§ 128

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Apoderado: Carlos Reinaldo Olarte García.

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Patente de Invención ⊗

Vía PCT fase nacional ⊗ Cap.I ☐ Cap. II ⊗

No. Sol. Internacional PCT/EP2005/012038

Fecha de Presentación Internal. 09/nov/2005

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1. Descripción: Folios: 143 a 320 Como se radicó inicialmente.

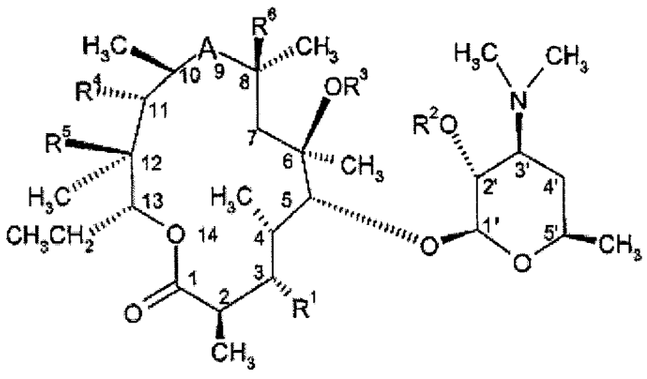
1.2. Reivindicaciones: Folios: 321 a 338 Como se radicó inicialmente
Folios: 397 a

1.4Prioridad: Folio 1: GB 0424959.5; 11/nov/2004

1. Objeto de la invención

§ Título de la solicitud: MACROLONAS-QUINOLONAS AMINO SUSTITUIDAS

§ El objeto de la invención refiere a macrolidos derivados, especialmente dirigidas a las sustituciones de la posición 4" con un separador- quinolin-4(1H)-ona-sustituida, cubiertas bajo la fórmula Markush:



(I)

-Reivindicaciones 1–11,13,14: Un compuesto de la fórmula (I):
-Reivindicación 12: Procedimiento de preparación de los compuestos (I).
-Reivindicación 15: Uso.
-Reivindicación 16: método de tratamiento.
-Reivindicación 17: Composiciones que contiene los compuestos (I).

§ El problema planteado en esta solicitud es la necesidad de compuestos que tengan actividad antimicrobiana.

§ Para solucionar este problema técnico la solicitud en estudio proporciona compuestos a macrolidos derivados, especialmente dirigidos a las sustituciones de la posición 4" con un separador- quinolin-4(1H)-ona-sustituida.

§ Se catalogó la invención, según la Clasificación Internacional de Patentes (IPC.): C07H17/08; A61K31/7048; A61P31/04.

2. De la solicitud de Patente

2.1. Reivindicaciones *(artículo 30 D 486 de la C.A.N.)*

Las reivindicaciones 13 y 14, son inconsistentes, porque se en cabeza como compuesto y el texto de las reivindicaciones es una mezcla de uso con método terapéutico, cuando lo correcto es definir el compuesto mediante sus características técnicas estructurales o mediante sus nombres químicos particulares.
Por lo tanto las reivindicaciones no cumplen con el requisito de claridad, concisión o sustento por la descripción de acuerdo al art. 30 de la Decisión 486.

3. Excepción a la patentabilidad *(artículo 20 literal d) D486 de la C.A.N.)*

La reivindicación 16 reclama un método de tratamiento para el cuerpo humano o animal, por lo tanto está comprendida dentro del ordenamiento del artículo 20 literal d) D486 de la C.A.N.

4. Reivindicaciones relativas a un uso o a un uso distinto *(artículos 14 y 21 D 486 de la C.A.N.)*

La reivindicación 15 reclama los usos y de acuerdo con la legislación actual vigente, el uso no se considera para protección, como se lee en el artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina "... Los Países Miembros otorgarán patentes para las invenciones sean de productos o procedimientos en todos los campos de la tecnología..."; Aquí NO se hace alusión al uso como factor patentable; los segundos usos no son patentables por aplicación del Art. 21. Asimismo, de conformidad con la sentencia del TJAC 89-AI-2000, los usos en general no son patentables.

5. Determinación del Estado de la Técnica

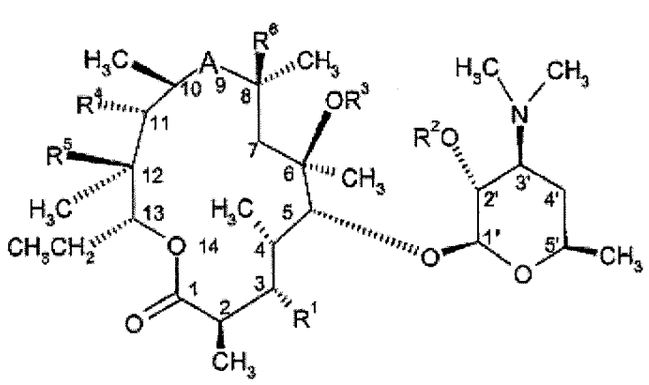
Considerando la fecha de prioridad reclamada de la presente solicitud de patente 11/nov/2004, se realizo la búsqueda del estado de la técnica, en bases de datos donde ésta oficina tiene acceso libre, para búsquedas de documentos relacionados con la materia que se reclama como nueva e inventiva en la presente solicitud.
Encontrándose los siguientes documentos relevantes

N°	Documento	Título	Fecha de Publicación*
D1	WO03042228	Macrolides	22/may/2003

6. Análisis de patentabilidad (según requisito) (artículo 14 D486)

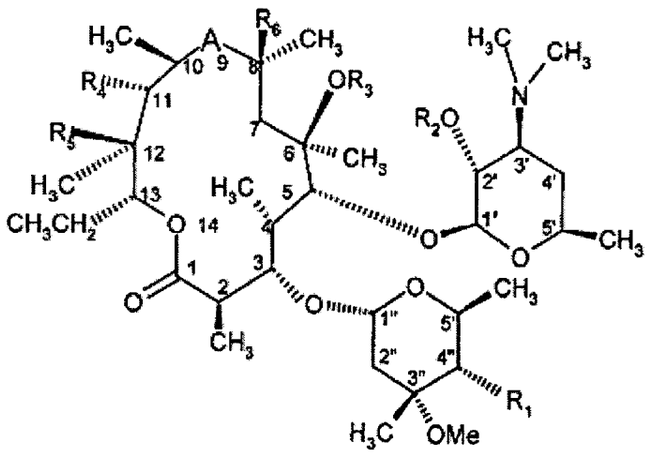
6.1. Novedad *(artículo 16 D486 de la C.A.N.)*

La solicitud reclama macrolidos derivados, especialmente dirigidas a las sustituciones de la posición 4" con un separador- quinolin-4(1H)-ona-sustituida, cubiertas bajo la fórmula Markush:



(I)

-La anterioridad D1 [WO0304228] describe macrolidos con sustituityentes en la posición 4" con un separador- quinolin-4(1H)-ona-sustituida, cubiertas bajo la fórmula (I):



(I)

A is a bivalent radical selected from:

-C(O)-, -C(O)NH-, -NHC(O)-, -N(CH_3)-CH_2-, -CH_2-N(CH_3)- or -C(NO$CH_2OCH_2CH_2OCH_3$)-;

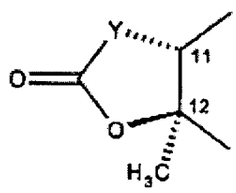
R_1 is $OC(O)(CH_2)_nXR_7$;

R_3 is hydrogen, C_{1-4}alkyl or C_{3-6}alkenyl optionally substituted by 9 to 10 membered fused bicyclic heteroaryl;

R_4 is hydroxy or C_{3-6}alkenyloxy optionally substituted by 9 to 10 membered fused bicyclic heteroaryl;

R_5 is hydroxy or

R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:

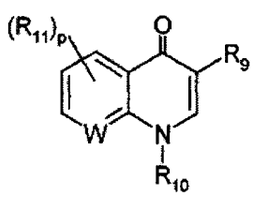


wherein Y is a bivalent radical selected from:

-CH_2-, -CH(CN)-, -O-, -N(R_8)- and -CH(SR_8)-;

R_6 is hydrogen or fluorine;

R_7 is a heterocyclic group having the following structures:



X is -U$(CH_2)_m$Z-.

