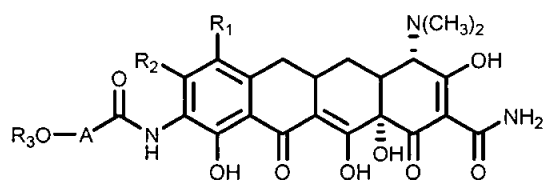


Y hacer reaccionar dicha mezcla anhídrida con una 9-aminotetraciclina-7,8-diubstituida de la fórmula



donde R_1 , y R_2 son como se definió anteriormente

en la presencia de trietilamina y 1,3-dimetil-3,4,5,6-tetrahidro-2(1H)-pirimidinona para dar un compuesto de Fórmula (I)

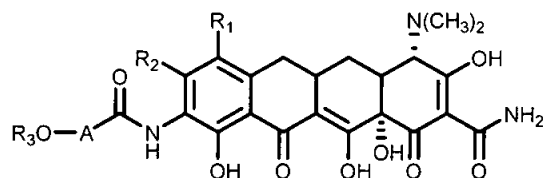


(I)

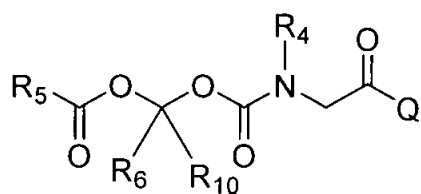
o una sal farmacéuticamente aceptable de estos y, si se desea, convertir el compuesto de Fórmula (I) en una sal farmacéuticamente aceptable de estos.

RESUMEN

Esta invención suministra compuestos de la Fórmula I que tienen la estructura:



donde R_1 , R_2 , R_3 y A se definen en la especificación o una sal farmacéuticamente aceptable de estos se utiliza como agentes antibacteriales. Los compuestos de acuerdo a la Fórmula (II):



en donde Q , R_4 , R_5 , y R_6 y A que se definen en la especificación se utilizan como intermedios químicos.

565

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) 01 February 2007 (01.02.2007)	To: MORAN, Daniel, B. Wyeth Patent Law Department Five Giralda Farms Madison, New Jersey 07940 ETATS-UNIS D'AMERIQUE
Applicant's or agent's file reference AM101559	IMPORTANT NOTIFICATION
International application No. PCT/US2006/033516	International filing date (day/month/year) 29 August 2006 (29.08.2006)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 31 August 2005 (31.08.2005)
Applicant WYETH et al	

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).

(If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, 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(c) 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.

(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 Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) 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
31 August 2005 (31.08.2005)	60/713,112	US	03 October 2006 (03.10.2006)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Athina Nickitas-Etienne Facsimile No. +41 22 338 90 84 Telephone No. +41 22 338 94 43

Telex No. +41 22 338 82 70

PCT/IB/304 (October 2005)

1/C40R6PI50

INTERNATIONAL COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

To:
WYETH
Attn. Moran, Daniel B.
Patent Law Department
Five Giralda Farms
Madison, NJ 07940
ETATS-UNIS D'AMERIQUE

(PCT Rule 44.1)

Applicant's or agent's file reference AM101559	Date of mailing (day/month/year) 13/02/2007
International application No. PCT/US2006/033516	International filing date (day/month/year) 29/08/2006
Applicant WYETH	

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 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no 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 30 months from the priority date.

Within **19 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 20 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 19 months.

See the Annex to Form PCT/IB/301 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.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Sylvia Lampreia

NOTES TO FORM PCT/ISA/220

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 and the written opinion of the International Searching Authority, 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 latter 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 (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

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 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit 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 Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is 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, on account 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 (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

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.

INTERNATIONAL COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference AM101559	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2006/033516	International filing date (day/month/year) 29/08/2006	(Earliest) Priority Date (day/month/year) 31/08/2005
Applicant WYETH		

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 5 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
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 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 No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

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

569

INTERNATIONAL SEARCH REPORT

Inventor's national application No
PL 1/US2006/033516

A. CLASSIFICATION OF SUBJECT MATTER				
INV. C07C237/26	C07C271/22	C07D209/42	C07D213/80	C07D215/48
C07D333/38	A61K31/165	C07D319/06		