U and Z independently are a divalent radical selected from:

-N(R_{13})-, -O-, -S(O)q- , -N(R_{13})C(O)-, -C(O)N(R_{13})-, -N[C(O)R_{13}]-,

W is a carbon or a nitrogen atom;

n is 0 or an integer from 1 to 5;

m is an integer from 2 to 8;

p is 0, 1 or 2;

q is 0, 1 or 2;

and pharmaceutically acceptable salts and solvates thereof.

Véase todo el D1, especialmente pága-1-10; 13-20; ejemplos 1-119; reivindicaciones 1-11.

Tal como puede verse los compuestos de fórmula Markush (I) de la solicitud en estudio no cumplen con el requisito exigido en el artículo 16 D486 de la C.A.N.

7. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:
**Una solicitud que no tiene novedad obviamente carece de nivel inventivo, toda vez que los compuestos que no están comprendidos en el estado de la técnica citado, se argumenta y reclaman que tienen el mismo efecto que los comprendidos en la anterioridad.*

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO030422	1-17	Novedad, nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiendo que contra él no procede recurso alguno en la vía gubernativa.

JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 23 ABR. 2012

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,

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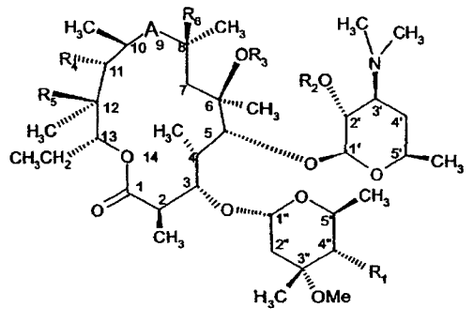
(54) Title: MACROLIDES



(I)

(57) Abstract: The present invention relates to 14 or 15 membered macrolides substitued at the 4" position of formula (I) and pharmaceutically acceptable salts and solvates thereof, to processes for their preparation and their use in therapy or prophylaxis of systemic or topical bacterial infections in a human or animal body.

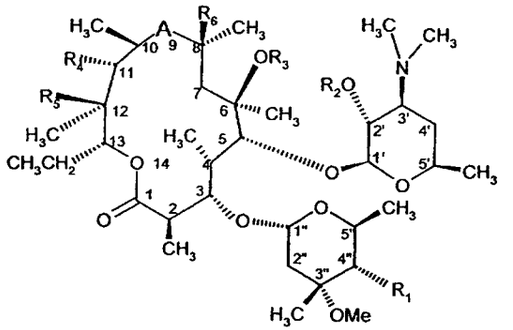
WO 03/042228 A1

D1

Macrolides

The present invention relates to novel semi synthetic macrolides having antibacterial activity. More particularly this invention relates to 14 or 15 membered macrolides substituted at the 4" position, to processes for their preparation, to compositions containing them and to their use in medicine.

Thus, the present invention provides compounds of general formula (I)



(I)

wherein

A is a bivalent radical selected from:

-C(O)-, -C(O)NH-, -NHC(O)-, $-N(CH_3)-CH_2-$, $-CH_2-N(CH_3)-$ or $-C(NOCH_2OCH_2CH_2OCH_3)-$;

R_1 is $OC(O)(CH_2)_nXR_7$;

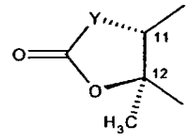
R_2 is hydrogen or a hydroxyl protecting group;

R_3 is hydrogen, C_{1-4}alkyl or C_{3-6}alkenyl optionally substituted by 9 to 10 membered fused bicyclic heteroaryl;

R_4 is hydroxy or C_{3-6}alkenyloxy optionally substituted by 9 to 10 membered fused bicyclic heteroaryl;

R_5 is hydroxy or

R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:



wherein Y is a bivalent radical selected from:

$-CH_2-$, -CH(CN)-, -O-, $-N(R_8)-$ and $-CH(SR_8)-$;

R_6 is hydrogen or fluorine;

R_7 is a heterocyclic group having the following structures:

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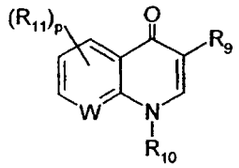
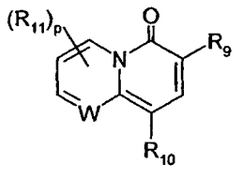
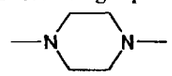


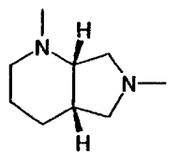
or



R_8 is hydrogen or C_{1-4}alkyl substituted by a group selected from:
optionally substituted phenyl,
optionally substituted 5 or 6 membered heteroaryl,
optionally substituted 9 to 10 membered fused bicyclic heteroaryl;
R_9 is hydrogen, $C(O)OR_{12}$, $C(O)NHR_{12}$ or $C(O)CH_2NO_2$;
R_{10} is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, optionally substituted phenyl or benzyl;
R_{11} is halogen, C_{1-4}alkyl, C_{1-4}thioalkyl, C_{1-4}alkoxy, NH_2, $NH(C_{1-4}alkyl)$ or $N(C_{1-4}alkyl)_2$;
R_{12} is hydrogen or C_{1-4}alkyl;
R_{13} is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, optionally substituted phenyl or benzyl, acetyl or benzoyl;
X is $-U(CH_2)_mZ-$ or X is a group selected from:



or



U and Z independently are a divalent radical selected from:
$-N(R_{13})-$, -O-, -S(O)q- , $-N(R_{13})C(O)-$, $-C(O)N(R_{13})-$, $-N[C(O)R_{13}]-$,
W is a carbon or a nitrogen atom;
n is 0 or an integer from 1 to 5;
m is an integer from 2 to 8;
p is 0, 1 or 2;
q is 0, 1 or 2;
and pharmaceutically acceptable salts and solvates thereof.

Suitable pharmaceutically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable organic or inorganic acids, for example hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonates), phosphates, acetates, citrates, succinates, tartrates, fumarates and maleates.

The solvates may, for example, be hydrates.

References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable acid addition salts together with pharmaceutically acceptable solvates.

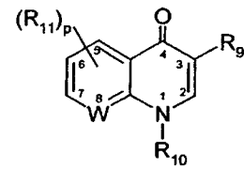
The compound of formula (I) and salts thereof may form solvates (e.g. hydrates) and the invention includes all such solvates.

In the general formula (I) as drawn the solid wedge shaped bond indicates that the bond is above the plane of the paper. The broken bond indicates that the bond is below the plane of the paper.

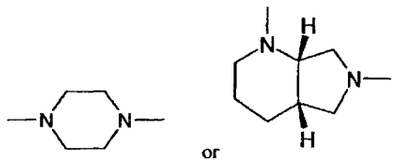
Compounds wherein R_2 represents a hydroxyl protecting group are in general intermediates for the preparation of other compounds of formula (I).

When the group OR_2 is a protected hydroxyl group this is conveniently an ether or an acyloxy group. Examples of particularly suitable ether groups include those in which R_2 is a trialkylsilyl (i.e. trimethylsilyl). When the group OR_2 represents an acyloxy group, then examples of suitable groups R_2 include acetyl or benzoyl.