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, 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.
X	WO 01/74761 A (TUFTS COLLEGE [US]) 11 October 2001 (2001-10-11) claims 1,55,83,86 -----	1-5,7, 12, 16-25,39
X	WO 02/072031 A2 (PARATEK PHARMACEUTICALS INC [US]) 19 September 2002 (2002-09-19) claims 1,43,72 -----	1-5,12, 16-25
X	P.-E SUM ET AL: "Glycylcyclines. 1. A new generation of potent antibacterial agents through modification of 9-aminotetracyclines" JOURNAL OF MEDICINAL CHEMISTRY., vol. 37, no. 1, 1994, pages 184-188, XP002417786 USAMERICAN CHEMICAL SOCIETY. WASHINGTON. page 185; example 24 ----- -/-	1,3,5,6, 12, 16-22, 35,38,39

☒ Further documents are listed in the continuation of Box C.	☒ See patent family annex.

- * Special categories of cited documents :

 - *A* document defining the general state of the art which is not considered to be of particular relevance
 - *E* earlier document but published on or after the international filing date
 - *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 - *O* document referring to an oral disclosure, use, exhibition or other means
 - *P* document published prior to the international filing date but later than the priority date claimed
- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 - *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 - *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
 - *G* document member of the same patent family

Date of the actual completion of the international search 1 February 2007	Date of mailing of the international search report 13/02/2007
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer VOYIAZOGLOU, D

570

INTERNATIONAL SEARCH REPORT

International application No PCT/US2006/033516

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 639 742 A (LEE VING JICK [US] ET AL) 17 June 1997 (1997-06-17)	1,5,6, 16-22,39
A	column 8, last paragraph; claims 1,68	36,37
X	US 5 494 903 A (HLAVKA JOSEPH J [US] ET AL) 27 February 1996 (1996-02-27)	1-25,39
X	US 5 442 059 A (SUM PHAIK-ENG [US] ET AL) 15 August 1995 (1995-08-15) & compound with RN:157551-18-3; claims 1,82	1,5,6, 16-25,39
X	US 5 607 691 A (HALE RON L [US] ET AL) 4 March 1997 (1997-03-04) & compounds with RN:154146-67-5 and 154146-63-1 column 80, line 33	26,31

521

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/033516

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 24 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

572

INTERNATIONAL SEARCH REPORT

Info. on patent family members

International application No
PCT/US2006/033516

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0174761	A	11-10-2001	AR 033361 A1 AU 5115701 A	17-12-2003 15-10-2001
WO 02072031	A2	19-09-2002	CA 2440757 A1 EP 1381372 A2 JP 2005504722 T	19-09-2002 21-01-2004 17-02-2005
US 5639742	A	17-06-1997	AT 267164 T CA 2120374 A1 DE 69433784 D1 DE 69433784 T2 DK 618190 T3 EP 0618190 A1 ES 2217259 T3 JP 7138220 A PT 618190 T US 5371076 A	15-06-2004 03-10-1994 24-06-2004 25-05-2005 12-07-2004 05-10-1994 01-11-2004 30-05-1995 31-08-2004 06-12-1994
US 5494903	A	27-02-1996	NONE	
US 5442059	A	15-08-1995	AT 205472 T AU 4461193 A BR 1100987 A3 CA 2103845 A1 CN 1087899 A CZ 9301574 A3 DE 69330733 D1 DE 69330733 T2 DK 582829 T3 EP 0582829 A1 ES 2161220 T3 FI 933568 A HK 1009960 A1 HU 71594 A2 HU 66660 A2 HU 9500665 A3 IL 106672 A JP 3633640 B2 JP 6199758 A MX 9304756 A1 NO 932873 A NZ 248342 A PH 30006 A PL 300068 A1 PL 173448 B1 PL 174073 B1 PT 582829 T RU 2123999 C1 SG 52326 A1 SK 84893 A3 US 5495030 A ZA 9305890 A	15-09-2001 17-02-1994 07-12-1999 14-02-1994 15-06-1994 16-03-1994 18-10-2001 04-07-2002 15-10-2001 16-02-1994 01-12-2001 14-02-1994 28-12-2001 29-01-1996 28-12-1994 30-10-1995 22-02-1998 30-03-2005 19-07-1994 28-02-1994 14-02-1994 26-07-1995 29-10-1996 21-02-1994 31-03-1998 30-06-1998 30-01-2002 27-12-1998 28-09-1998 08-06-1994 27-02-1996 11-03-1994
US 5607691	A	04-03-1997	NONE	