When R_7 is a heterocyclic group having the following structure:

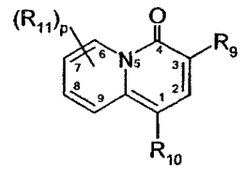


wherein W is carbon or nitrogen, said heterocyclic is linked in the 7 or 6 position to the Z group as above defined or to one of the nitrogen atoms contained in the following structures:

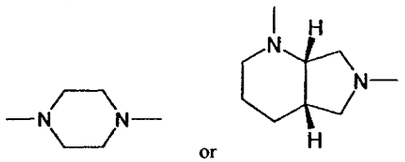


or

When R_7 is a heterocyclic group having the following structure:

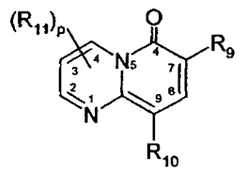


said heterocyclic is linked in the 8 or 7 position to the Z group as above defined or to one of the nitrogen atoms contained in the following structures:

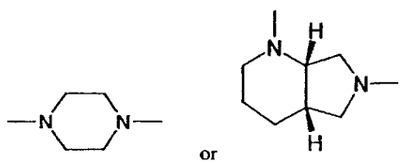


or

When R_7 is a heterocyclic group having the following structure:



said heterocyclic is linked in the 2 or 3 position to the Z group as above defined or to one of the nitrogen atoms contained in the following structures:



or

The term C_{1-4}alkyl as used herein as a group or a part of the group refers to a straight or branched alkyl group containing from 1 to 4 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl.

The term C_{2-6}alkenyl group as used herein as a group or a part of the group refers to a straight or branched alkenyl group containing from 2 to 6 carbon atoms; examples of such groups include 2-propenyl, 1-propenyl, isopropenyl, 2-butenyl, 2-pentenyl, 2-hexenyl and the like. It will be appreciated that in groups of the form -O-C_{2-6}alkenyl, the double bond is preferably not adjacent to the oxygen.

The term C_{3-7}cycloalkyl group means a non-aromatic monocyclic hydrocarbon ring of 3 to 7 carbon atoms such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term 5 or 6 membered heteroaryl as used herein as a group or a part of the group refers to furanyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, pyridyl, pyridinium, pyridazinyl or pyrimidinyl.

The term halogen refers to a fluorine, chlorine, bromine or iodine atom.

The term C_{1-4}alkoxy group may be a straight chain or a branched chain alkoxy group, for example methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or methylprop-2-oxy.

The term 9 to 10 membered fused bicyclic heteroaryl as used herein as a group or a part of the group refers to quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, benzofuranyl, benzimidazolyl, benzothienyl, benzoxazolyl, 1,3-benzodioxazolyl, indolyl, benzothiazolyl, furylpyridine, oxazolopyridyl or benzothiophenyl.

The terms optionally substituted phenyl, optionally substituted 5 or 6 membered heteroaryl or optionally substituted 9 to 10 membered fused bicyclic heteroaryl refer to a group which is substituted by 1 to 3 groups selected from:
halogen, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxy, nitro, cyano, amino, C_{1-4}alkylamino or diC_{1-4} alkylamino, phenyl or 5 or 6 membered heteroaryl.

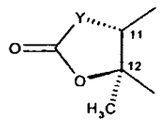
Preferred compounds of formula (I) are those wherein R_2 is hydrogen.

In one embodiment, R_3 is hydrogen or C_{1-4}alkyl, for example methyl, ethyl or propyl.

When A is –C(O)-, R_6 is preferably hydrogen and R_3 is preferably C_{1-4}alkyl (i.e. methyl) or R_6 is preferably fluorine and R_3 is preferably hydrogen.

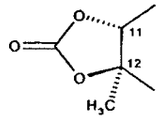
When A is –C(O)-, R_4 and R_5 are preferably hydroxy or R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:

A35



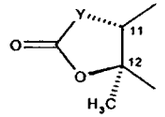
wherein Y is preferably –N(R_8)- and R_8 is hydrogen or C_{1-4}alkyl such as methyl or ethyl.

When A is –NHC(O)-, -C(O)NH-, -N(CH_3)-CH_2- -CH_2-N(CH_3)- or -C($NOCH_2OCH_2CH_2OCH_3$)- and R_4 or R_5 is hydroxy or R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:



R_6 is preferably hydrogen and R_3 is preferably hydrogen, C_{1-4}alkyl (i.e. methyl) or 2-propenyl.

When A is –NHC(O)-, -C(O)NH-, -N(CH_3)-CH_2-, -CH_2-N(CH_3) or -C($NOCH_2OCH_2CH_2OCH_3$)- and R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:

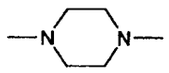


wherein Y is a bivalent radical selected from -CH_2-, -CH(CN)-, -N(R_8)-, R_6 is preferably hydrogen and R_3 is preferably C_{1-4}alkyl (i.e. methyl) or 2-propenyl.

When n is 0, U is preferably selected from -N(R_{13})- , -O- and -S-.

In the compounds of formula (I) n is preferably 1 or 2. Within this class, compounds wherein n is 2 are particularly preferred.

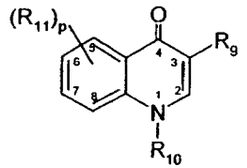
Preferred class of compounds of formula (I) are those wherein X is $NH(CH_2)_{2-5}NH$ or



;within this class, compounds in which X is $NH(CH_2)_{2-3}NH$ are particularly preferred.

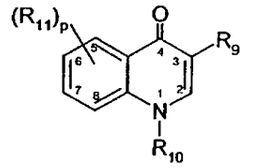
Another preferred class of compounds of formula (I) are those wherein X is $N(R_{13})(CH_2)_{2-3}NH$ and R_{13} is C_{1-4}alkyl such as methyl, or acetyl.

A further preferred class of compounds of formula (I) is that wherein R_7 is a heterocyclic of the following formula:



Within this class of compounds, those compounds wherein p is 0 or 1, R_{11} is halogen (i.e. chloro or fluoro) at position 6 or 7, R_9 is carboxy and R_{10} is methyl, ethyl or cyclopropyl are particularly preferred.

A particular preferred class of compounds according to the invention are those wherein R_2 is hydrogen, X is $NH(CH_2)_{2-3}NH$, R_7 is a heterocyclic group of the following formula:

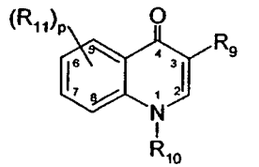


wherein p is 0 or 1, R_{11} is halogen (i.e. chloro or fluoro) at position 6 or 7, R_9 is carboxy and R_{10} is ethyl or cyclopropyl.

Another preferred class of compounds are those wherein R_9 is C(O)OR_{12} and R_{12} is C_{1-4}alkyl, in particular methyl.

A further preferred class of compounds are those wherein R_{11} is C_{1-4}alkoxy, for example methoxy at position 8.

When R_3 is C_{3-6}alkenyl substituted by 9 to 10 membered fused bicyclic heteroaryl, 9 to 10 membered fused bicyclic heteroaryl is preferably 2-quinolyl or 3-quinolyl, R_4 and R_5 are preferably hydroxy and R_6 is hydrogen. Within this class of compounds, the compounds in which R_2 is hydrogen, X is $NH(CH_2)_{2-3}NH$, R_7 is a heterocyclic of the following formula:



wherein p is 1, R_{11} is halogen (i.e. chloro or fluoro) at position 6 or 7, R_9 is carboxy and R_{10} is ethyl or cyclopropyl are particularly preferred.

In one embodiment, Y is a bivalent radical selected from $-CH_2-$, -CH(CN)-, -O- and $-N(R_8)-$.

Particularly preferred compounds of the invention are:

4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino]ethyl]amino]propionyl]-8a-aza-8a-homoerythromycin A;

4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl) amino] ethyl]amino] propionyl]-8a-aza-8a-homoerythromycin A;

4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino] ethyl]amino] propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A;

4"-O-[3-[(2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A;

4"-O-[3-[[2-[(7-chloro-1-cyclopropyl-1,4-dihydro-3-methoxycarbonyl-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A;

4"-O-[3-[[2-[(3-carboxy-1,4-dihydro-1-ethyl-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-6-*O*-methyl-8a-aza-8a-homoerythromycin A;

4"-O-[3-[(2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-6-*O*-methyl-8a-aza-8a-homoerythromycin A ;

4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-6-O-ethyl-8a-aza-8a-homoerythromycin A;

4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-6-O-propyl-8a-aza-8a-homoerythromycin A;

4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino] ethyl]amino] propionyl]-6-O-methyl-9a-aza-9a-homoerythromycin A;

4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-11,12-dideoxy-6-O-methyl-11,12-(methylaminocarbonyloxy)-erythromycin A;

11,12-(aminocarbonyloxy)-4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino]ethyl]amino]propiony]-11,12-dideoxy-6-O-methyl-erythromycin A;

11,12-(aminocarbonyloxy)-4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)amino]ethyl]amino]propiony]-11,12-dideoxy-6-O-methyl-erythromycin A;

4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A;

4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-quinolinyl)-amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A;

4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino]ethyl]amino]propionyl]-6-*O*-methyl-erythromycin A;

4"-O-[3-[[2-[(3-carboxy-7-chloro1,4-dihydro-1-ethyl-4-oxo-6-quinolinyl)amino]ethyl]amino]propiony]-6-O-methyl-erythromycin A and 4"-O-[3-[[2-[(3-carboxy-1,4-dihydro-1-ethyl-6-fluoro-4-oxo-7-quinolinyl)amino]ethyl]amino]propiony]-6-O-methyl-erythromycin A;

4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-6-*O*-methyl-erythromycin A;

(*11S, 11aR*)-11-(carboxycyanomethyl)-4"-O-[3-[[2-[(3-carboxy-1,4-dihydro-1-ethyl-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-11-deoxy-6-*O*-methyl-erythromycin A;

(*11S, 11aR*)-11-(carboxycyanomethyl)-4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-11-deoxy-6-*O*-methyl-erythromycin A;

(*11S, 11aR*)-4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-11-(carboxycyanomethyl)-11-deoxy-6-*O*-methyl-erythromycin A;

4"-O-[3-[4-(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-roxithromycin;

4"-O-[3-[4-(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-roxithromycin;

4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-3-quinolinyl)amino]ethyl]amino]propiony]-azithromycin;

11,12-carbonate-4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)amino]ethyl]amino]propiony]-11,12 dideoxy azithromycin;

4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-3-quinolinyl)amino]ethyl]amino]propiony]-6-O-methyl-azithromycin;

11,12-carbonate-4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-11,12-dideoxy-azithromycin;

11,12-carbonate-4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)amino]ethyl]amino]propiony]-11,12 dideoxy azithromycin.

Further preferred compounds of the invention are:

4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino] ethyl]amino] propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A;

11,12-carbonate-4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-11,12-dideoxy-azithromycin;

11,12-carbonate-4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)amino]ethyl]amino]propiony]-11,12 dideoxy azithromycin;

11,12-carbonate-4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]-amino]propiony]-11,12-dideoxy-azithromycin;

4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propiony]-azithromycin;

4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-11,12-dideoxy-11,12-(ethylaminocarbonyloxy)-6-O-methyl-erythromycin A;

4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A;

4"-O-[3-[[2-[(3-carboxy-1,4-dihydro-1-ethyl-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A;

4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-6-*O*-methyl-crythromycin A;

4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino]ethyl]amino]propionyl]-6-*O*-methyl-erythromycin A;

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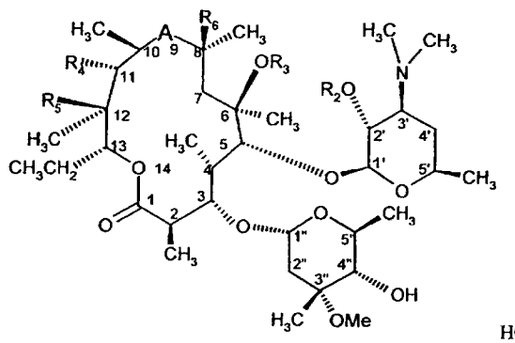
(11*S*, 11a*R*)-4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-11-(carboxycyanomethyl)-11-deoxy-6-*O*-methyl-erythromycin A;
(*11S, 11aR*)-11-(carboxycyanomethyl)-4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-11-deoxy-6-*O*-methyl-erythromycin A;
4"-O-[3-[4-(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-roxithromycin;
4"-O-(3-(2-(3-carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino)ethyl)-methyl-amino)propionyl)-11,12-dideoxy-11,12-(ethylaminocarbonyloxy)-6-O-methylerythromycin A;
4"-O-{3-[(2-[(3-carboxymethyl-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolin yl)amino]ethyl)amino]propiony}-6-O-methyl-erythromycin A;
11,12-(aminocarbonyloxy)-4"-O-{3-[(2-[(3-carboxy-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino]ethyl)amino]propionyl}-11,12-dideoxy-6-O-methyl-erythromycin A;
4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]-methyl-amino]propionyl]-azithromycin;
11,12-carbonate-4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl) amino] ethyl] methylamino] propionyl]-11,12-dideoxy-azithromycin;
4"-O-(3-{[2-(7-chloro-1-cyclopropyl-3-methoxycarbonyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethyl]-amino}-propionyl)-azithromycin;
4"-O-(3-{[2-(7-chloro-1-cyclopropyl-3-methoxycarbonyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethyl]-methyl-amino}-propionyl)-azithromycin;
4"-O-{3-[(2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl)methylamino]propionyl}-azithromycin; and
4"-O-[3-[[2-[(3-carboxy-1-ethyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A.

Compounds according to the invention also exhibit a broad spectrum of antibacterial activity against a wide range of clinical pathogenic microorganisms. For example, using a standard microtiter broth serial dilution test, compounds of the invention have been found to exhibit useful levels of activity against a wide range of pathogenic microorganisims including strains of Staphylococcus aureus, Streptopococcus pneumoniae, Moraxella catarrhalis, Streptococcus pyogenes, Haemophilus influenzae, Chlamydia pneumoniae, Mycoplasma pneumoniae and Legionella pneumophila. The compounds of the invention may therefore be used for treating a variety of diseases caused by pathogenic bacteria in human beings and animals. The compounds of the invention may also be active against resistant strains, for example erythromycin resistant strains. In particular, the compounds of the invention may be active against erythromycin resistant strains of Streptococcus pneumoniae and Streptococcus pyogenes.

Thus, according to another aspect of the present invention, we provide a compound of formula (I) or a physiologically acceptable salt thereof for use in the therapy or prophylaxis of systemic or topical bacterial infections in a human or animal subject.

Compounds of formula (I) wherein n is an integer 1 to 5, may be prepared by reaction of 4'' hydroxy of formula (II) with a suitable activated derivative of the carboxylic acid (III), followed where necessary by subsequent removal of the hydroxyl protecting group R_2.