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2006/033516

International filing date (day/month/year)
29.08.2006

Priority date (day/month/year)
31.08.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07C237/26 C07C271/22 C07D209/42 C07D213/80 C07D215/48 C07D333/38 A61K31/165 C07D319/06

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") except that 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 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

VOYIAZOGLU, D

Telephone No. +31 70 340-3355



574

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2006/033516

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
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) 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:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic 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**International application No.
PCT/US2006/033516**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 24

because:

☒ the said international application, or the said claims Nos. 24 relate to the following subject matter which does not require an international search (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

576

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2006/033516

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

1. Statement

Novelty (N)	Yes: Claims	8-11,13-22,27-30,32-34,36,37
	No: Claims	1-7,12,23-26,31,35,38,39
Inventive step (IS)	Yes: Claims	27-30,32-34,36,37
	No: Claims	1-26,31,35,38,39
Industrial applicability (IA)	Yes: Claims	1-23,25-39
	No: Claims	

2. Citations and explanations

see separate sheet

577

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2006/033516

Re Item III.

Claim 24 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claims (Article 34(4)(a)(I) PCT).

Re Item V.

1 Reference is made to the following documents:

D1 : WO 01/74761 A (TUFTS COLLEGE [US]) 11 October 2001 (2001-10-11)

D2 : WO 02/072031 A2 (PARATEK PHARMACEUTICALS INC [US]) 19 September 2002 (2002-09-19)

D3 : P.-E SUM ET AL: "Glycylcyclines. 1. A new generation of potent antibacterial agents through modification of 9-aminotetracyclines" JOURNAL OF MEDICINAL CHEMISTRY., vol. 37, no. 1, 1994, pages 184-188, XP002417786 USAMERICAN CHEMICAL SOCIETY. WASHINGTON.

D4 : US 5 639 742 A (LEE VING JICK [US] ET AL) 17 June 1997 (1997-06-17)

D5 : US 5 494 903 A (HLAVKA JOSEPH J [US] ET AL) 27 February 1996 (1996-02-27)

D6 : US 5 442 059 A (SUM PHAIK-ENG [US] ET AL) 15 August 1995 (1995-08-15)

D7 : US 5 607 691 A (HALE RON L [US] ET AL) 4 March 1997 (1997-03-04)

2 INDEPENDENT CLAIM 1

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.

Document D1 discloses tetracycline antibacterial compounds substituted by a carbamate at position 9 (see claims 1,55,83 and 86).

2.2 Document D2 discloses tetracycline antifungal compounds substituted by a carbamate at position 9 (see claims 1,43 and 72).

2.3 Document D3 discloses an intermediate which is part of formula (I) in the case of A being present (see compound 24).

2.4 Document D4 discloses compounds which are part of formula (I) in the case of A

578

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2006/033516

being present (see column 8, last paragraph).

2.5 Document D5 discloses compounds which are part of formula (I) in the case of A being present (see claim 1).

2.6 Document D6 discloses compounds which are part of formula (I) in the case of A being present (see claims 1,82 and compound with RN:157551-18-3).

3 INDEPENDENT CLAIMS 23,24 AND 25

3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 23-25 is not new in the sense of Article 33(2) PCT. Document D1 discloses tetracycline antibacterial compounds substituted by a carbamate at position 9 (see claims 1,55,83 and 86).

3.2 Document D2 discloses tetracycline antifungal compounds substituted by a carbamate at position 9 (see claims 1,43 and 72).

3.3 Document D5 discloses antibiotic compounds which are part of formula (I) in the case of A being present (see claims 1,97).

3.4 Document D6 discloses antibiotic compounds which are part of formula (I) in the case of A being present (see claims 1,82 and compound with RN:157551-18-3).

4 INDEPENDENT CLAIM 26

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 26 is not new in the sense of Article 33(2) PCT.

Document D7 discloses compounds which are part of formula (II) as defined in claim 26 of the present application (see column 80, line 33 and compounds with RN:154146-67-5 and 154146-63-1).

5 INDEPENDENT CLAIMS 35,38,39

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 36 is not inventive in the sense of Article 33(3) PCT.