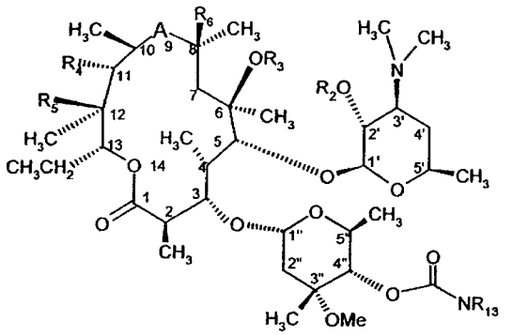
(II)

$HOC(O)(CH_2)_nXR_7$
(III)

Suitable activated derivatives of the carboxyl group include the corresponding acyl halide, mixed anhydride or activated ester such as a thioester. The reaction is preferably carried out in a suitable aprotic solvent such as a halohydrocarbon (e.g. dichloromethane) or N,N-dimethylformamide optionally in the presence of a tertiary organic base such as dimethylaminopyridine or triethylamine or in the presence of inorganic base (i.e sodium hydride) and at a temperature within the range of 0° to 120°C.

Compounds of formula (I) wherein n is 0, U is a group selected from:
$-N(R_{13})-$, -O- and $-S(O)_q-$ wherein q is 0,
may be prepared by reaction of compounds of formula (II), in which the 4" hydroxy is suitable activated, with a compound of formula XR_7 (IV), followed where necessary by subsequent removal of the hydroxyl protecting group R_2. Suitable activated derivatives of the 4" hydroxy group include for example carbonyl imidazole. The reaction is preferably carried out in a suitable aprotic solvent such as a halohydrocarbon (e.g. dichloromethane) or N,N-dimethylformamide optionally in the presence of a tertiary base such as dimethylaminopyridine or triethylamine and at a temperature within the range of 0° to 120°C.

Compounds of formula (I) wherein n is 0 and U is $-N(R_{13})C(O)-$, may be prepared by reaction of compounds of formula (V),



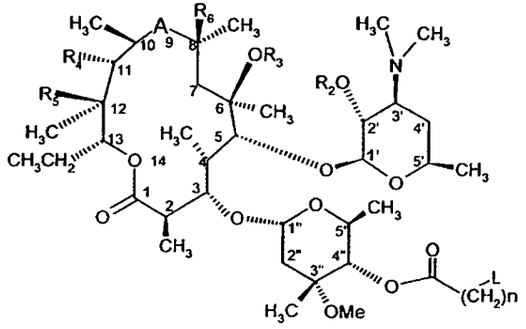
(V)

with a compound of formula $HOC(O)C(O)(CH_2)_mZR_7$(VI), followed where necessary by subsequent removal of the hydroxyl protecting group R_2. The reaction is preferably carried out in a suitable aprotic solvent such as a halohydrocarbon (e.g. dichloromethane) or N,N-dimethylformamide optionally in the presence of a tertiary base such as dimethylaminopyridine or triethylamine and at a temperature within the range of 0° to 120°C.

Compounds of formula (V) may be prepared by treatment of compounds of formula (II), in which the 4" hydroxy is suitable activated, with amine NR_{13}(VIIa). Suitable activated derivatives of the 4" hydroxy group include for example carbonyl imidazole.

Compounds of formula (I) wherein n is 0 and U is $-C(O)N(R_{13})-$ may be prepared by reaction of 4'' hydroxy of formula (II) with a suitable activated derivative of the carboxylic acid $HOC(O)N(R_{13})(CH_2)_mZR_7$(VIIb) followed where necessary by subsequent removal of the hydroxyl protecting group R_2.

In a preferred embodiment of the invention compounds of formula (I) wherein n is 1 to 5 and U is a group selected from $-N(R_{13})-$, -O-, -S-, may be prepared by reaction of compounds of formula (VII),

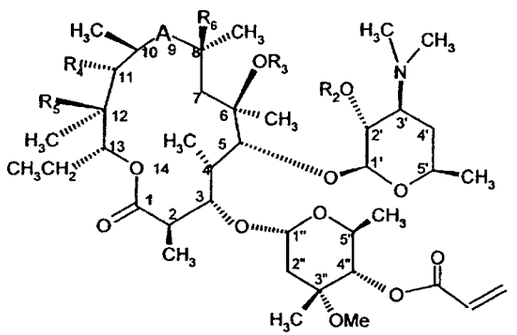


(VII)

wherein n is an integer from 1 to 5 and L is a suitable leaving group, with XR_7 (IV) in which U is a group selected from $-N(R_{13})-$, -O-, -S-. The reaction is preferably carried out in a solvent such as a halohydrocarbon (e.g. dichloromethane), an ether (e.g. tetrahydrofuran, dimethoxyethane), acetonitrile or ethyl acetate and the like), dimethylsulphoxide, N,N-dimethylformamide, 1-methyl-pyrrolidone and in the presence of a base, followed, if desired, by removal of the hydroxyl protecting group R_2. Examples of the bases which may be used include organic base such as diisopropylethylamine, triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, or inorganic base such as potassium hydroxide, cesium hydroxide, tetraalkylammonium hydroxyde, sodium hydride, potassium hydride and the like. Suitable leaving groups for this reaction include halogen (e.g. chlorine, bromine or iodine) or a sulfonyloxy group (e.g. tosyloxy or methanesulfonyloxy).

Compounds of formula (VII) may be prepared by reaction of a compound of formula (II), wherein R_2 is a hydroxyl protecting group; with a suitable activated derivative of the carboxylic acid $HOC(O)(CH_2)_nL$(VIII), wherein L is a suitable leaving group as above defined. Suitable activated derivatives of the carboxyl group are those defined above for carboxylic acid (III). The reaction is carried out using the condition described above for the reaction of a compound of formula(II) with carboxylic acid (III).

In a further embodiment of the invention compounds of formula (I) of wherein n is 2, U is a group selected from:
$-N(R_{13})-$, -O- and -S-,
may be prepared by Michael reaction of a compound of formula (IX), wherein R_2 is a hydroxyl protecting group



(IX)

with a compound of formula XR_7(IV). The reaction is suitably carried out in a solvent such as dimethylsulphoxide, N,N-dimethylformamide, 1-methyl-pyrrolidone, a halohydrocarbon (e.g. dichloromethane), an ether (e.g. tetrahydrofuran, dimethoxyethane), acetonitrile or ethyl

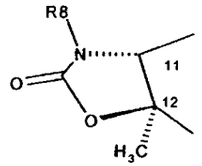
acetate or alchool(e.g methanol, isopropanol) and the like and in the presence of a base, followed ,if desired, by removal of hydroxyl protecting group R_2.

Compounds of formula (I) may be converted into other compounds of formula (I). Thus compounds of formula (I) wherein U is $-S(O)_q$ and q is 1 or 2 may be prepared by oxidation of the corresponding compound of formula (I) wherein q is 0. The oxidation is preferably carried out using a peracid, e.g. peroxybenzoic acid, followed by treatment with a phosphine, such as triphenylphosphine. The reaction is suitably carried out in an organic solvent such as methylene chloride.

Compounds of formula (II) wherein A is -C(O)NH- or -NHC(O)-, R_4 or R_5 are hydroxy, R_3 is hydrogen and R_6 is hydrogen are known compounds or they may be prepared by analogous methods to those known in the art . Thus they can be prepared according to the procedures described in EP 507595 and EP 503932.

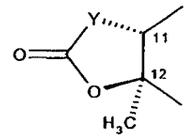
Compounds of formula (II), wherein A is -C(O)NH- or -NHC(O)-, R_4 or R_5 are hydroxy and R_3 is C_{1-4}alkyl or C_{3-6}alkenyl optionally substituted by 9 to 10 membered fused bicyclic heteroaryl and R_6 is hydrogen are known compounds or they may be prepared by analogous methods to those known in the art. Thus they can be prepared according to the procedures described in WO 9951616 and WO 0063223.

Compounds of formula (II), wherein A is -C(O)NH- or -NHC(O)-, $-N(CH_3)-CH_2-$, $-CH_2-N(CH_3)-$, R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:



R_3 is C_{1-4}alkyl, or C_{3-6}alkenyl optionally substituted by 9 to 10 membered fused bicyclic heteroaryl and R_6 is hydrogen are known compounds or they may be prepared by analogous methods to those known in the art. Thus they can be prepared according to the procedures described in USP N°6262030

Compounds of formula (II), wherein A is -C(O)-, R_4 or R_5 are hydroxy or R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:

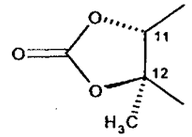


wherein Y is a bivalent radical selected from:

-O- and $-N(R_8)-$

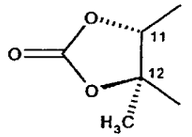
and R_3 is C_{1-4}alkyl, or C_{3-6}alkenyl optionally substituted by 9 to 10 membered fused bicyclic heteroaryl are known compounds or they may be prepared by analogous methods to those known in the art. Thus they can be prepared according to the procedures described in EP 307177, EP 248279, WO 0078773, WO 9742204.

Compounds of formula (II), wherein A is $-N(CH_3)-CH_2-$, $-CH_2-N(CH_3)-$, R_4 or R_5 are hydroxy or R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:



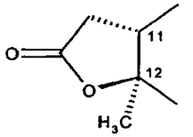
and R_6 is hydrogen are known compounds or they may be prepared by analogous methods to those known in the art. Thus they can be prepared according to the procedures described in EP 508699 and J.Chem. Res.Synop (1988 pages 152-153) , USP 6262030.

Compounds of formula (II), wherein A is $-C(NOCH_2OCH_2CH_2OCH_3)-$, R_4 or R_5 are hydroxy or R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:

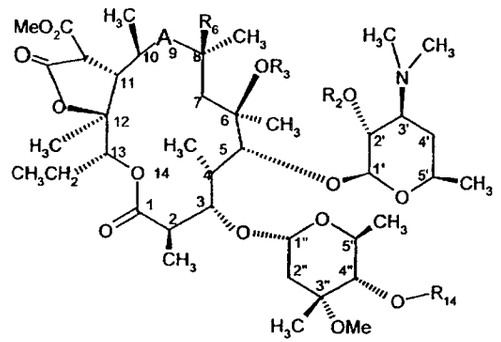


and R_6 is hydrogen ,are known compounds or they may be prepared by analogous methods to those known in the art. Thus they can be prepared according to the procedures described in EP 284203.

Compounds of formula (II), wherein A is C(O)-, R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:



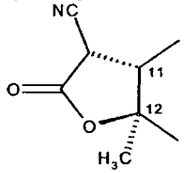
R_6 is hydrogen and R_3 is C_{1-4} alkyl may be prepared by decarboxylation of a compound of formula (X), wherein R_{14} is hydroxy protecting group, followed, if required by removal of the protecting group R_2 or R_{14}.



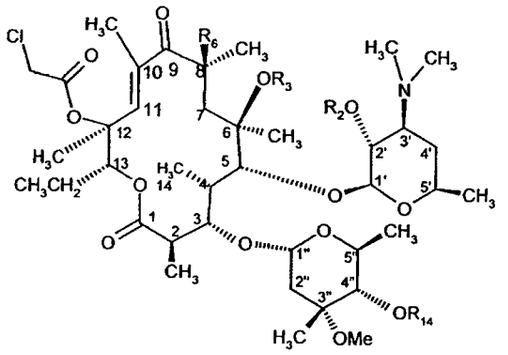
(X)

The decarboxylation may be carried out in the presence of a lithium salt such as lithium chloride, preferably in an organic solvent such as dimethylsulphoxide.

Compounds of formula (II), wherein A is C(O)-, R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:



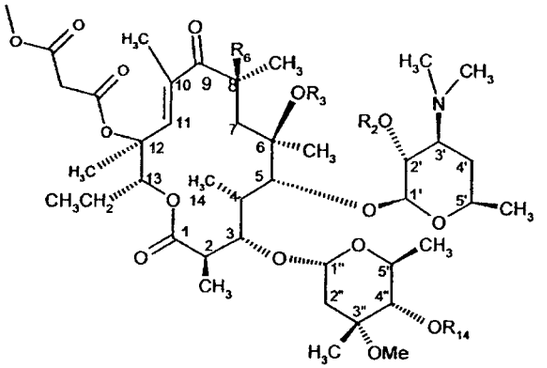
and R_3 is C_{1-4} alkyl may be prepared by cyclisation of chlorine derivatives (XI)



(XI)

with potassium cyanide and conveniently in the presence of a solvent such as N-N dimethylformamide.

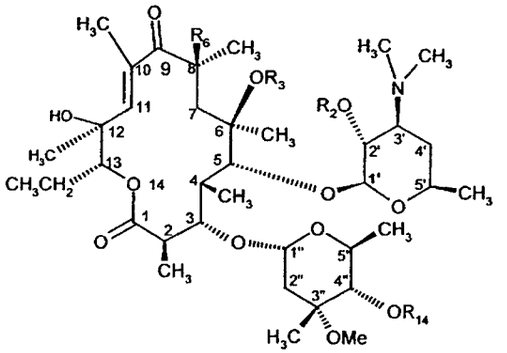
Compounds of formula (X) may be prepared by reaction of a compound of formula (XII)



(XII)

in the presence of a strong base such as 1,8 diazabicyclo [5.4.0]undec-7-ene. This reaction is conveniently carried out in an organic solvent such acetonitrile, N,N dimethylformamide and the like.

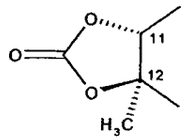
Compounds of formula (XII) may be prepared by a reaction of a compounds of formula (XIII)



(XIII)

with a acyl chloride of formula $ClCOCH_2COOMe$ (XIV), in the presence of a tertiary base such as pyridine, dimethylaminopyridine or triethylamine and at a temperature within the range of 0° to 30°C.

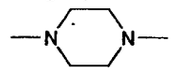
Compounds of formula (XIII) may be prepared by reacting a compound of formula (II) wherein R_{14} is hydroxy protecting group, R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:



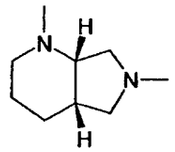
with a strong base such as 1,8 diazabicyclo [5.4.0]undec-7-ene.

Compounds of formula (XI) may be prepared by reaction of compounds of formula (XIII) with a suitable activated derivative of the acid $HOCOCH_2Cl$ (XV). Thus, for example, the esterification may be carried out by reaction with anhydride $(ClCH_2CO)_2O$ (XVI) in a suitable aprotic solvent such as a halohydrocarbon (e.g. dichloromethane) or N,N-dimethylformamide and in the presence of a tertiary base such as pyridine, dimethylaminopyridine or triethylamine and at a temperature within the range of 0° to 120°C.

Compounds of formula (III) wherein X is $-U(CH_2)_mN(R_{13})-$, in which U is $-N(R_{13})-$, -O- or -S- or X is a group selected from:

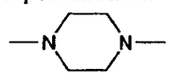


or

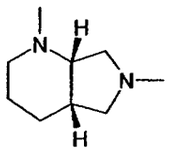


may be prepared by reaction of XR_7 (IV), wherein X has the meaning defined above with $R_{15}OC(O)(CH_2)nL$(XV) wherein R_{15} is carboxyl protecting group and L is a suitable leaving group, followed by removal of R_{15}.