Document D3 discloses a method preparation of 9-substituted tetracyclines which

579

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2006/033516

involves reacting the 9-aminotetracycline compound with an activated acylderivative (see reaction on page 185 involving compounds 5 and N-t-Boc-glycine N-hydroxysuccinimide ester). The present application uses acyl equivalents which are obvious alternatives to the reactant used already in D3.

6 DEPENDENT CLAIMS 2-22, 31

Dependent claims 2-22, 31 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).

7 INDEPENDENT CLAIMS 27-30,32-34, 36,37

7.1 The subject-matter of claims 27-30,32-34 is novel and inventive in the sense of Articles 33(2) and 33(3) PCT. The compounds mentioned in those claims are neither mentioned nor suggested in D7 as intermediates for the preparation of tetracycline derivatives. Also, the skilled person, having read D7 would not use those compounds to prepare new tetracycline derivatives.

7.2 The subject-matter of claims 36 and 37 is novel and inventive in the sense of Articles 33(2) and 33(3) PCT. In none of the already mentioned documents a process mentioned in these claims has been mentioned or an obvious alternative method has been suggested.

8 COMMENTS

For the assessment of the present claim 24 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such compound for the manufacture of a medicament for a new medical treatment.

500

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2006/033516



Industria y Comercio

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

TARJETA ARCHIVO PROPIETARIOS

582

PATENTE DE INVENCION PCT X MODELO DE UTILIDAD DISEÑO INDUSTRIAL

(21) N° de solicitud: **TENDENCIA**

(22) Fecha de solicitud:

(51) Clasificación Internacional: C07D 237/26, A61K 31/165, C07C 271/22, C07D 209/42, C07D 213/80, C07D 215/48, C07D 319/06, C07D 333/38

(71) Solicitante(s) **WYETH**

(72) Inventor(es) **SUM, Phaik-Eng; MANSOUR, Tarek Suhayl; HOW, David Brian; HOPPER, Darrin William; VERA, Matthew Douglas; SABATINI, Joshua James y SHIM, Jaechul**

(74) Apoderado: **ALVARO CORREA ORDONEZ**

(30) Prioridad

(31) **No. Prioridad**

(32)

Fecha

(33) **País**

60/713,112

31/08/05

US

(85) Fecha inicio fase nacional: **31/03/08**

(87) Publicación internacional

(86) Datos relativos a la presentación de la solicitud PCT

Fecha: **08/03/07**

Fecha de presentación de la solicitud: **29/08/06**

N° publicación:

WO/2007/027599

No. de solicitud

PCT/US2006/033516

(54) Título:

DERIVADOS DE GLICILICLINAS SUSTITUIDOS CON 9-AMINOCARBONILO

Industria y Comercio

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

583

TARJETA ARCHIVO TEMATICO

SUPERINTENDENCIA PATENTE DE INVENCION PCT X MODELO DE UTILIDAD DISEÑO INDUSTRIAL

Nº de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional : C07D 237/26, A61K 31/165, C07C 271/22, C07D 209/42, C07D 213/80, C07D 215/48, C07D 319/06, C07D 333/38

(71) Solicitante(s)

WYETH

(72) Inventor(es) SUM, Phaik-Eng; MANSOUR, Tarek Suhayl; HOW, David Brian; HOPPER, Darrin William; VERA, Matthew Douglas; SABATINI, Joshua James y SHIM, Jaechul

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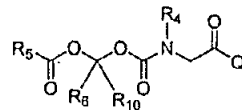
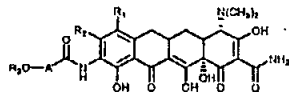
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DERIVADOS DE GLICILCICLINAS SUSTITUIDOS CON 9-AMINOCARBONILO

(57) Resumen: Esta invención suministra compuestos de la Fórmula I que tienen la estructura:

donde R1, R2, R3 y A se definen en la especificación o una sal farmacéuticamente aceptable de estos se utiliza como agentes antibacteriales. Los compuestos de acuerdo a la Fórmula (II):

en donde Q, R4, R5, y R6 y A que se definen en la especificación se utilizan como intermedios químicos.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Industria y Comercio
SUPERINTENDENCIA

**REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT**

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 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 presenta la solicitud []
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

ESQUEMA DE TRAZADO []

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

COMPLETA []

INCOMPLETA []

Irma Responsable

Fecha Febrero 28-2008

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