Compounds of formula (IV) wherein X is $-U(CH_2)_mZ$ in which Z is $-N(R_{13})-$, -O-, or -S- or X is a group selected from:



or



may be prepared by reaction of a compound of formula R_7L (XVI), wherein L is a suitable leaving group such as chlorine, fluorine or bromine, with a compound of formula-$U(CH_2)_mZ$ (XVII) in which Z is $-N(R_{13})-$, -O-, or -S- or with piperazine or with 1H-pyrrolo[3,4-b]pyridine, octahydro.

Suitable hydroxy protecting reagents are those described by T.W. Greene and P.G.M Wuts in Protective Groups in Organic Synthesis 2nd ed., John Wiley & Son, Inc 1991, which is incorporated by reference. Examples of suitable hydroxy protecting reagents include acetic anhydride, benzoic anhydride or a trialkylsilyl chloride in a protic solvent. Examples of aprotic solvents are dichloromethane, N,N-dimethylformamide, dimethylsulfoxide, tetrahydrofuran and the like. Suitable R_{15} carboxyl protecting group include t-butyloxy, allyl or benzyloxy.

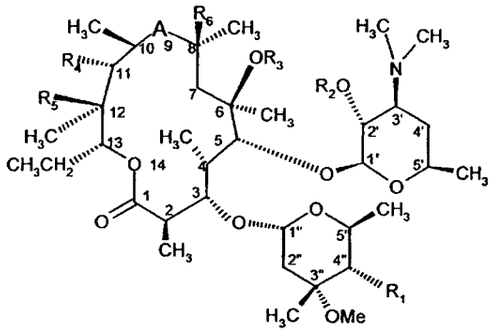
Acid addition salts of the compounds of general formula (I) may prepared by various methods known to those skilled in those art. For example, an aqueous solution of an acid such as hydrochloric acid may be added to an aqueous suspension of a compound of formula (I) and the resulting mixture evaporated to dryness (lyophilised) to obtain the acid addition salt as a solid. Alternatively, a compound of formula (I) may be dissolved in a suitable solvent, for example an alcohol such as isopropanol, and the acid may be added in the same solvent or another suitable solvent. The resulting acid addition salt may then be precipitated directly, or by addition of a less polar solvent such as diisopropyl ether or hexane, and isolated by filtration.

In order that the invention may be more fully understood the following examples are given by way of illustration only.

In the Preparations and Examples, unless otherwise stated:
Proton Magnetic Resonance (^{1}H-NMR) spectra were recorded on Bruker Avance DRX 300 and DRX 500 or Varian 500 MHz as solutions in chloroform d-1, unless otherwise stated. Chemical shifts are reported in ppm downfield (δ) from Me_4Si, used as internal standard, and are assigned as singlets (s), doublets (d), doublets of doublets (dd), triplets (t), quartets (q) or multiplets (m).
Carbon Magnetic Resonance (^{13}C-NMR) spectra were recorded on Bruker Avance DPX 75 and DRX 125 MHz as solutions in chloroform d-1, unless otherwise stated. Chemical shifts are reported in ppm downfield (δ) from Me_4Si, used as internal standard.
Mass spectra were acquired with a Hewlett Packard 1100 MSD system equipped with a binary pump (Agilent Technologies), operating in positive electrospray ionisation mode.
LC/MS data were obtained by using a HP 1100 LC system (Agilent Technologies) equipped with a Sedex Evaporative Light Scattering Detector model 75 (Sedere) coupled with a Platform LCZ Mass Spectometer (Micromass) operating in positive electrospray ionisation mode. The chromatographic analysis conditions were: column Waters XTerra MS C18 (4.6 x 30mm, 2.5μm); flow rate 0.8mL/min; mobile phase: aqueous solution of NH_4OAc (10mM, pH 6.8) (A) and acetonitrile (B).
LC purifications were performed with a Waters 600 semi-preparative system equipped with a binary pumping system and a Jasco-UV detector. The chromatographic analysis conditions were:

Claims

1. A compound of formula (I)



(I)

wherein

A is a bivalent radical selected from:

-C(O)-, -C(O)NH-, -NHC(O)-, -N(CH_3)-CH_2-, -CH_2-N(CH_3)- or -C($NOCH_2OCH_2CH_2OCH_3$)-;

R_1 is $OC(O)(CH_2)_nXR_7$;

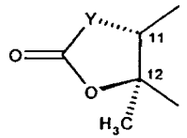
R_2 is hydrogen or a hydroxyl protecting group;

R_3 is hydrogen, C_{1-4}alkyl or C_{3-6}alkenyl optionally substituted by 9 to 10 membered fused bicyclic heteroaryl;

R_4 is hydroxy or C_{3-6}alkenyloxy optionally substituted by 9 to 10 membered fused bicyclic heteroaryl;

R_5 is hydroxy or

R_4 and R_5 taken together with the intervening atoms form a cyclic group having the following structure:

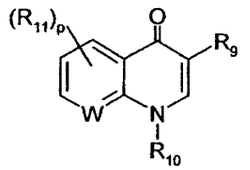


wherein Y is a bivalent radical selected from:

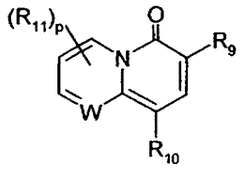
-CH_2-, -CH(CN)-, -O-, -N(R_8)- and -CH(SR_8)-;

R_6 is hydrogen or fluorine;

R_7 is a heterocyclic group having the following structures:



or



R_8 is hydrogen or

C_{1-4}alkyl substituted by a group selected from:

optionally substituted phenyl,

optionally substituted 5 or 6 membered heteroaryl,

optionally substituted 9 to 10 membered fused bicyclic heteroaryl;

R_9 is hydrogen, $C(O)OR_{12}$, $C(O)NHR_{12}$ or $C(O)CH_2NO_2$;

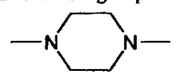
R_{10} is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, optionally substituted phenyl or benzyl;

R_{11} is halogen, C_{1-4}alkyl, C_{1-4}thioalkyl, C_{1-4}alkoxy, NH_2, NH(C_{1-4}alkyl) or N(C_{1-4}alkyl)$_2$;

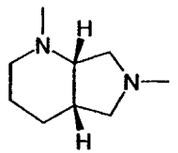
R_{12} is hydrogen or C_{1-4}alkyl;

R_{13} is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, optionally substituted phenyl or benzyl, acetyl or benzoyl;

X is -U(CH_2)$_m$Z- or X is a group selected from:



or



U and Z independently are a divalent radical selected from:

-N(R_{13})- , -O-, -S(O)q- , -N(R_{13})C(O)-, -C(O)N(R_{13})-, -N[C(O)R_{13}]-,

W is a carbon or a nitrogen atom;

n is 0 or an integer from 1 to 5;

m is an integer from 2 to 8;

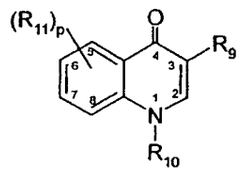
p is 0, 1 or 2;

q is 0, 1 or 2;

and pharmaceutically acceptable salts and solvates thereof.

2. A compound according to claim 1 wherein X is $NH(CH_2)_{2-3}NH$.

3. A compound according to claim 1 or 2 wherein R_7 is a heterocyclic group having the following structure:



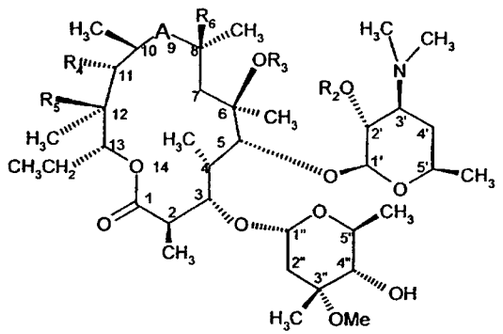
wherein R_9, R_{10}, R_{11} and p are as defined in claim 1.

4. A compound according to claim 1 as defined in any one of Examples 1 to 119, or a pharmaceutically acceptable salt or solvate thereof.

5. A compound selected from
4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-8a-aza-8a-homoerythromycin A;
11,12-carbonate-4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-11,12-dideoxy-azithromycin;
11,12-carbonate-4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-quinolinyl)amino]ethyl]amino]propiony]-11,12 dideoxy azithromycin;
11,12-carbonate-4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]-amino]propiony]-11,12-dideoxy-azithromycin;
4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propiony]-azithromycin;
4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-11,12-dideoxy-11,12-(ethylaminocarbonyloxy)-6-O-methyl-erythromycin A;
4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A;
4"-O-[3-[[2-[(3-carboxy-1,4-dihydro-1-ethyl-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A;
4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-6-*O*-methyl-erythromycin A;
4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino]ethyl]amino]propionyl]-6-*O*-methyl-erythromycin A;
(11*S*, 11a*R*)-4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-11-(carboxycyanomethyl)-11-deoxy-6-*O*-methyl-erythromycin A;
(*11S, 11aR*)-11-(carboxycyanomethyl)-4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl]amino]propionyl]-11-deoxy-6-*O*-methyl-erythromycin A;

4"-O-[3-[4-(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-roxithromycin;
4"-O-(3-(2-(3-carboxy-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino)ethyl)-methyl-amino)propionyl)-11,12-dideoxy-11,12-(ethylaminocarbonyloxy)-6-O-methylerythromycin A;
4"-O-{3-[(2-[(3-carboxymethyl-7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino]ethyl)amino]propiony}-6-O-methyl-erythromycin A;
11,12-(aminocarbonyloxy)-4"-O-{3-[(2-[(3-carboxy-1-cyclopropyl-4-oxo-1,4-dihydro-6-quinolinyl)amino]ethyl)amino]propionyl}-11,12-dideoxy-6-O-methyl-erythromycin A;
4"-O-[3-[[2-[(3-carboxy-7-chloro-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]-methyl-amino]propionyl]-azithromycin;
11,12-carbonate-4"-O-[3-[[2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]methylamino]propionyl]-11,12-dideoxy-azithromycin;
4"-O-(3-{[2-(7-chloro-1-cyclopropyl-3-methoxycarbonyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethyl]-amino}-propionyl)-azithromycin;
4"-O-(3-{[2-(7-chloro-1-cyclopropyl-3-methoxycarbonyl-4-oxo-1,4-dihydro-quinolin-6-ylamino)-ethyl]-methyl-amino}-propionyl)-azithromycin;
4"-O-{3-[(2-[(3-carboxy-1-cyclopropyl-1,4-dihydro-4-oxo-7-quinolinyl)amino]ethyl)methylamino]propionyl}-azithromycin; and
4"-O-[3-[[2-[(3-carboxy-1-ethyl-1,4-dihydro-4-oxo-6-quinolinyl)amino]ethyl]amino]propionyl]-6-O-methyl-erythromycin A.

6. A process for the preparation of a compound as claimed in claim 1 which comprises:
a) reacting a compound of formula (II)



(II)

$HOC(O)(CH_2)_nXR_7$
(III)

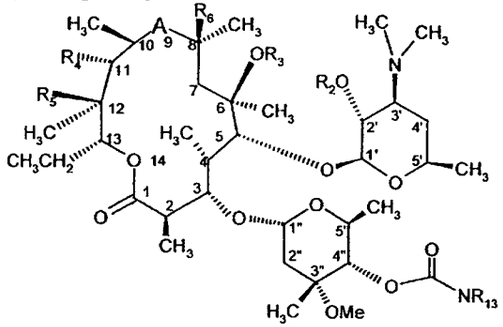
with a suitable activated derivative of the acid (III), wherein n is an integer 1 to 5, X and R_7 have the meanings defined in claim 1, to produce a compound of formula(I) wherein n is an integer 1 to 5;

b) reacting a compound of formula (II), in which the 4" hydroxy is suitable activated, with a compound of formula XR_7(IV), wherein R_7, m and Z have the meanings defined in claim 1 and X is $-U(CH_2)mZ-$, in which U is a group selected from selected from:

$-N(R_{13})-$, -O-, -S-,

to produce a compound of formula (I) wherein n is 0 and U is a group selected from $-N(R_{13})-$, -O-, -S-;

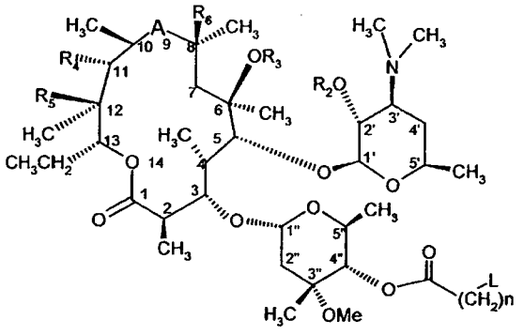
c) reacting a compound of formula (V)



(V)

wherein R_{13} has the meaning defined in claim 1 with a suitable activated derivative of the carboxylic acid $HOC(O)C(O)(CH_2)_mZR_7$(VIIb), wherein R_7 and Z have the meanings defined in claim 1, to produce a compound of formula (I) wherein n is 0 and U is $-N(R_{13})C(O)-$;

d) reacting a compound of formula (VII)

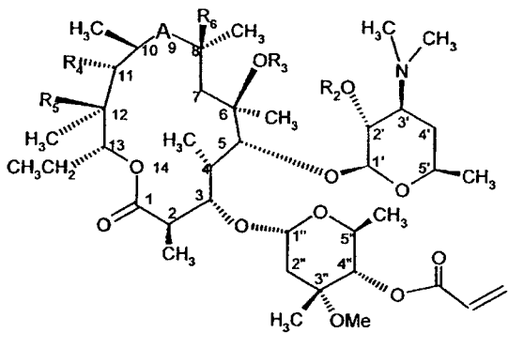


(VII)

with a compound of formula XR_7 (IV), wherein R_7 and X have the meanings defined in claim 1 in which U is a group selected from $-N(R_{13})-$, -O-, -S-, and L is suitable leaving group, to produce a compound of formula (I) wherein n is 1 to 5 and and U is a group selected from:

$-N(R_{13})-$, -O-, -S-;

e) reacting a compound of formula (IX), with a compound of formula XR_7 (IV),



(IX)

wherein R_7 and X have the meanings defined in claim 1, in which U is a group selected from $-N(R_{13})-$, -O-, -S-, to produce a compound of formula (I) wherein n is 2 and U is a group selected from:

$-N(R_{13})-$, -O-, -S-,

and thereafter, if required, subjecting the resulting compound to one or more of the following operations:

i) removal of the protecting group R_2 and

ii) conversion of the resultant compound of formula (I) into a pharmaceutically acceptable salt and solvates thereof.

7. A compound as claimed in any one of claims 1 to 5 for use in therapy.

8. The use of a compound as claimed in any one of claims 1 to 5 in the preparation of a medicament for use in the therapy of systemic or topical bacterial infections in a human or animal body.

9. The use of a compound as claimed in any one of claims 1 to 5 for use in the treatment or prophylaxis of systemic or topical bacterial infections in a human or animal body.

10. A pharmaceutical composition comprising a compound as claimed any one of claims 1 to 5 in admixture with one or more pharmaceutically acceptable carriers or excipients.

11. A method for the treatment of the human or non human animal body to combat bacterial infection comprising administration of an effective amount of a compound as claimed in any one of claims 1 to 5.

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